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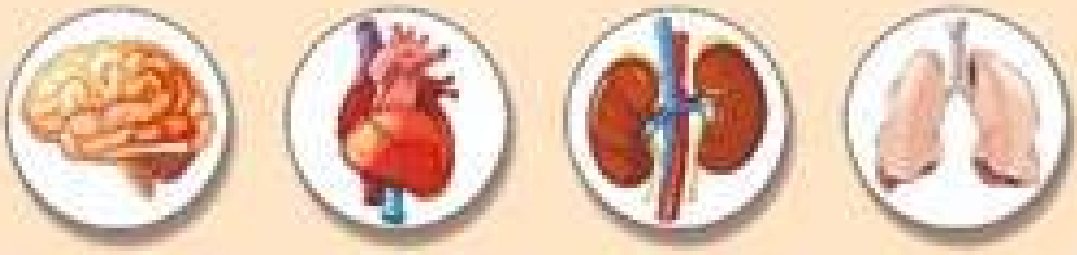

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Section 1

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COVID-19

CHAPTER

1

COVID-19 and Hypertension

K Tewary

Abstract

The COVID-19 pandemic has taken us unprecedented, and management of comorbidities has become challenging as a consequence. Presence of comorbidities has shown to be an increased risk factor for critical illness. Since it's a relatively new disease, there is a lack of robust clinical data concerning COVID-19 infection and presence of comorbidities. Among the COVID-19 patients who died in Italy, it was observed that those with comorbidities including hypertension (69%), diabetes (31%), ischemic heart disease (27%), atrial fibrillation (21%), and heart failure (16%) were the most important factors for the increased mortality rates observed (Gruppo Della database, 2020).

Introduction

The COVID-19 pandemic has taken us unprecedented, and management of comorbidities has become challenging as a consequence. Presence of comorbidities has shown to be an increased risk factor for critical illness. Since it's a relatively new disease, there is a lack of robust clinical data concerning COVID-19 infection and presence of comorbidities. Among the COVID-19 patients who died in Italy, it was observed that those with comorbidities including hypertension (69%), diabetes (31%), ischemic heart disease (27%), atrial fibrillation (21%), and heart failure (16%) were the most important factors for the increased mortality rates observed (Gruppo Della database, 2020). The highest percentage of association was with hypertension. In a meta-analysis done, it was shown that the extent of hyperglycemia was lower in survivors and non-severe subset of patients. Similarly, presence of hypertension was associated with higher mortality rates and necessity of ICU care.[1] So far there is no evidence to show that hypertension reduces immunity or increases the predisposition toward getting infected with COVID-19.[2]

Management of Hypertension in the COVID-19 Era and the Possible Role of RAAS Inhibitors

With the current scenario, it becomes very crucial to manage cardiovascular risk factors to reduce significant morbidity and mortality. A significant proportion of these patients are on renin-angiotensin-aldosterone system (RAAS) inhibitors as therapy for their hypertension. The European Society of Cardiology (ESC) has come up with a recent guidance document under the expert panel of health-care professionals managing COVID-19 concomitantly with cardiovascular disease. Multivariable adjusted models have shown cardiac injury, especially elevated cardiac troponin-T levels to be a significant mortality indicator. Studies have reported that in a significant proportion of COVID-19 patients, direct myocardial injury resulting in elevated cardiac troponins is the main effect seen (approximately 8–12% patients). Presence of pre-existing cardiac disease tends to worsen this.[3,4] Additionally, COVID-19 associated pneumonia

has shown to induce long-term hypercoagulable state, which again contributes to worsening cardiovascular outcomes. The viral myocarditis has also been responsible for precipitating arrhythmias. Taken into consideration all these factors, ESC has suggested that it's vital to communicate to seek immediate medical guidance if a patient has been diagnosed with COVID-19 and has significant cardiovascular comorbidities. The emphasis is not to discontinue any of the drugs, either aspirin or RAAS inhibitors unless as advised by the treating specialist.

In a large retrospective study in 2,877 patients admitted with COVID-19 at Huo Shen Shan hospital, Wuhan, 29.5% presented with a history of hypertension. Interestingly, it was observed that in patients who had a history of hypertension but were not under current therapy for the same, the mortality rate was twice as those who were being managed with pharmacotherapy for the same [HR:2.17,(1.03-4.57, p=0.04)]. In fact, the mortality rates were similar for those on RAAS inhibitors versus those on other classes of antihypertensive drugs [HR: 0.85, (0.28-2.58,p = 0.774)], although the results were not statistically significant.[5] In the largest study of its kind, 884 COVID-19 positive patients were enrolled out of which 149 had hypertension, and interestingly majority of the patients were treated with calcium channel blockers. Compared to those without a history of hypertension, this subgroup of patients presented with more severe respiratory symptoms requiring more intensive therapy including use of intravenous immunoglobulin therapy and ultimately longer ICU stay. This again emphasizes the importance of aggressive BP management for better outcomes.[6] In another study from Wuhan province, Yang et al. attempted to understand the role of hypertension further. To remove the possibility of bias due to various confounding variables that may skew the analysis, a propensity score matching (PSM) was done. In the cohort of 226 COVID-19 patients studied, analysis revealed that presence of hypertension could increase death rate significantly (HR: 3.317, CI: 1.709-6.44, p<0.001). Interestingly, elevated D-dimer levels and higher neutrophil-lymphocyte ratio was found to increase mortality risk overall. However, this difference was not significant across the age groups, whether less than 65 years of age or above.

In a larger scale epidemiological study from Spain, involving 1,139 COVID-19 patients on concurrent therapy with RAAS inhibitors, further attempt was made to understand the effect of this class of drugs (cases) as compared to those on other classes of antihypertensives acting as control subjects. The cases were control matched by a factor of 10 to give a total of 11,390 controls. Interestingly, there was no increase in the severity of COVID-19 symptoms requiring hospital admission or increase in the complication rate leading to more fatality for the cases relative to the controls (OR: 0.94, CI: 0.77–1.15). In another large cohort study of 5,700 COVID-19 patients from the Northwell area, New York, it was seen there was no significant difference in mortality rates between those managed with RAAS inhibitors versus those on other classes of antihypertensives. It's an established fact that these drugs increase the mRNA expression of cardiac ACE2, but yet their role in determining outcomes in COVID-19 patients remains ambiguous.[7] Although the data studied were observational studies and not randomized control trials (RCTs), there is a certain degree of reassurance that RAAS inhibitors can be safely continued in spite of the infection.[8] One of the studies reportedly employed a Bayesian method of analysis in COVID-19 subjects to determine whether any of the five classes of antihypertensive drugs (ACE-inhibitors, ARBs, beta-blockers, calcium channel blockers and thiazide diuretics) played a role in the severity of infection. One of the advantages of using a Bayesian analysis is that unobserved variables can be accommodated in the process whenever there's a diagnostic or clinical error thus rendering the analytic process more robust. None of these classes of drugs were associated with worsening outcomes in COVID-19 disease.[9] There has also been reports of usage of RAAS inhibitors resulting in attenuation of inflammatory markers like IL-6; the authors have also reported that calcium channel blockers as a class has also shown mortality benefits;[10] they have also emphasized the use of telemedicine platforms in this pandemic era to provide better access to health-care resources and for better outcomes. Mobile health services have been emphasized especially for the populations with limited access to health-care resources. With just an application on the mobile phone, patients can continuously communicate with the health-care providers as long as self BP monitoring (SBPM) training is provided. In another retrospective review based in Shenzen Third People's Hospital, 42 COVID-19 positive patients were categorized as those on RAAS inhibitors versus other classes of antihypertensives.

The percentage of patients ending up with severe disease was lower for those RAAS inhibitors (23.5%) with no mortality numbers whereas those on non-RAAS inhibitors the percentage was higher (48%) and one patient died. Also levels of inflammatory markers, IL-6, CRP were lower in the former; in addition the CD3+, CD4+, CD8+ cell count was higher for those on RAAS inhibitors with lower viral load. Although no direct causality can be established with use of RAAS inhibitors and severity of disease, the authors assume that the differences observed could be attributed to the higher levels of Angiotensin-II for those on non-RAAS inhibitors.[11] In a similar retrospective study, 282 hypertensive patients admitted for COVID-19 were identified, out of which 41 subjects were managed with RAAS inhibitors versus 241 who were on alternate class of drugs. Primarily, the authors noted that hypertensive patients as a group were more likely end up critically ill. All cause mortality was higher in this group as per cox regression analysis. Additionally, use of RAAS inhibitors was associated with lower CRP levels and higher CD4+ cell count, with better outcomes.[12] Hence, they emphasize on a holistic approach on managing patients and continuing the antihypertensive therapy no matter what the class of drugs being used.

RAAS Inhibitors Mechanism of Action and the Pathway of COVID-19 Infection

There are multiple mechanisms through which RAAS inhibitors work on the cardio-metabolic axis and could potentially interfere with the clinical course of COVID-19 infection.

As far as the discussion above is concerned, there is couple of factors that needs to taken into account. Firstly, how much does hypertension play a definite role in the severity of COVID-19. Sisnieguez et al. has commented in a review study about the possibility of confounding factors that could possibly lead to false conclusions about the association between hypertension and COVID-19 outcomes. They go to explain that the increased mortality observed in the elderly with COVID-19 could be confounded due to increased prevalence of cardiovascular disease in the elderly which has been well established in the multivariate model (where the association between cardiovascular disease and COVID-19 is well established), but this has not been established with hypertension per se. Therefore, before any conclusions could be made concerning hypertension and severity of COVID-19 infection, these confounding factors should be adjusted appropriately.[13] Secondly, the role of RAAS inhibitors in the outcomes of COVID-19 infection seems ambiguous and more research is needed to ascertain further as to whether their use results in better or adverse clinical outcomes in the COVID-19 scenario **(Fig. 1 and Flowchart 1)**.

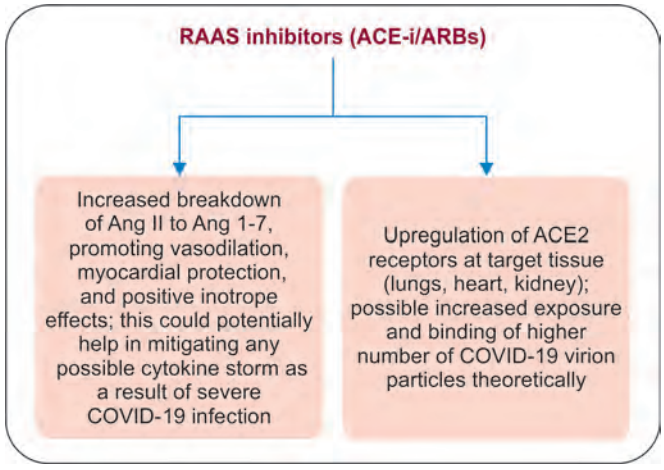
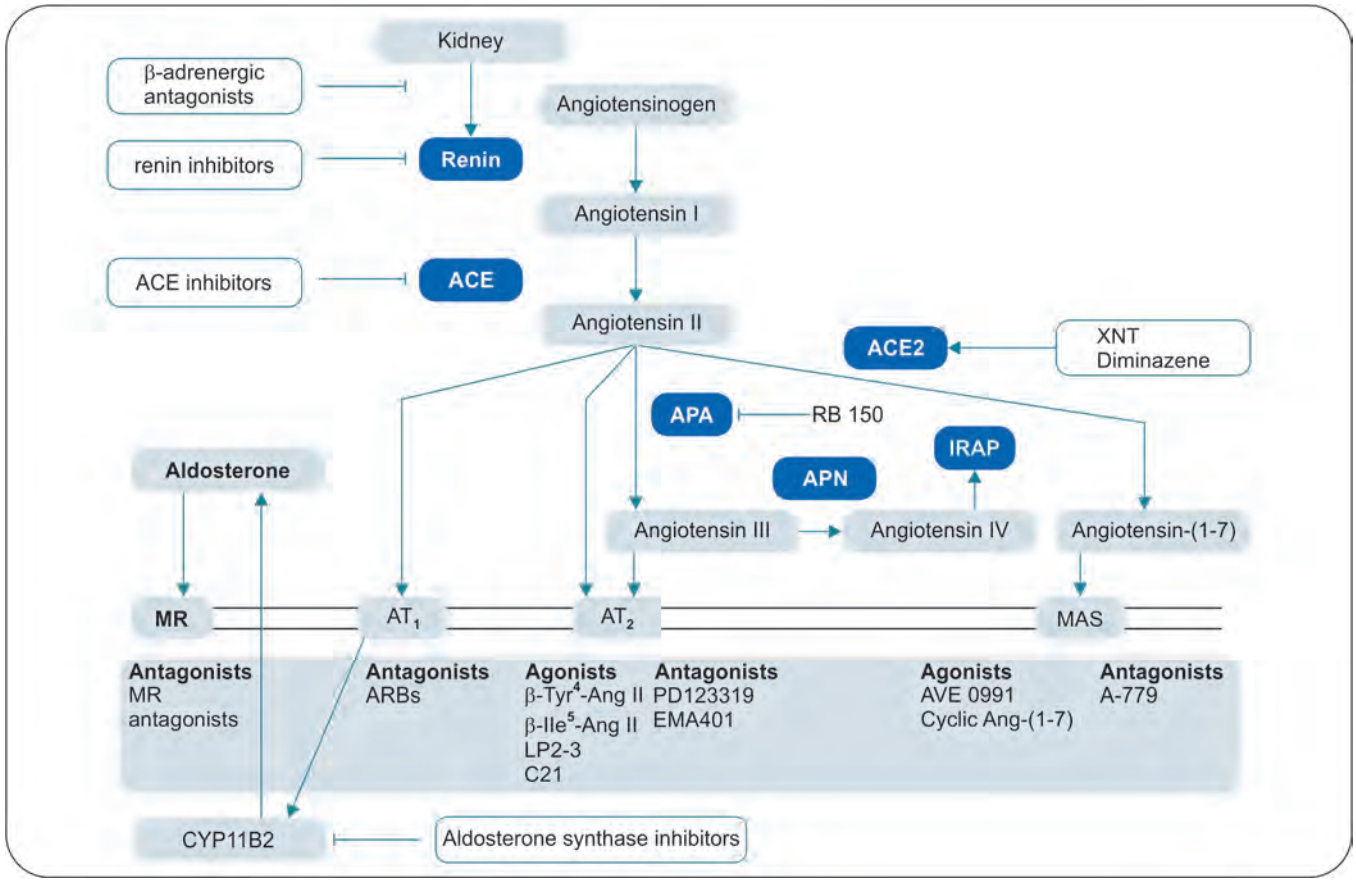


Fig. 1: Ambiguous role of RAAS inhibitors in the COVID-19 disease pathogenesis

Where do we Stand with the Available Data?

It's not surprising that majority of COVID-19 patients are hypertensive and does not necessarily imply any causality between the two conditions. It just is a finding that hypertension as comorbidity is very common in the elderly and COVID-19 is an infection that the elderly are particularly vulnerable to and prone to develop severe clinical presentation of the disease.[14] Hence, most of the data that's available so far is more of a clinical guidance and not conclusive evidence. In the current pandemic situation, owing to the limited allocation of time and resources so far to deal with the unprecedented situation, most of the data that's available is observational study data and not RCTs and may not be the best in terms of hierarchy of evidence. We have had prior scenarios where there was discordance between observational and RCT studies, which was attributed to various factors including selection bias, presence of confounding factors, differences in

Flowchart 1: Should ACE-inhibitors and ARBs be stopped with COVID-19



statistical power of the study, and issues with study adherence throughout. A classic example was the finding that bisphosphonates decrease risk of postmenopausal breast cancer as ascertained by observational study which was later refuted based on the results from a couple of RCTs.[15] Hence, one needs to be careful in forming conclusions about the association of hypertension and COVID-19 infection and also about the use of RAAS inhibitors. Yet, it would be reasonable to assume that managing hypertension and other comorbidities would be of high priority. Since there's no conclusive data showing the deleterious effect of any class of hypertensive drugs, it would be wise to continue the drug to maintain BP control. As discussed earlier, for newly detected hypertension, classes of drugs other than RAAS inhibitors could be considered for initiation of therapy due to the paucity of conclusive evidence concerning either the benefits or possible deleterious effects of RAAS inhibitors on the severity of COVID-19 infection.

Conclusion

For newly detected hypertension, classes of drugs other than RAAS inhibitors could be considered for initiation of therapy due to the paucity of conclusive evidence concerning either the benefits or possible deleterious effects of RAAS inhibitors on the severity of COVID-19 infection.

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CHAPTER

2

COVID-19: An Overview

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Abstract

Emerging and reemerging infectious diseases have plagued mankind and have been potential killers since historic times. The current pandemic of COVID-19 is the latest crisis that has challenged leadership and health infrastructures globally. COVID-19, caused by SARS-CoV-2, began as an outbreak of pneumonia of unknown cause at a local seafood market in Wuhan, China, and soon spread globally claiming more than a million of lives. The virus has a wide spectrum of symptoms due to the ability of its S protein to bind to h-ACE2 receptors on various tissues like lung, heart, kidneys, GI tract, and olfactory epithelium. It transmits predominantly as a respiratory droplet infection from person to person and by direct contact with contaminated surfaces. COVID-19 encompasses a spectrum of asymptomatic/presymptomatic, mild, moderate, and severe to life threatening critical illness. Most common symptoms are cough (53%), fever (43%), myalgia (36%), headache (34%), dyspnea (29%), and sore throat (20%); less common are diarrhea, nausea, vomiting, anosmia, dysguesia, and dermatological manifestations. Risk factors for severe disease are old age, uncontrolled hypertension, diabetes, COPD, cardiovascular disease, obesity (BMI > 30), and malignancy and immunocompromised status. Patients of COVID-19 develop complications like pneumonia with or without respiratory failure, cardiomyopathy, acute myocardial ischemia, arrhythmias, thromboembolic complications, cytokine release syndrome, encephalopathy, ileus, mesenteric ischemia, secondary bacterial infection, sepsis, and septic shock in second week of illness due to inflammatory cytokines. Lab findings reveal lymphopenia, elevated transaminases, CRP, LDH, D-dimer, serum Ferritin, and Troponin-T with most common imaging finding being bilateral peripheral lower lung zone ground glass opacities on HRCT chest. RT-PCR of nasopharyngeal or oropharyngeal swab confirms the diagnosis. There is no magic bullet yet to treat COVID-19 with available options of antivirals (Remdesivir) and immunomodulators (Dexamethasone and Tocilizumab). Even with effective vaccine stringent measures like social distancing, mask wearing, and hand hygiene are our only defense against this infection. Effective governance and efficient health sector alone can help combat the pandemic by dispersing the facts and curbing the myths.

Introduction

Twenty-first century saw the advent of several infectious diseases that wreaked havoc on human civilization leading WHO to generate a list of blue print priority[1] diseases including a disease "X" with a pandemic potential to be caused by an organism yet unknown **(Table 1)**.

Soon enough Disease "X" emerged in late December 2019, when a bunch of pneumonia cases with unknown etiology emerged from the local seafood market in Wuhan, capital of Hubei province in China and heralded a global pandemic of zoonotic origin engulfing most countries of the world except the Antarctica continent. The novel pandemic was christened as Coronavirus disease or COVID-19 caused by the *betacorona* virus SARS-CoV-2, closely akin to SARS-CoV-1 (2002) and the MERS (2012). The virus was isolated from human respiratory epithelial

TABLE 1 Blueprint priority diseases by WHO

Blueprint Priority Diseases*
Given their potential to cause a public health emergency and the absence of efficacious drugs, vaccines, or both, there is an urgent need for accelerated research and development for the following diseases: • Crimean–Congo hemorrhagic fever (CCHF) • Ebola virus disease and Marburg virus disease • Lassa fever • Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS) coronavirus • Nipah and Henipaviral diseases • Rift Valley fever (RVF) • Zika • Disease X

*From the World Health Organization. Known diseases are listed in alphabetical order.

cells and after genomic sequencing was identified as seventh member of the family *betacoronavirus*, subfamily *Orthocoronavirus*, quite similar to bat coronaviruses.[2] This virus has several dynamic facets from causing asymptomatic to critical life threatening respiratory manifestations. Our understanding of COVID-19 has ever been evolving since its emergence. This formidable foe with its contagiousness and virulence abetted by global trade and tourism was declared a global pandemic on March 11th, 2020, by WHO and continues to be a global threat with both cure and prevention not yet distinctly visible (at the time of writing this chapter). Combating this malevolent virus requires sifting of facts from myths by means of worldwide available accurate scientific information that takes high moral ground and conveys research driven narratives.

Virology, Epidemiology, and Transmission

SARS-CoV-2 is a positive sense ssRNA enveloped virus with viral spike(S) peplomers, belonging to the human *betacoronavirus* family, order Nidovirales, and subgenus Sarbecovirus similar to SARS-CoV-1 and MERS but a different clade.[2] The S protein contains the region that binds the human-angiotensin converting enzyme 2 receptor ACE-2 (h-ACE2) receptor on respiratory epithelial cells.[3] Phylogenetic analysis[4] of the virus revealed two different strains designated as the L type (70%) and S type (30%). High viral titers are detected in nasopharyngeal secretions in the early phase of illness (in first week post exposure) and decline after that.[5] Virus is also detected in other body fluids such as blood, saliva, semen, and stools but role in transmission is unclear.[6] The virus after its initial emergence in Wuhan, spread rapidly across whole of China and to Italy, Iran, Japan, South Korea, the US, and across the globe by means of community transmission and super spreading events. It predominantly affects middle aged adults and elderly and males.[7] Though no gender or age group has been spared. Usually respiratory coronavirus outbreaks are seen during winter in northern hemisphere but in some parts of the world like Thailand they persist throughout the year, whereas SARS-CoV-2 shows no such seasonality.

Early transmission dynamics revealed the major mode of transmission to be large droplet mediated direct person to person (within ~6 ft distance) as well as through direct contact with contaminated surfaces. Aerosol (droplets of size 20–500 μm) transmission is a major mode of transmission to health care workers in hospital settings.[8] Airborne and animal to human transmission is yet debatable. SARS-CoV-2 has a median survival of ~1.1–3 hours in aerosol and up to 72 hours on inanimate objects.[9] Asymptomatic or pre-symptomatic viral shedding is the major mode of disease transmission since, serial interval (SI) (mean 5.8 days) is shorter than the incubation period (IP). Infectiousness begins 2.3 days before symptom onset (pre-symptomatic transmission), peaks 0.7 day before symptom onset and declines within 7 days.[10] Shorter SI (SI<IP), higher reproductive numbers (R0: 2.2–2.7 in initial phase) and secondary attack rate of up to 15%[11] make the virus highly contagious and difficult to contain.

Pathogenesis

SARS-CoV-2 virus enters human respiratory epithelial cells through attachment of its spike (S) protein to the h-ACE2, similar to SARS-CoV-1 aided by cellular protease TMPRSS2. This is followed by the initial replicative phase and phase of innate immunity in the early phase causing influenza like illness with mild symptoms due to direct cytopathic effect of the virus. If no intervention occurs at this stage, it leads to phase of adaptive immunity leading to massive cytokine release syndrome and complications like acute respiratory distress syndrome (ARDS) and multi-organ dysfunction.[12]

TABLE 2 Stages of severity of COVID-19 infection

Mild	*Moderate*	*Severe (14%)*	*Critical illness (5%)*
Fever and/or uncomplicated upper respiratory tract infection without dyspnea or hypoxemia	• Pneumonia with no signs of severe disease • Chest X-ray: Bilateral lung infiltrates involving <50% of lung fields • RR ≥24/min • SpO_2 <94% on room air	• Severe respiratory distress requiring mechanical ventilation (invasive or noninvasive) • Chest X-ray: Bilateral lung infiltrates involving ≥50% of lung fields • RR ≥30/min • SpO_2 <90% on room air	• Rapidly progressive Type 1 respiratory failure • Sepsis and septic shock • Multi-organ dysfunction (MODS) • Altered mental status

Clinical Features

Asymptomatic Infection

This has been well documented in several studies to an approximate magnitude of 30–40% across the globe but not systematically studied.[13] Objective findings on HRCT chest are seen even with asymptomatic infection. Several of them develop symptoms (they are pre-symptomatic) over the period of 3–7 days.[14]

Spectrum of Illness (Table 2)

It ranges from mild to severe and critical illness. The overall case fatality rate is 2.3% with no fatality in mild cases.[15] High case fatality has been documented in those with multiple underlying comorbidities.

Clinical Signs and Symptoms (Table 3)

IP is 14 days[16] (median IP is 5.1–5.2 days) with interquartile time (IQT) of 2–7 days implying dispersion of 50% cases in this period.[17] Though predominantly a respiratory pathogen SARS-CoV-2 has myriad extra-pulmonary manifestations.

Clinical course of COVID-19: Patients infected by the SARS-CoV-2 virus develop symptoms usually after a mean IP of 5.1–5.2 days (14 days) and majority (80%) recover without further progression or complications. Amongst the hospitalized patients 40% progress to develop dyspnea after 7 days of symptom onset and yet a minority (14%) and (5%) progress to develop severe and critical illness respectively after approximately 10 days of symptom onset **(Fig. 1)**.[20]

Laboratory findings **(Table 4)**:[21] Most common lab findings in COVID-19 are severe lymphopenia, elevated aminotransferases, CPK, Troponin T, and elevated inflammatory markers like CRP, serum LDH, Ferritin, IL-6, and D-dimer. They are associated with worse prognosis and mortality.

TABLE 3 Clinical spectrum of COVID-19: Constitutional, pulmonary and extrapulmonary

General[18]
• Cough (50%)
• Fever (43%), subjective or >100.4°F/38°C; course may be prolonged and intermittent
• Myalgia or Fatigue (36%)
• Headache (34%)
• Dyspnea (29%)
• Sore throat (20%)
• Diarrhea (19%)
• Nausea and Vomiting (12%)
• Loss of taste (dysgeusia) or smell (anosmia) (<10%); possible symptom in early infection, but not distinctive of COVID-19, may also be seen with other viral infections
• Abdominal pain & rhinorrhea <10% each
Extrapulmonary[19]
Cardiac: Takotsubo cardiomyopathy, Myocardial injury/myocarditis, Cardiac arrhythmias, Cardiogenic shock, Myocardial ischemia, Acute cor pulmonale
Thromboembolism: Deep vein thrombosis, Pulmonary embolism Catheter-related thrombosis
Renal: Acute kidney injury, Proteinuria, Hematuria
Neurologic: Headache, Dizziness, Encephalopathy, Guillain-Barré, Ageusia, Myalgia, Anosmia, Stroke
Gastrointestinal: Diarrhea, Nausea/vomiting, Abdominal pain, Anorexia
Endocrine: Hyperglycemia, Diabetic ketoacidosis
Dermatological: Petechiae, Livedo reticularis, Erythematous rash, Urticaria, Vesicles, Pernio-like lesions (COVID TOE)

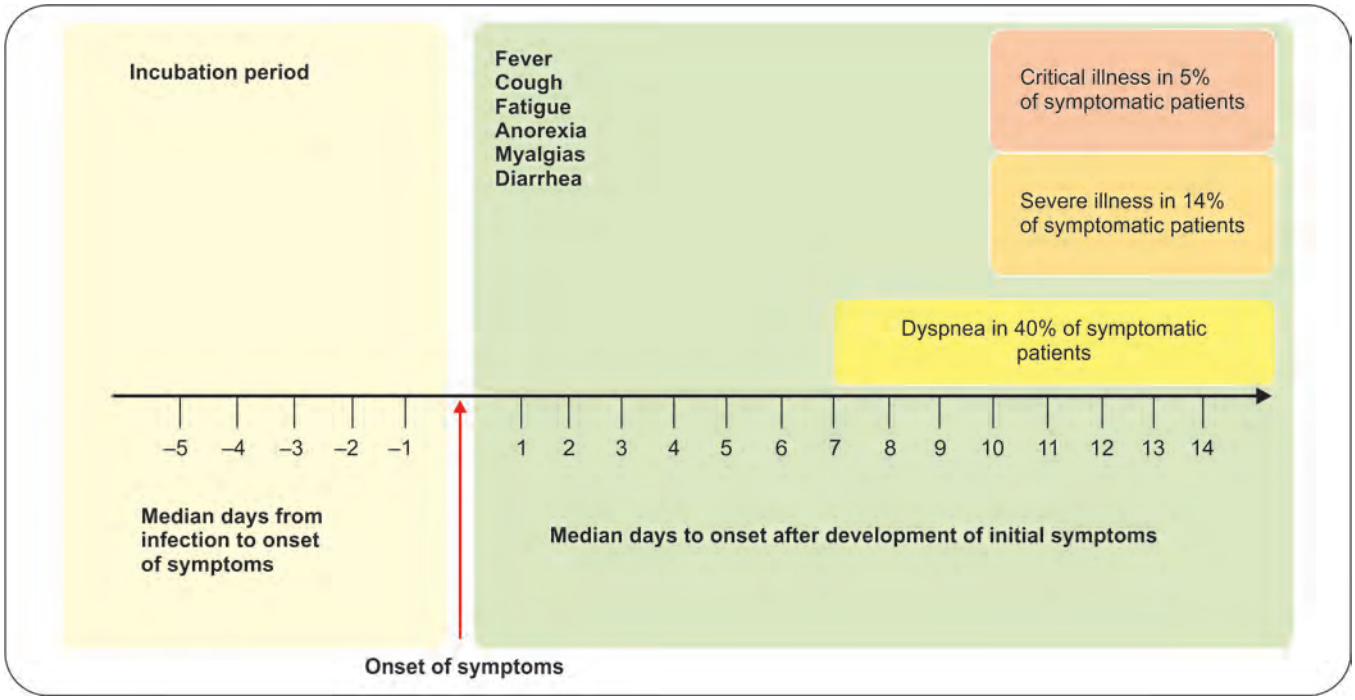


Fig. 1: Timeline of symptoms of coronavirus disease (COVID-19)

TABLE 4 Laboratory findings in COVID-19

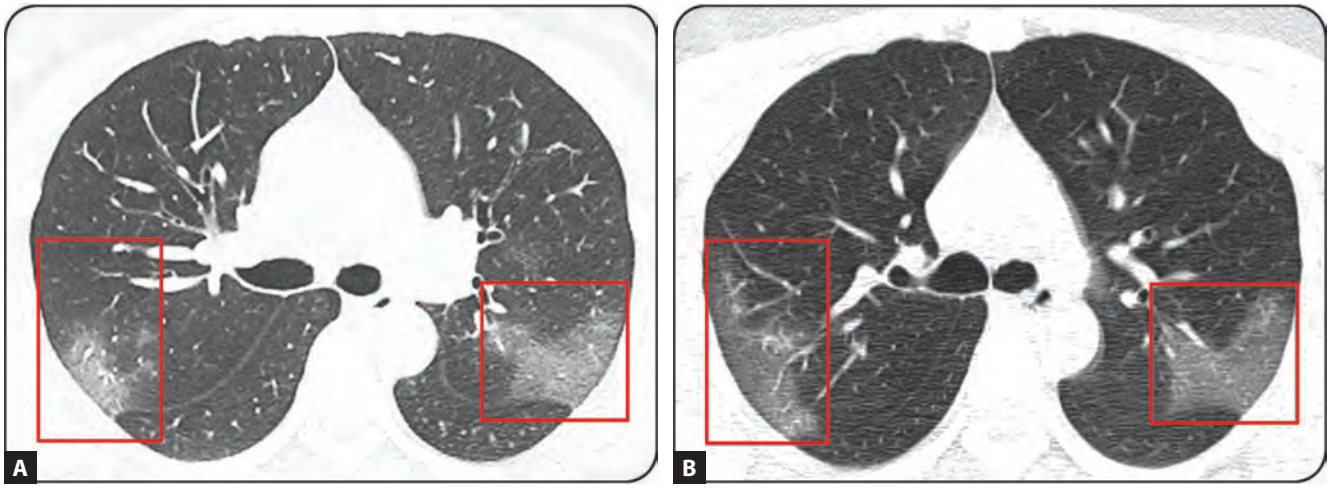
Laboratory findings
• Leukopenia, Leukocytosis, and Lymphopenia (N:L Ratio 3.1)
• **absolute lymphocyte count < 0.8 × 10^9/L**
• Elevated Aminotransferases
• Elevated Procalcitonin (remains low in first 7–10 days; can rise later without sepsis)
• Elevated CRP (**>10 times normal** implies poor prognosis)
• High D-dimer (**>1 µg/mL** implies poor prognosis)
• Elevated Troponin T-mortality is higher in patients with elevated TnT (59.6% vs. 8.9%)
• Elevated CPK (**Twice the ULN** implies poor prognosis)
• Elevated IL-6
• Decreased Albumin
• Elevated LDH (**>245 U/L** implies poor prognosis)
• Ferritin **>500 µg/L**

Imaging:

- Chest X-ray: During early or mild phase of the illness chest radiographs are normal. Common abnormal findings are consolidation and ground glass opacities in bilateral, peripheral lower lung fields with a peak in severity 10–12 days post-symptom onset.[22]
- HRCT Chest: In a systematic review by *Bao et al.*[23] of 2,700 patients of COVID-19 most common abnormalities were ground-glass opacifications (83%), ground-glass opacifications with mixed consolidation (58%) and adjacent pleural thickening (52%) followed by interlobular septal thickening (48%) and air bronchograms (46%). Less common findings are crazy paving pattern, bronchiectasis, pleural effusion, pericardial effusion, and lymphadenopathy **(Figs. 2A and B)**.

Risk factors for severe disease **(Table 5)***:* These include epidemiological, clinical, and laboratory factors. Age is a major factor impacting case fatality; with mortality rate being 8% and 15% amongst those aged 70–79 years and ≥80 years respectively according to a report from the Chinese Centre for Disease Control and Prevention. Other factors are:[24]

Complications of COVID-19: Major complications of COVID-19 are ARDS in almost 17–29% cases developing at a median of 8 days post-symptom onset in most cases;[25] acute kidney injury, cardiac complications



Figs. 2A and B: HRCT images showing bilateral ground glass opacities (GGO's) in peripheral lower lung zones

TABLE 5 Underlying risk factors and prognostic factors of COVID-19

Epidemiological category 1	*Vital signs category 2*	*Labs category 3*
Age ≥65 years	Heart rate >125/min	Admission absolute lymphocyte count <0.8 × 10^9/L
Pre-existing pulmonary disease	Respiratory rate >24/min	LDH >245 U/L
Chronic kidney disease	PaO_2/FiO_2 <300 mm Hg	CRP >100
Diabetes with HbA1c >7.6%	SpO_2 ≤94% on room air	CPK >Twice the ULN
History of hypertension		Elevated troponin T
History of cardiovascular disease		D-dimer >1,000 ng/mL
Obesity (BMI ≥30 kg/m^2)		Ferritin >500 µg/L
Use of biologicals		
History of transplant or other immunosuppressive medications		
Uncontrolled HIV (Viremic or CD4 <200)		

like cardiomyopathy (33%), arrhythmias (17%), acute cardiac injury (7%), and shock (9%);[25] thromboembolic complications such as pulmonary thromboembolism and acute cor pulmonale, acute stroke; inflammatory syndromes such as cytokine release syndrome and multisystem inflammatory syndrome; secondary bacterial and fungal infections (8%);[26] sepsis, septic shock, MODS, and DIC; coagulopathy; and APLA and CNS encephalitis. Cytokine release syndrome (CRS) is the most devastating complication characterized by increased levels of inflammatory cytokines such as IL-6, TNF-α, and IL-10 and activation of T lymphocytes, macrophages, and endothelial cells leading to fever and multi-organ dysfunction. Severe form of CRS needs rapid intervention with steroids and immunomodulators such as Tocilizumab[27] (anti IL-6 antibody).

Differential Diagnosis[28]

COVID-19 pneumonitis must be differentiated from other respiratory infections like bacterial, fungal, and viral pneumonias (influenza, parainfluenza, rhinovirus, other coronavirus, human metapneumovirus, adenovirus, etc.). Most of these have similar clinical and laboratory features and only molecular test can clinch the diagnosis.

Diagnosis

COVID-19 cannot be definitively distinguished from other respiratory viral illnesses based merely on clinical symptoms and laboratory findings. A high clinical suspicion in people presenting with respiratory tract symptoms as well as those who have resided in or travelled from areas of community spread as well as those who have had close contact with a suspected or confirmed case must be subjected to testing **(Table 6)**. Tests currently approved by the FDA are molecular tests such as RT-PCR which are confirmatory and serological tests have been approved under emergency usage. Viral cultures are not recommended. Rapid antigen tests though easy to perform are not recommended due to high false positive and negative rates.

RT-PCR of nasopharyngeal swab specimens has a sensitivity of ~63%, depending on assay used, sample procurement method and stage of illness.[29] False-negative rates[30] have ranged from <5% to 40%. Hence, negative results must be correlated clinically and if suspicion is high the test may be repeated after 24–48 hours after the initial negative result. Lower respiratory tract samples such as BAL yield better results. The test yield of RT-PCR is maximum from day 1–3 of symptom onset.

TABLE 6 Triage for ensuring optimal testing in COVID-19

Triage testing
PRIORITY 1: Ensure optimal care options for all hospitalized patients, reduce the risk of nosocomial infections and maintain integrity of the health care system: • **Hospitalized patients** • **Symptomatic health-care workers**
PRIORITY 2: Ensure rapid identification and appropriate management of those who are at highest risk of complications of infection: • **Patients in long-term care facilities with symptoms** • **Patients ≥65 years of age with symptoms** • **Patients with underlying conditions with symptoms**
PRIORITY 3: If resources allow, test individuals in the surrounding community of rapidly increasing hospital cases to decrease community spread and ensure health of essential workers: • **Critical infrastructure workers with symptoms** • **Individuals who do not meet any of the above categories with symptoms** • **Health care workers and first responders** • **Individuals with mild symptoms in communities experiencing high COVID-19 hospitalizations**
NON-PRIORITY: Individuals without symptoms

The reliability of *serological tests* depends on the duration of illness, seroprevalence and specific assay. According to a study, serological response in the form of IgM occurs after median of 5 days and IgG after 14 days of symptom onset.[31] Useful when patient presents after 2 weeks into the illness, when RT-PCR is negative. A positive test for IgM and IgG is diagnostic for COVID-19, but a negative result does not rule out the disease. False positive results may be obtained due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as HKU1, NL63, OC43, or 229E. Thus, serological tests should not be used as confirmative tests and must be interpreted with caution.

Management of COVID-19 (Fig. 3)

Outpatient

Suspected and mild cases can be managed on an outdoor basis by telemedicine and home isolation along with good hand and respiratory hygiene. Since, 80% cases are asymptomatic or have mild to moderate illness which can be managed on an outpatient basis, thereby reducing the burden on our already pummeling health system. Home isolation is recommended for 10–14 days post-symptom onset and post-positive test result in symptomatic and asymptomatic individuals respectively.

Hospitalized Patients

- General measures include oxygenation, hemodynamic resuscitation, and awake prone positioning. Empirical antibiotics are not recommended unless there is evidence of coexisting bacterial or fungal infection. Statins and ACEI and ARBs to be continued if already prescribed. Prophylaxis for thromboembolic complication is mandatory. Steroids to be used in patients who need supplemental oxygen early in the course of illness.
- Specific treatment: Include *Antivirals* and *Immunomodulators*. None of them are a recommended specific therapy though and are under trials. Like influenza antivirals if effective need to be initiated early in the course of illness. Drugs are as follows:

Hydroxychloroquine/Chloroquine: Prevents binding to ACE-2 receptors, interferes with cellular acidification in the phagolysosome and blocks endosomal transport.

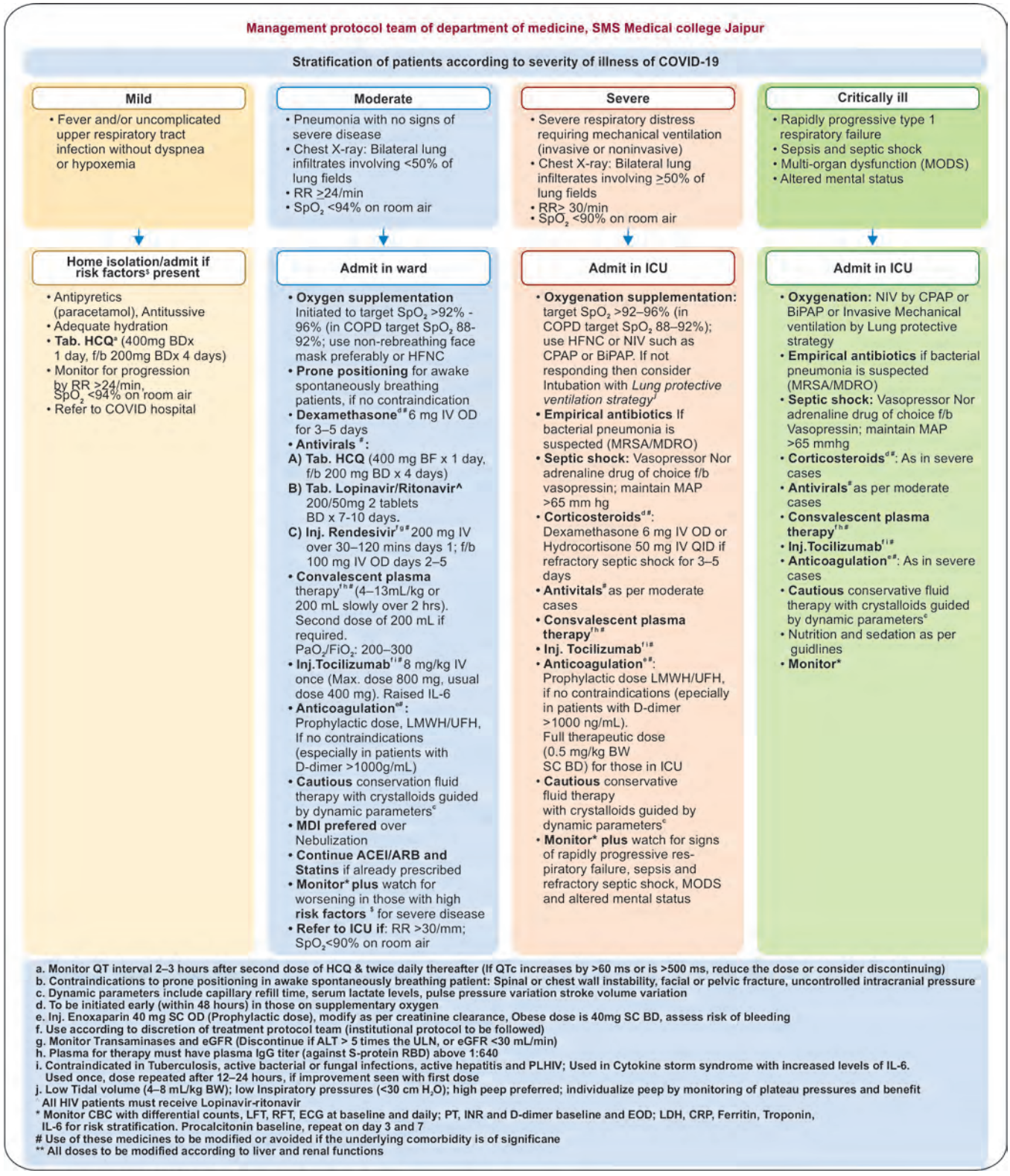


Fig. 3: Management of COVID-19: Institutional protocol

Very low quality evidence for treatment of COVID-19. May cause QT prolongation and needs monitoring. A large multicentre study[32] concluded that use of a regimen containing hydroxychloroquine (HCQ) or chloroquine (with or without a macrolide) was associated with no evidence of benefit, but instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for inhospital death with COVID-19. As per ICMR recommendations, it should be used in moderate to severe and critically ill and in mild cases associated with comorbidities like elderly, DM, hypertension, CKD, and others mentioned earlier in the chapter. About 821 individuals were randomly assigned to HCQ or placebo folate within 4 days of a household or occupational exposure to SARS-CoV-2 in a double-blind trial,[33] HCQ did not reduce the rate of RT-PCR confirmed COVID-19 or consistent symptoms within 14 days (11.8 vs. 14.3% with placebo).

Lopinavir-ritonavir: A randomized controlled trial[34] in hospitalized adults who also received other medications yielded no benefit but was given relatively late in the disease course. May be considered in moderate to severe cases, especially in those with multiple comorbidities and HIV patients.

Remdesivir: It was used in treatment of Ebola. It is a nucleotide analogue that inhibits viral RNA polymerase with in vitro activity against SARS-CoV-2 and MERS. A placebo-controlled, double-blind, randomized trial[35] of IV Remdesivir in hospitalized adults with COVID-19 pneumonitis concluded that Remdesivir was better compared to placebo in shortening the time to recovery in patients with COVID-19 pneumonitis. It is recommended that if available it should be used in severe and critical cases of COVID-19. Combination with HCQ is not advisable due to adverse drug interaction.

Favipiravir: Anti-influenza drug, RNA polymerase inhibitor which is available in India for treatment of mild COVID-19. In a study[36] use of Favipiravir in patients with mild disease was associated with rapid rates of viral clearance and radiographic improvement as compared to Lopinavir-ritonavir.

Interferon beta: In one open-label randomized trial from Hong Kong,[37] in 127 adults hospitalized with nonsevere COVID-19 use of INF-β within 7 days of symptom onset along with Ribavarin and Lopinavir-ritonavir was associated with early recovery and viral clearance. It needs further study, and is currently under evaluation in the WHO "*SOLIDARITY*" trial.

Immunomodulators (Tocilizumab): An FDA approved anti-IL6 agent for CAR-T cell cytokine release syndrome. It is more effective if used early in ARDS before more advanced lung and multi-organ dysfunction sets in. An unpublished study from China of 21 severe and critically ill patients concluded that use of Tocilizumab was associated with improved oxygenation, better CT findings, and survival in 1 week. Other immunomodulators under study are Sarilumab, Anakinra, and Siltuximab.

Convalescent plasma therapy: FDA approved for use in severe and critical COVID-19 cases. Early usage in treatment within 5–6 days of symptom onset is advocated before patients own antibodies form. Eligibility of donor includes age ≥18 years, male or nulliparous female >55 kg weight, prior RT-PCR documented diagnosis, and complete resolution of symptoms at least 28 days prior to donation or 14 days prior to donation with two negative RT-PCT results 24 hours apart. A randomized controlled trial[38] among patients with severe and critical COVID-19 convalescent plasma therapy added to standard therapy versus standard therapy alone did not result in a statistically significant improvement in time to clinical improvement within 28 days. Adverse events include pathogen transmission, allergic reactions, transfusion-related acute lung injury, and circulatory overload. To be avoided in those with IgA deficiency and immunoglobulin allergy.

Intravenous immunoglobulin (IVIg): Pooled IVIg reduces inflammation via multiple mechanisms such as lessening interrupting complement cascade and reducing activated CD4+ and CD8+ T-cells. It has been proposed in viral mediated lung injury or ARDS due to disordered regulatory T-cell hyperimmune response. It needs further studies.

Prevention

Numerous vaccines are being evaluated including viral-vector vaccines, nucleic acid-based (DNA and mRNA) vaccines and inactivated or recombinant protein vaccines. Impact of *BCG immunization*[39] on COVID-19 is unknown; hence, its use in COVID-19 is not recommended by WHO.

Prognosis

Recovery from the illness and its long-term sequelae depend on age, underlying comorbidities, and severity of illness. According to WHO, mild cases recover in 2 weeks and severe cases recover in 3–6 weeks.[40] The overall global mortality of COVID-19 is 3.4% as of March 3rd 2020. The mortality rate attributed to SARS-CoV-2 is less than that commonly ascribed to community acquired pneumonia (12–15%), but more than seasonal influenza (~0.1%). Critically ill COVID-19 cases face the perils of post-intensive care syndrome (persistent impairments in mental health, physical function, and cognition), although the incidence is unknown.

Conclusion

Escalated globalization, expanding human population, increasing human-animal interactions, altered ecosystems clubbed with viral genetic recombination, mutation, and reassortment have led to emergence of several novel pathogens that have wreaked havoc on not just the global economy but on the very existence of a healthy life. The emergence of global pandemic of COVID-19 exposed the Achilles heel of our preparedness toward unanticipated epidemics and pandemics despite use of spatial epidemiology or mathematical models to predict such emerging and re-emerging pathogens. In an era of universal distrust and rising global tension with overload of information it becomes imminent that we as medical fraternity aid the public in sifting out facts from myths by sceptically scrutinizing every bit of life saving scientific research that is disseminated globally without ourselves getting swindled by availability bias. Rising global panic, financial market hysteria, constantly evolving data on SARS-CoV-2 with misinformation has only made this petrifying pandemic more grim. Our only bastion of defense in this conundrum is worldwide dissemination of truthful and accurate scientific data. The knowledge of the disease is changing so fast that what seems true today, might not be so in the future.

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CHAPTER

3 Hydroxychloroquine for Cytokine Storms: Pros and Cons

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Abstract

Hydroxychloroquine is a most economic therapeutic agent with a proven track record in rheumatoid arthritis, systemic lupus erythematosus, and for the last 6 years in Diabetes Mellitus. Its clinical value in abating or preventing the cytokine storm in COVID-19 is a subject of controversy: in India we continue to use this agent both for prevention and for management albeit Western reports on arrythmias have installed a caution in its use if there is QT prolongation. Possible mechanisms of its action in correcting inflammation and hyperglycemia are discussed. Like corticosteroids and ivermectin, hydroxychloroquine is likely to remain a part of the low cost anti COVID-19 strategies.

Introduction

One of the most keenly argued facets in the context of Coronavirus Disease 2019 (COVID-19) is the use of hydroxychloroquine (HCQ/HYQ) for management or prophylaxis, and this is evidenced by sharp swings in WHO/FDA recommendations as well as the marked divergence between advisories and regimes in different countries.[1-15] ICMR continues to approve the prophylactic use of this in asymptomatic healthcare workers/ surveillance workers and asymptomatic contacts of laboratory confirmed cases.[2] It has been in use since 1955 in rheumatoid arthritis and lupus, and figures in the WHO Essential List of Medicines. The Central Drugs Standard Control Organization approved its use in rheumatoid arthritis in 2001, polymorphic light eruptions in 2006, lupus erythematosus in 2008 and diabetes mellitus in 2014. Its action was regarded as anti-inflammatory. When the COVID-19 pandemic emerged it was suggested as of being of possible benefit both for prophylaxis as well as for treatment.

However, some reports suggested that it predisposes to cardiac arrhythmia by causing QTc prolongation and even Torsades de Pointes—a dangerous disorder. This led to various recommendations for prior QT assessment before instituting chloroquine/HCQ demarcating green/ orange/red zones for use analogous to traffic signals.[16-18] Because HCQ had often been used with azithromycin in COVID-19, and azithromycin had itself been incriminated for sometimes causing QT prolongation, the combined use of these two was especially controversial.

But HCQ had been used in rheumatoid arthritis for 65 years, and in diabetes for the last decade and had not been cited for causing rhythm disorders. The anti HYQ article in the Lancet which led to the WHO initially suspending the HCQ arm of the solidarity anti COVID trials was discovered to be based on dubious data by Surgisphere, and was subsequently retracted. The WHO resumed this arm after this retraction, but again suspended this arm after UK reports about the lack of benefit by HCQ. Some of the anti HCQ comments were allegedly related to pressure by the makers of more expensive anti COVID

drugs[19] as well as the political controversies aroused by the endorsement of HCQ by the US President! The recent FDA withdrawal of permission for the use of HYQ[7] was based on a randomized trial on postexposure prophylaxis,[8] showing lack of benefit, but not cardiac rhythm disorders.[8]

We have suggested that a detailed analysis of the experience of persons on prior HCQ use for diabetes or rheumatoid arthritis during the pandemic should be rewarding.[20]

Chloroquine has an even longer history of use as an antirheumatoid and antimalarial drug as compared to hydroxychloroquine, but HYQ has overshadowed it as its hydroxyl group limits the crossing of the blood retinal barrier and further, HCQ clears faster from the retinal pigment cells and accumulates less than chloroquine. An ophthalmological cohort of 526 patients showed no retinopathy in the first 6 years, and 0.5% after 8.7 years.[21,22]

HCQ as an Anti-inflammatory Reagent

The anti-inflammatory action of HCQ has been attributed to inhibiting the formation of the cytokines IL1, IL6, and TNF alpha, reducing C reactive protein, inhibition of leukocyte migration, and activation, as well as of prostaglandin synthesis and an antiplatelet effect.[23,24] It also inhibits nitric oxide and extracellular oxidant production from neutrophils and macrophages.[25,26]

The cardiovascular effects of HCQ in the diabetes context, which include lowering of cholesterol[27] both total and LDL, lowering of triglycerides, and antiplatelet, antithrombotic, and antihypertensive effects are worth recalling in the context of its alleged cardiovascular deleterious effects in COVID-19.

Postulated Mechanisms of Action of HYQ in COVID-19

HYQ causes alkalization of the intracellular milieu. This inactivates the insulin degrading enzymes making it released from the cell ready to act again.

Patients with diabetes, elevated BMI, high cortisol levels have a higher mortality rate in COVID! Diabetes is the most prevalent comorbidity in COVID-19, second only to obesity!

Hyperglycemia Worsens Viral Respiratory Diseases

Hyperglycemia increases glucose content of airway secretions, increases influenza virus infection in vitro in pulmonary epithelial cells, increases vascular permeability, and a collapsed alveolar epithelium in the lungs, and may suppress the antiviral immune response.

The role of anti-inflammatory agents including HCQ in management of diabetes type 2 has been recently reviewed.[28]

Postulated mechanisms of action of HYQ in COVID-19 other than anti-hyperglycemia action are also related to its rendering the cytosol alkaline. The increased pH of the endosomes and lysosomes inhibits endolysosome function prevents the fusion of virus with the host cells and subsequent replication.[7] HCQ also enters the antigen presenting cells and prevents autoantigen presentation to T cells. It attenuates the possibility of the cytokine storm by inhibiting the transcription of pro inflammatory genes. HYQ interferes with terminal glycosylation of ACE 2 and reduces binding of spike protein coronavirus to host cells.

The beneficial actions of HCQ in human disease according to a Pub Med search through MESH is multifaceted including diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases, and malignancies may have multiple mechanisms, including altered signaling through cellular receptors, post-glycosylation modifications of infectious agents, changes in levels of inflammatory mediators, and inhibition of autophagy.[29] Since COVID-19 behaves like an infectious agent induced inflammatory coagulopathy with hyperglycemia and cytokine release, several of these actions can be involved!

Dosage

Hydroxychloroquine dosage recommended has varied. The ICMR national task force on 22/5/2020 suggested 400 mg twice daily on Day 1, followed by 400 mg once weekly for next 7 weeks to be taken with meals for asymptomatic health-care workers involved in care of suspected or confirmed COVID cases. The same regime was advised for asymptomatic household contacts of laboratory confirmed cases. This also can be used weekly beyond 8 weeks with strict monitoring of clinical and EKG parameters under medical supervision.[2]

For patients the AIIMS COVID-19 preparedness Document Version 1.3 dated 10th June, 2020, suggests 400 mg BD × 1 day followed by 400 mg OD × 4 days for high-risk cases testing positive. For moderate disease, AIIMS suggests to consider 400 mg BD for 1 day, then 400 OD × 4 days.[5] Exclusions/contraindications include retinopathy/hypersensitivity/G6PD deficiency/preexisting cardiomyopathy and cardiac rhythm disorders. Rarely the drug causes a self limiting blurring of vision which improves on discontinuation of the drug.

Role of HCQ in Cytokine Storm

Whether HCQ is of value in the prevention or control of cytokine storms in COVID is most important to consider! The jury is still out!

A number of agents are now in use in the prevention and/or treatment of the cytokine storm. Corticosteroids are the sheet anchor of therapy and prevention, and a dropping pO_2 measured by a pulse oximeter is an early indicator of silent hypoxia. Other acute phase reactants that are looked for include elevated Trop T, C reactive protein, ferritin, D dimer, neutrophil/lymphocyte ratios. High resolution chest CT has now been supplemented by chest X-ray to diagnose lung involvement,[30] and artificial intelligence is being explored to enable remote diagnosis on the chest X-ray (Shukla AK: Personal Communication).[31]

Since immunosuppressive drugs are of value in therapy, but also can promote infections there was an initial apprehension that during prophylaxis HCQ immunosuppressive action may even promote infection?

However, today in India HYQ is being used for immunoprophylaxis,[2,5] except in subjects with contraindications such as cardiac arrhythmias or QT prolongation.

Whether HCQ can prevent cytokine storms is moot as evident from the variety of opinions.[1-15]

The respiratory syndrome in HCQ is now categorized into H and L subtypes—the former with water logging, which usually demands ventilation and the latter without waterlogging in which ventilation can damage the lungs!

Tocilizumab blocking interleukin 6, Kineret (Anakinra) blocking interleukin 1, Prazosin an alpha blocker, which blocks IL6 production by interrupting a self amplifying feed forward loop, Calquence (acalabrutinib), which blocks cytokine production by inflammatory macrophages. Remdesivir and Favipiravir are all under evaluation both for the cytokine storm, and even more important, for reducing viral RNA production.

Another approach is extracorporeal adsorption of cytokines using cartridges such as CYTOSORB/DEPURPO and OXIRIS: these are expensive but Indian analogues patented by our group for endotoxin removal need to be developed![32] These can be used in series with ECMO-extracorporeal membrane oxygenators.

Other agents being evaluated are herbs such as Turmeric, Tinospora cordifolia (Giloy), Ashwagandha (Withania somnifera), Cinnamon, and Boswellia.

Ultraviolet blood irradiation biophotonic therapy, rapamycin, low dose lung irradiation, nicotine, electroacupuncture, Cox 2 inhibitors, ibuprofen are other approaches that have been suggested!

The hypotension is managed by inotropes: noradrenaline being preferred to dopamine.

Azithromycin and doxycycline are antibiotics that have been used.

There are Australian and Bangladesh reports on the use of ivermectin to prevent or treat COVID infection.

Convalescent serum and injectable hyaluronidase and niacin are beneficial in anecdotal cases.

BOX 1 Changing clinical pictures and multi-system features

Observing the changing clinical picture of the COVID pandemic, from a flu-like lung illness to a multisystem picture, one is reminded of Lorraine Daston's historical perspective[33]

To quote her,

Historically:

It's natural to cast about for answers at the dawn of a pandemic

"At moments of extreme scientific uncertainty"

"Observation, usually treated as the poor relation of experiment and statistics in science, comes into its own"

Confronting a new disease, doctors have no choice but to turn to "suggestive single cases, striking anomalies, partial patterns"

Slowly, as our ideas about "what works and what doesn't" help tell us "what to test, what to count," the picture clarifies

Until then, "we are back in the seventeenth century, the age of ground-zero empiricism, and observing as if our lives depended on it"

One patient at a time, we have to work our way into the present!

Conclusion

The value of HCQ in preventing and treating COVID-19 is being extensively evaluated, ever since the French report and the US Presidents advocacy.

India which produces the majority of the world's HCQ was recently extolled and thanked for making it available to countries around the world, including the USA, Brazil, and African countries.

Its inexpensive character suggests that, like corticosteroids, it will play an important role in the COVID pandemic, albeit with care, prudence, and cautious medical supervision including periodic QT measurement from ECG or monitors.

The changing clinical picture especially the multisystem involvement including: gastrointestinal, neurological, renal, endocrine, and dermatological presentations is discussed in **Box 1**.

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CHAPTER

4 Hematological Manifestations of COVID-19

Sudhir Mehta, Nidhi Sharma

Abstract

COVID-19 disease has prominent manifestations on the hematopoietic system. Complete blood count parameters that may assess the worsening of COVID-19 infection are: absolute neutrophilia, absolute decrease in lymphocyte count, absolute decrease in monocyte count, and an increase in neutrophil to lymphocyte ratio (NLR). In addition, the coagulation system needs to be evaluated by regularly monitoring of hemostatic markers—D-Dimer, prothrombin time, and platelet count—in all patients presenting with COVID-19. Risk stratification for venous thromboembolism should be performed for all inpatients with COVID-19. In the absence of contraindications, the vast majority of inpatients, including with severe COVID-19 should receive prophylactic anticoagulation. Delay in recognizing the hematological manifestations may have a negative impact on the clinical conditions and outcomes of patients, especially those with more aggressive diseases.

Introduction

On 11th March 2020, Dr Tedros Adhanom Ghebreyesus, WHO Director-General, declared COVID-19 as a pandemic. As we stand today, COVID-19 has spread globally. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses named the etiologic agent of COVID-19 as "Severe Acute Respiratory Syndrome related Coronavirus 2", or SARS-CoV-2.[1]

The lungs are the initial target organ for COVID-19. However, the infection has a significant impact on the hematopoietic system and hemostasis. The involvement of hematopoietic system in patients with novel coronavirus pneumonia was brought to light by Guan et al.[2] This was followed by a series of case reports and papers further highlighting the involvement of hematopoietic system in the pathogenesis of COVID-19.

It is very important to analyze the hematological parameters critically to pick up the essential diagnostic and prognostic information. The effect on each lineage and the various hemostatic mechanisms is discussed here.

Effect on Neutrophils

Neutrophilia has been described in most of the COVID-19 patients. The median peak absolute neutrophil count (ANC) impacts the possibility of ICU admission (11.6×10^9/L in ICU patients as compared to 3.5×10^9/L in the non-ICU group (P value < .001).[3] Rather, than the absolute neutrophil count; an elevated neutrophil to lymphocyte ratio (NLR) correlates more with pneumonia progression.[4] In addition, the myeloid series shows a left shift, which is manifested in the peripheral blood as a leukoerythroblastic picture.[5]

Effect on Lymphocytes

Earlier in the course of the disease (1–4 days), peripheral blood leukocyte and lymphocyte counts are normal or slightly reduced. Lymphocytopenia sets in 83.2% infected patients around 7–14 days after the incubation period.[2] Nadir of lymphocytes counted on day 7 from symptom onset followed by its restoration serves an important

prognostic marker. Therefore, instead of a single value of lymphocyte count, it is the serial assessment which may be predictive of outcome. In particular, two readings are given importance. If the percentage of lymphocytes is less than 20 at days 10–12 from the onset of symptoms and less than 5 at days 17–19, it depicts as the worst prognosis.[6] Hence, repletion of lymphocytes plays a role in recovery.[7]

The activated lymphocytes are seen morphologically as lymphoplasmacytoid cells (69%).[8] However, there is no change in the $CD4^+/CD8^+$ lymphocyte ratio as depicted by immunophenotyping. Functionally though, impairment of the function of $CD4^+$ helper and regulatory T-cells occurs which promotes an initial hyperactivation of cytotoxic $CD8^+$ T-cells followed by its rapid exhaustion.[9]

Why does Lymphopenia Ensue?

- Expression of the ACE2 receptor on lymphocytes surface causes SARS-CoV-2 to directly infect these cells and causes their lysis.
- Cytokine storm, which sets in later in the disease course, may promote lymphocyte apoptosis and atrophy of lymphoid organs and spleen impacting lymphocyte turnover tremendously.
- Coexisting lactic acid acidosis, in debilitating conditions like cancer puts these patients at an increased risk for complications from COVID-19 by inhibiting the lymphocyte proliferation.[10]

Effect of COVID on Platelets

Thrombocytopenia is not uncommon and has been shown to be present in 36.2% COVID positive patients.[2] A meta-analysis of nine studies has suggested that thrombocytopenia is significantly associated with the severity of the COVID-19.[11] Those presenting with a peak in the platelet count during the disease course also had poorer prognosis. But what has emerged as a stronger parameter than the absolute platelet counts is the platelet to lymphocyte ratio at the time of platelet peak as this may give a reflection of the ensuing cytokine storm.[12]

Coagulation Anomalies in COVID Patients

COVID-19-associated coagulopathy (CAC) is common in patients with COVID-19. CAC manifests as elevated levels of D-dimer (46.4%) and fibrin degradation products, reflecting a highly prothrombotic state.[2] The prothrombin time (PT) and activated partial thromboplastin time (aPTT) are only mildly prolonged. Later, if progressive consumptive coagulopathy continues, there is a decrease in antithrombin III, a rise in PT and aPTT, and further increase of D-dimer (>15.0 µg/mL). Fibrinogen levels are usually high in the initial phase, but returns to normal and decreases further in non-survivors. One study has reported disseminated intravascular coagulation (DIC) in 15 out of 21 non-survivors (8% of the total cohort).[13] **Table 1** summarizes the risk of various complications at different D dimer levels.

TABLE 1 Risk of various complications at different D-dimer levels

D-dimer value	*Risk*
Greater than 0.5 µg/mL	60% of patients with severe disease[2]
D-dimer level of 3.0 µg/mL	Severe disease with a reported sensitivity, specificity, and positive predictive value of 70.0%, 96.7%, and 87.5%, respectively
D-dimer >1 µg/mL vs <0.5 µg/mL on admission	An odds ratio of death of 18.42 (2.64–128.55)
D-dimer >1.5 µg/mL	Increased risk of venous thromboembolism (VTE)[14]
Median D-dimer 2.4 mg/L	Patients requiring ICU treatment

Venous Thromboembolism in CAC

Critically ill COVID-19 patients who do not have any predisposing risk factors for thrombosis can also manifest various thrombotic events including microvascular thrombosis, deep vein thrombosis (DVT) (25%), pulmonary thromboembolism, and acute arterial thrombosis (31%).[14,15] The reported incidence of thrombotic complications is between 16–49% in patients with COVID-19 admitted to intensive care. Thrombotic complications include stroke, acute limb ischemia, and acute coronary syndromes. However, data supporting routine screening for VTE using either lower limb ultrasound or computed tomography pulmonary angiography for all patients of COVID-19, is lacking. But the clinical suspicion for VTE should always be always there. It might be possible that the reported prevalence of VTE and PE is far less since the access to imaging techniques may be limited in critically ill patients.

Autoimmune Thrombotic Thrombocytopenic Purpura-Like Syndrome Associated with COVID-19

COVID-19 associated acute respiratory distress syndrome (ARDS) probably results from endotheliopathy-associated vascular microthrombotic disease (EA-VMTD).[15,16] This could be secondary to an imbalance between low ADAMTS13 and excessive exocytosis of ultra large von Willebrand factor multimers (ULVWF) from Weibel-Palade bodies present on endothelial cells. Endothelial derived ULVWF multimers bound to the endothelial surface of the vascular wall recruit platelets and might initiate microthrombogenesis thus leading to large microthrombi composed of platelet and eULVWF complexes.[17] Platelets adhered to eULVWF strings get activated resulting in platelet aggregation and recruitment of leukocytes dependant on P-selectin. The aggregates grow further and ultimately enter circulation. Numerous circulating complexes of endothelial derived ULVWF and platelet microthrombi result in the genesis of EA-VMTD triggering complement activation and resulting in a thrombocytopenic purpura (TTP)-like syndrome. This would require a recombinant Anti-CD59, recombinant ADAMTS13, Glycoprotein IIb/IIIa receptor blocker, therapeutic plasma exchange, and anticomplement therapy.

Lupus Anticoagulants in CAC

There is perhaps more to CAC as numerous reports of positive tests for lupus anticoagulant is being documented in COVID positive patients (91% of cases of elevated aPTT).[18] One case series of three patients with lower-extremity ischemia described an association of antiphospholipid antibodies (Apl Ab) and coagulopathy of COVID-19.[19] The interference of heparin on lupus anticoagulants (LAC) could lead to false positive detection of lupus anticoagulant.[13] However, Bowles et al. have noted that the dilute Russell's viper venom time (DRVVT) assay contains heparinase, which neutralizes any heparin effect.[18] The presence of aPL Ab alone is not a specific indication for anticoagulation and nor does the presence of aPL Ab represent a clinical diagnosis of antiphospholipid syndrome (APS). Hence, presence of aPL Abs in COVID-19 patients should be cautiously interpreted. It is perhaps too early to determine the role, if any, of lupus anticoagulant in the pathogenesis of COVID-19 thrombosis.[20]

Pathogenesis of CAC

The few proposed pathways are as follows:[21]

- Immune deregulation and endothelial dysfunction
- Prolonged immobilization, dehydration, coexisting comorbidities, presence of cardiovascular disease, previous history of VTE and genetic predisposition such as heterozygous Factor V Leiden mutation may increase VTE risk.
- Activation of ACE2 receptor in the endothelium could result in endothelial cell activation/damage due to the virus binding.
- The release of a large amount of inflammatory mediators may lead to an increased blood viscosity may cause further hypercoagulability.
- Interventions like mechanical ventilation, central venous catheterization, and surgery may induce additional vascular endothelial damage and activation of coagulation system.

Management of CAC

Risk assessment models (RAM) such as IMPROVE-VTE/modified IMPROVE-VTE RAM should be used to identify high VTE risk patients requiring thromboprophylaxis. Dynamic D-dimer evaluation and ultrasound venous echo-Doppler or bedside echocardiography can further risk stratify the patients for VTE.[22,23] If there are no contraindications, all patients with severe COVID-19 should receive prophylactic anticoagulation.

Low molecular weight heparins (LMWH), or unfractionated heparin (UFH) should be preferred over direct oral anticoagulants (DOACs) as drug-drug interactions with concomitant antiviral (especially anti-HIV protease inhibitors such as ritonavir) and antibacterial (such as azithromycin) treatment is a risk. Such treatments interfering with CYP3A4 and/or P-gp pathways can augment the bleeding risk or reduce the antithrombotic effect.[24]

Cytokine Release Syndrome in COVID-19

Cytokine release syndrome (CRS) also known as cytokine storm syndrome, macrophage activation syndrome, and haemophagocytic lymphohistiocytois are the terms used for the frequently fatal hyperinflammatory conditions seen in COVID-19. The most accepted pathophysiological pathways that result in CRS is the defective lymphocyte

killing via the perforin pathway. Homozygous defects in perforin pathway genes cause familial hemophagocytic lymphohistiocytosis, and heterozygous mutations are associated with secondary hemophagocytic lymphohistiocytosis. However, the role of similar or novel genetic defects in the severity of COVID-19-associated CRS is unknown. Perhaps, genomic sequencing of patients with COVID-19-associated CRS would provide an insight.[25] Elevated proinflammatory cytokines (IL-1, IL-6, and interferon-γ) produced by a dysregulated host immune response sets the soil for CRS. COVID-19-associated CRS, however, has early acute respiratory distress syndrome and clotting and surprisingly higher serum ferritins and lower IL-6 concentration.[25] Hyperferritinemia and high LDH levels are common. Usually, low fibrinogen levels and cytopenias of more than two cell lineages by hemophagocytosis are not reported in COVID-19 in contrast to CRS associated with other causes. So, the pathophysiology of COVID-19 overlaps with low-grade HLH. Anticytokine management should be used for treating COVID-19-associated CRS. Ruxolitinib, a JAK1/2 inhibitor, tyrosine kinase inhibitors (TKIs), and the anti-CD26 antibody begelomab have proved efficacious in this setting. IL-1 blockade with anakinra (a recombinant human IL-1 receptor antagonist) notably improved survival.[26]

Conclusion

The pathogenetic pathways discussed are evolving as our understanding of this disease is becoming clearer day by day. There is still much to be learned about the manifestations of COVID-19, and hence the literature is adding up new information. There is still a long way before we demystify this organism and are well acquainted by its effects. Whether there will be any chronic conditions or whether any further mutation in the virus would bring in some more acute complications, only time will tell.

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CHAPTER

5 Effect of COVID-19 on Health-care Workers

KC Shashidhara, Spoorthy Raj

Abstract

COVID-19 (Corona virus disease 2019) is a respiratory viral infection, caused by SARS-CoV-2 (Severe acute respiratory syndrome Corona virus 2) that has spread across the world and has assumed a pandemic status. With ever increasing case load, lack of efficient treatment and vaccine for prevention, there is increased demand on health-care workers, in terms of work hours, and also, they are faced by, increased risk of infection, physical stress, and associated physical illness due to use of personal protection equipment, mental health issues, and social issues.

Thorough understanding of the impact of the ongoing pandemic on health-care work force is pivotal in appropriate management of the pandemic, as well as in ensuring the physical and mental well-being of health-care workers and prevent attrition of health-care work force.

Introduction

COVID-19 (Corona Virus Disease 2019) is a viral respiratory illness caused by novel corona virus, SARS-CoV-2. It is an RNA virus, belonging to the subgenus Sarbecovirus of the genus beta coronavirus of the family coronaviridae. The virus was first detected, while investigating the cause of cluster of pneumonia cases in Wuhan, Hubei province, China. Since then the virus has spread exponentially all around the world. Human to human transmission has found to be via respiratory droplets.[1] COVID-19 was declared as pandemic by WHO on February 11th, 2020.[2]

Health-care Workers (HCWs): All people serving in health-care settings, either paid or unpaid, who are at risk of getting exposed, either directly or indirectly to infectious materials, contaminated medical equipment, hospital surfaces, or contaminated air are considered as health-care workers. This includes doctors, nursing staff, technicians, pharmacists, students, trainees, administrative personnel, and engineering and facilities management staff.[3]

HCWs work in contaminated environment and stay in close contact with virus infected individuals, and hence face higher risk of getting infected. Also, excess work load, risky working environment, social stigma exert deleterious effects on their mental health.[3]

Problem Statement

COVID-19 is a rampantly spreading pandemic. Globally, total number of cases (as on 24 July) were 15,659,529 with 6,36,599 deaths. India is burdened with 12,91,623 cases with 30,658 deaths. The exact statistics pertaining to infection and deaths among HCWs is not available; however, as per CDC reports, there are more than 71,000 cases and 375 deaths among US health professionals as on June 2020. In India, according to the study published in IJMR, the incidence rate of COVID-19, among HCWs was 0.8%. The number of deaths is estimated to be 104 among doctors, 10 among nurses, and 15 among other health-care workers; however, the exact numbers are suspected to be much higher.[4]

Effect of COVID-19 on Health-care Workers

COVID -19 is a fast spreading pandemic and currently there is enormous ongoing research to understand the disease dynamics and develop safe and effective vaccine and treatment strategy. However, in the absence of such vaccine and clear treatment guidelines there is increased pressure on global health-care work force **(Fig. 1)**. This occurs in two forms:

- Overwhelming case load
- Loss of health-care work force due to adverse effects on health of HCWs

The effects on health-care workers can be conceptualized as follows:

- Risk of hospital acquired infection
- Effects on physical health due to demanding work environment
- Effects on mental health
- Social issues

Risk of Hospital-acquired Infection

HCWs are at increased risk of hospital acquired infection due to following reasons:

- Work environment, demanding close contact with infected patients
- Longer duration of exposure due to long working hours
- Inadequate supply of personal protection equipment
- Inadequate training, preparedness, and motivation regarding use of personal protection equipment.

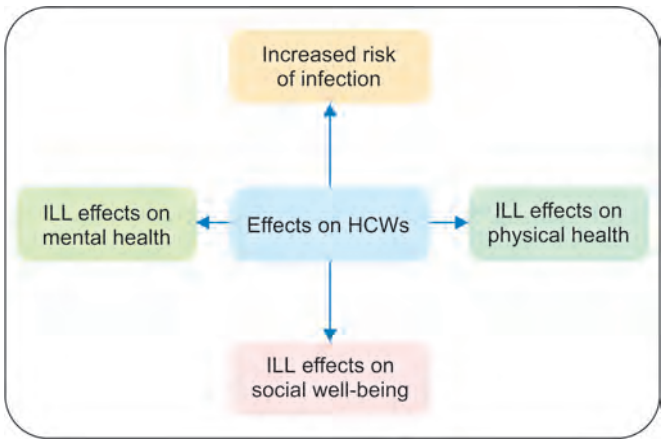


Fig. 1: Effects on HCWs

Effects on Physical Health due to Demanding Work Environment

It is mandatory for HCWs to use proper PPE for prevention of nosocomial spread of infection. However, prolonged use of PPE is associated with side effects like:

- PPE (N95 mask and protective eye wear) associated de-novo headache as well as worsening of pre-existing primary headache syndromes like migraine, which affect the work efficiency and sleep quality.[5]
- PPE associated dermatosis like: Heat stress, dehydration, Acne, skin irritation, irritant contact dermatitis, allergic contact dermatitis, contact urticarial dermatitis, pigmentation, and frictional erosions.[6]

Effects on Mental Health

Health-care workers work in demanding work environments during times of crisis, like the present COVID-19 pandemic. Due to increased work load and stress they face increased risk of mental health disorders like depression, generalized anxiety disorder, obsessive compulsive disorder, panic attacks, post-traumatic stress disorder, insomnia, and a wide array of somatic symptoms.

Features responsible for mental health problems among HCWs include:[7]

- Speculations about unforeseen modes of transmission of disease
- Rapidity of spread
- Spread from asymptomatic patients
- Lack of definitive treatment protocol and non-availability of vaccines
- Widespread global connectivity and extensive media coverage resulting in catastrophic reactions to outbreak
- Complete uncertainty
- Unprepared health infrastructure

According to the study conducted by Chatterjee et al.,[8] the prevalence of depressive symptoms among HCWs, during COVID-19 was 35%. The prevalence of symptoms related to stress and anxiety was 39.5% and 33%, respectively. Similarly, Korean study showed the prevalence of depressive symptoms among doctors to be 26.6%,[9] and a study conducted in Singapore showed the prevalence of anxiety, depression, stress, and post-traumatic disorder to be 14.5%, 8.9%, 6.6%, and 7.7%, respectively.[10]

With further loss of health-care work force due to acquisition of nosocomial infection, the work load on prevailing work force will manifold by several times and further worsens their mental health status.[8] Mental health issues are more prevalent among HCWs working in emergency, ICUs, and infectious diseases wards.

Social Problems

- Violence on doctors
- Concern regarding being source of spread to family members especially among those caring for elderly and children
- Social stigma

Measures to Safeguard Health and Safety of HCWs

Measures to Reduce Infection among HCWs[11]

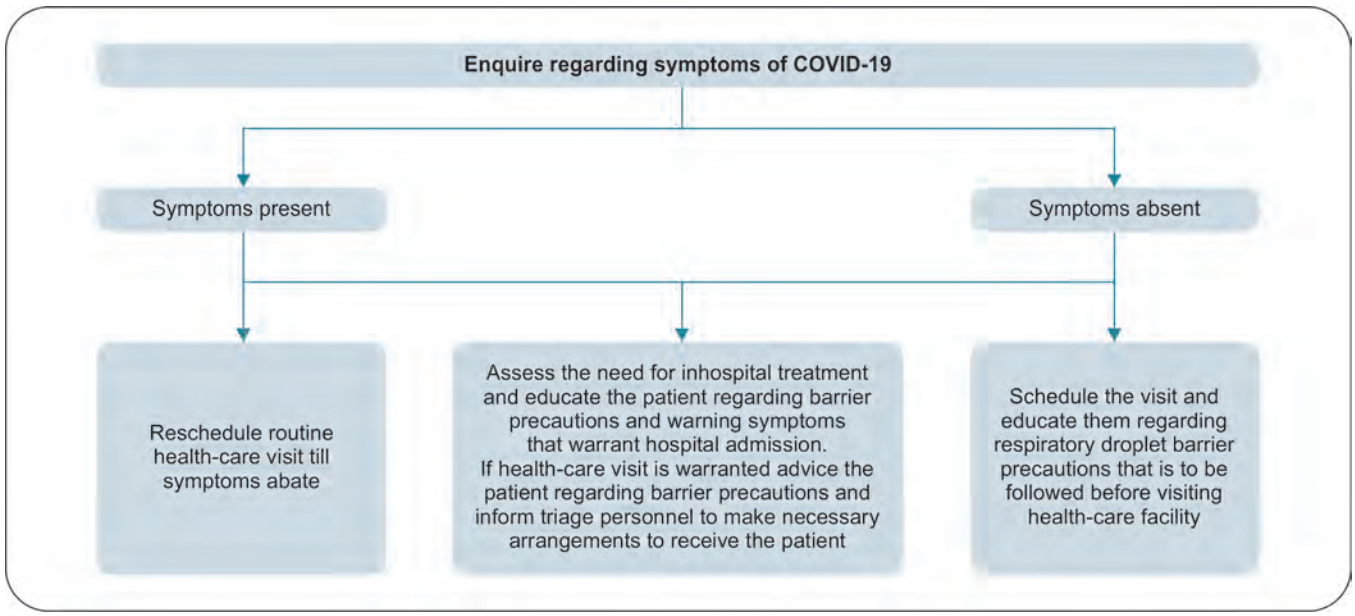
CDC recommendations include:[12]

- Recommendations for routine health-care delivery
- Recommendations for care of suspected and confirmed cases of COVID-19

Recommendations for routine health-care delivery include:

- Use of telehealth and nurse directed triage protocols **(Flowchart 1)**. It is advised to schedule appointments for routine medical care through phone call. At the time of scheduling such appointments for routine health-care delivery, care should be taken to prevent crowding of patients in waiting areas.
- All patients and visitors entering a health-care facility are to be screened for signs and symptoms of COVID-19.
- Visual alerts, regarding use of face mask, hand hygiene practices and cough and sneeze etiquette are to be posted at entrance and strategic places to ensure compliance for the same.
- Provision of alcohol-based hand sanitizers and face masks to patients entering health-care facility.
- Patients waiting for consultation should be placed in such rooms, which allow for adequate social distancing, are well ventilated and have easy access to respiratory hygiene supplies.
- Provision of a separate area at the heath-care facility for provision of services to patients with symptoms of COVID-19.
- Admitted patients are to be revaluated every day for development of signs and symptoms of COVID-19.
- Application of source control measure such as use of cloth face covering or face mask to all patients and visitors, considering the potential for transmission from asymptomatic and pre-symptomatic patients.

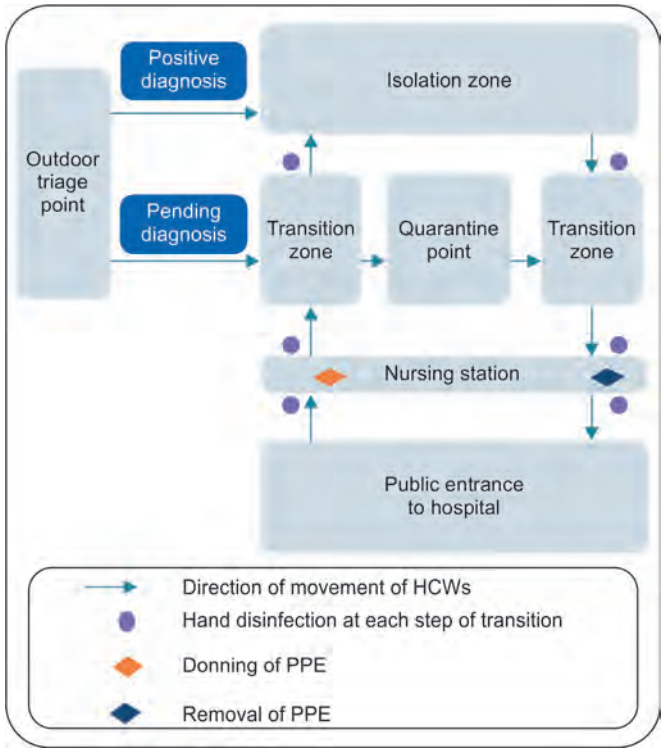
Flowchart 1: Algorithm for use of telehealth and nurse directed triage protocol



- Health-care workers to maintain adequate physical distancing whenever possible.
- Health-care workers to practice source control measures and physical distancing even in non-patient care areas so as to prevent transmission from unprotected exposures to asymptomatic or pre-symptomatic coworkers.
- HCWs to be provided with break areas, which allow scope for maintaining adequate social distancing.
- HCWs to be advised to wear protective eye wear in addition to facemask during patient care encounters.
- HCWs are advised to use N95 or equivalent or higher-level respirator while aerosol producing procedures like intubation.
- It is advisable to perform targeted SARS-CoV-2 testing for asymptomatic patients to further reduce the transmission risk in health-care setting.
- Engineering controls are to be optimized to reduce or eliminate exposures to HCWs and other patients from infected individuals. For example, use of physical barriers and dedicated pathways to guide symptomatic patients through triage areas.

  Traffic control bundle: It begins with outdoor triage. Patients are grouped into three categories at the triage station which is established at the entry to health-care facility. *Hot zone:* Patients with symptoms and consistent for COVID-19 or who are already tested positive for COVID-19 are directed to individual isolation rooms for further care. *Intermediate zone:* Patients with atypical symptoms and inconclusive SARS-CoV-2 test results are directed to quarantine ward and observed for the extent of their incubation period. *Clean zone:* patients without symptoms or signs consistent of COVID-19 are placed in clean zone. Patients designated to hot zone and intermediate zone are provided separate paths so that they do not cross the paths of health-care workers or patients moving to clean zone. HCWs while transiting from clean zone to intermediate and hot zones are instructed to follow appropriate hand hygiene and use personal protection equipment. Also while moving from hot zone to clean zone they are advised to de-gown and practice hand hygiene. Each transition zone is to be clearly labeled and necessary personal protection measures to be followed is to be clearly mentioned to ensure compliance **(Flowchart 2)**.[11]

Flowchart 2: Traffic control bundle



- Air handling systems to be optimized.
- Portable solutions like HEPA filtration units can be added to augment air quality.
- Each health-care facility to be equipped with designated staff to address health-care related exposures among HCWs.

Recommendations for care of suspected or confirmed cases of COVID-19:

- Assess for the need for hospitalization. If deemed necessary, it is advisable to give separate rooms with door and dedicated bathroom to each patient. If not feasible then all COVID-19 patients are to be placed in one room which is equipped with enough facilities to maintain physical distancing and source control precautions.
- Patients on whom aerosol generating procedures are planned are to be placed in airborne infection isolation room.
- There should be dedicated HCW assigned for care of COVID-19 patients and same HCW should not be used to provide care to other patients during the same duty shift.

- All HCWs providing care to COVID-19 patients should use personal protection equipment, which includes protective eyewear, NIOSH approved N95 or equivalent or higher respirator, clean non-sterile gloves and isolation gown.
- Health-care workers are advised to practice hand hygiene measures like washing hands with soap and water for at least 20 seconds or using alcohol-based hand sanitizer with 60–95% alcohol, before and after patient contact, contact with potentially infectious material, and before putting on and after removing PPE, including gloves. Hand hygiene supplies are to be made easily available to all health-care personnel at every care location.
- HCWs are advised to monitor themselves for signs and symptoms of COVID-19 and report promptly to the designated team in the health-care facility and refrain from providing patient care during the period of infectious symptoms.
- It is advised to minimize the movement of COVID-19 patients outside their designated wards. Whenever moving the patient is necessary, the information regarding the same should be communicated to respective departments and necessary precautions are to be taken before transferring the patient.
- It is advised to refrain HCWs from entering the patient rooms soon after discharging or transferring the patient. Sufficient time should be provided for adequate number of air exchanges and then should be appropriately cleaned and surface disinfection to be carried out before returning it back to routine use.
- It is advised to minimize the number of visitors to health-care facility. Alternative measures like video calls can be encouraged to ensure patient visitor interactions.
- Use of dedicated medical equipment for provision of care to COVID-19 patients.
- It is advised to follow routine cleaning and disinfection of all non-dedicated medical equipment.
- It is advised to follow cleaning and disinfection of the environment consistently.
- Routine standards are to be maintained while handling laundry, medical waste, and food services.
- It is advised to redeploy health-care workers who have medical conditions which predispose them to severe infection or death, if infected with SARS-CoV-2, away from high-risk sites.

Measures to improve mental health among HCWs:[12]

- Prompt screening for presence of mental health concerns.
- Use of proper duty roster to reduce long working hours.
- Educational interventions targeting nonmedical health-care workers enabling them to understand and use infection control measures.
- Psychological support including counseling services and development of support systems among colleagues.
- Provision of enough scope for rest breaks, food breaks, and decompression time for health-care workers and ensuring adequate communication and feedback sessions with local managers to help HCWs maintain compliance with personal safety measures and stay focused on provision of care.

Measures to improve social health of HCWs:

- Improving awareness among public to reduce social stigma and marginalization of those involved in care of COVID-19 patients.
- Strengthening social support systems to provide care for elderly and children.
- Provision of adequate information and practical solutions for health-care workers to improve environmental safety at home and prevent transmission to family members. For example, changing from hospital scrubs to personal clothing during return to home from work, showering on return to home, separation of living spaces, and bathrooms.

Conclusion

Health-care workers are the main personnel involved in the management of this raging pandemic; however, as individuals they are faced with increased risk of infection, physical and psychological stress. They are also constantly worried by the concern about family transmission, specifically to elderly members with chronic medical conditions, and immunocompromised which needs to addressed in a better way. It is therefore essential to promptly address physical, mental, and social health concerns affecting the health-care workers and take appropriate measures to improve the same.

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CHAPTER

6 Diabetes and COVID-19: What Is the Connection?

Viswanathan Mohan

Abstract

Diabetes and COVID-19 have a lot of interactions. Uncontrolled diabetes can make outcomes and prognosis in a person with COVID-19 worse. Conversely, COVID-19 can precipitate diabetes or worsen pre-existing diabetes in several ways. This article discusses the relation between Diabetes and COVID-19. It also deals with the treatment of diabetes in a person with COVID-19. Finally, it talks about how COVID-19 and the lockdown changed the way diabetes is treated and led to the growth of Telemedicine in India.

Introduction

The COVID-19 pandemic is one of the most unprecedented in the recent history of mankind. Already, millions have been affected in all continents of the world (except Antarctica) and hundreds of thousands have died due to COVID-19. There is convincing evidence that uncontrolled diabetes and hypertension and cardiovascular disease are associated more severe outcomes and higher mortality in COVID-19.

This article will deal with the connection between diabetes and COVID-19 and will try to answer the following questions:

- Are people with diabetes more prone to COVID-19?
- Are those with diabetes likely to have worse outcomes compared to those without diabetes?
- How does diabetes worsen COVID-19?
- Are any changes to treatment of diabetes to be made if they develop COVID-19?
- How did COVID-19 and lockdown change the practice of diabetes?

Are People with Diabetes more Prone to COVID-19?

It is well known that individuals with diabetes are more susceptible to viral, bacterial, and fungal infections as compared to those without diabetes. This is mainly because those with diabetes (especially uncontrolled diabetes) have less robust immune function. Moreover, glucose can serve as a medium for microorganisms to grow. With respect to respiratory infections, it has been recognized that while individuals with diabetes are more likely to get lower respiratory infection, no such increased predisposition when it comes to upper respiratory infection such as rhinitis, sinusitis, and pharyngitis. Therefore, it is probably not surprising that there is no evidence to suggest that people with diabetes are actually more prone to COVID-19, which starts off as an upper respiratory infection in most cases. The American Diabetes Association (ADA) has also issued a statement that people with diabetes are not more prone to COVID-19 than the general population.[1]

Are People with Diabetes Likely to Get more Severe Form of the Disease and are Outcomes Worse in those with Diabetes?

If those with diabetes do contract COVID-19, they are indeed likely to develop more severe form of the disease particularly if the diabetes is uncontrolled.[2] Data from Wuhan, China, confirms that approximately 20% of severe cases of COVID-19 do show diabetes, as comorbidity.[3] Data from Italy also showed similar findings in that more than two-thirds of those who died due to COVID-19 had diabetes.[4] Another retrospective study from Wuhan revealed that out of 41 COVID-19 patients, 32% of them had an underlying disease among which 20% was accounted for by diabetes.[5] A retrospective study focusing on outpatients at Fujian Provincial Hospital, China, included 135 elderly patients and concluded that those with type 2 diabetes (T2D) had worse outcomes. According to reports from India, of the first 125 deaths on COVID-19, 56% had diabetes, 47% had hypertension, and over a third had both diabetes and hypertension.[6]

A large observational report from China including showed that of the 173 patients with severe COVID-19, comorbidities like hypertension, diabetes, or cardiovascular disease were seen frequently.[7] In another study of 140 COVID-19 inpatient admission, hypertension and diabetes were present in 30% and 12%, respectively.[8]

Of the 72,314 COVID-19 cases reported from China, the overall fatality rate was 2.3% but this increased to 10.5% if CVD was present and to 7.3% and 6%, respectively if diabetes or hypertension were present.[9]

Another worrying finding is that people with diabetes potentially have milder early symptoms of COVID-19, which makes the subsequent rapid deterioration much more difficult to predict and prevent.[10]

What are the Mechanisms by which Diabetes Worsens COVID-19?

An important feature of T2D is low-grade inflammation. There is long-term immune system imbalance, metabolic syndrome, or nutrient excess associated with obesity.[11,12] Also, in individuals with diabetes, there is an exaggeration of proinflammatory responses, especially interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNFα). This may be further worsened in those with severe COVID-19. Prolonged hyperglycemia alters the host immune system. Dysfunctions in leukocytes, monocyte and macrophage chemotaxis and phagocytosis, and damaged specific immunity have also been reported in subjects with diabetes.[13,14] Moreover, diabetes shares the common features promoting disease progression with infectious disorders such as the proinflammatory state and endothelial dysfunction.[15]

Role of ACE2 in Diabetes and COVID-19

The role of ACE2 has been discussed in earlier articles[16] and hence is not dealt with in detail here.

Drugs like ACE inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) are widely used in diabetes since hypertension and albuminuria are common in people with diabetes. ACE2 is the receptor to which the Spike (S1) protein of the virus binds to gain entry into the respiratory tract epithelial cells. It is believed that ACE2 receptor stimulation might ease the entry of SARS-CoV-2 into the pneumocytes and thus result in worse outcomes in diabetic patients.

One study from China by Chen et al.[2] claimed that viral clearance is delayed by diabetes, hypertension in males and in old people, which may worsen the prognosis of COVID-19 infection, likely due to the increased expression of ACE2. The authors recommended that the use of ACE1 inhibitors be carefully considered in such population, as it may lead to upregulation of ACE2. However, there is another school of thought that ACE2 overexpression may in fact help as it converts angiotensin-2 into angiotensin 1-7, which has effects exactly opposite to that of angiotensin-2, meaning that it can balance angiotensin-2 in the body so that it is potentially *useful* or *protect* against ARDS and the cytokine storm.[2] Therefore, ACE2 seems to attract the virus into the pneumocytes, but on the other hand, perhaps also equips the cells against a cytokine storm. Thus, some authors have contended that blockage of the renin angiotensin aldosterone system (RAAS) by ACEi/ARBs can actually be beneficial in protecting against COVID-19.[17]

Current evidence does not support the discontinuation of ACE inhibitor treatment due to concerns regarding Coronavirus infection.[18] Moreover, the European Society of Cardiology, Council on Hypertension; ACC/AHA/HFSA (American College of Cardiology, the American Heart

Association and the Heart Failure Society of America) and the American Society of Hypertension have stated that patients should continue treatment with their usual antihypertensive therapy because there is lack of scientific evidence to incriminate ACE inhibitors or angiotensin receptor blockers in COVID-19 infection.

Other drugs like pioglitazone and liraglutide can also lead to upregulation of the ACE2 in animals.[19,20] It is not clear whether these drugs should be discontinued in COVID-19 but pioglitazone is not favored in COVID due to the chances of fluid retention.

Management of Diabetes: What Changes Need to be Made?

Glycemic control is the first and foremost factor in diabetes management; otherwise, complications associated with long-term hyperglycemia are not only frequent causes of premature mortality but also virtual drivers of indirect costs. Some studies have shown that the glucose concentration in the airway secretion is directly proportional to the blood glucose concentration.[21]

Can all Anti-diabetic Drugs be Continued?[22]

There is as yet no direct evidence on the effects of the various categories of antidiabetic medications on the risk of developing COVID-19 infection or the adverse outcomes of the same.

In those with Mild or Well-controlled Diabetes

In general, patients with T2D, who have mild symptoms of COVID-19 and asymptomatic patients, can continue their usual dose of medications, with appropriate titration if necessary so as to maintain good glycemic control. If the control is inadequate, addition of insulin would be warranted. There is no data on whether use of metformin, sulfonylurea, DPP4 inhibitors alpha-glucosidase inhibitors or insulin influences outcomes of COVID-19 over and above their effects on glycemic control.[16] As regards the other classes of antidiabetic agents:

- SGLT2 inhibitors are best avoided in severely symptomatic and hospitalized COVID-19 patients, primarily on account of the risk of dehydration and diabetic ketoacidosis. Also, these agents are known to upregulate renal ACE2, although the implications of this upregulation in the context of COVID-19 are unknown.
- Hydroxychloroquine (HCQ), approved and used as a third-line antidiabetic agent in India, also seems to have beneficial effects in COVID-19, and in India has been approved for prophylaxis of COVID-19 among health-care professionals treating COVID-19 patients and for asymptomatic close contacts of such patients. However, issues related to QT prolonged must be kept in mind. Also recent reports suggest that HCQ may not be beneficial in COVID-19 management and HCQ use remains a contention issue.[23-25]
- Many patients with COVID-19 infection report loss of taste and smell sensation, and hence have poor appetite. Many also have GI symptoms such as nausea, diarrhea, and vomiting. The antidiabetic drug regimen should be closely titrated so as to account for fluctuations in food intake caused by these symptoms.

Role of Anti-diabetic Drugs in COVID-19

Table 1 shows the role of anti-diabetic drugs in COVID-19.[26]

If Diabetes is Severe or in Hospitalized Patients and those in ICU

Severe COVID-19 infection can lead to deterioration of glycemic control and some patient could develop diabetic ketoacidosis on account of the excessive outpouring of counter regulatory (stress) hormones. In all such severe cases or in hospitalized patients, insulin would be the antidiabetic agent of choice. Treatment with basal-bolus insulin regimens or IV insulin infusion will usually be needed in such cases. However, the treatment has to be individualized on a case to case basis.

How did COVID-19 and Lockdown Change the Practice of Diabetes?

Following the COVID-19 pandemic many countries introduced a total lockdown and did not permit movement of people outside of their houses. This means that routine in person diabetic clinics applicants were not possible.

In India, the lockdown was introduced on March 25th 2020 initially for a period of 21 days but this was extended thrice and as of now the lockdown is in force till May 17th. With India's population currently at 1.366 billion, this is probably the largest lockdown in human history.

TABLE 1 Role of anti-diabetic drugs in COVID-19[26]

Drugs	*Benefits*
Metformin	• Has anti-proliferative and immunomodulatory effects—Protective[27] • Decreased mortality in lower respiratory infections[28] • Risk of lactic acidosis
Thiazolidinediones (TZDs)	• Seen to increase risk of pneumonia compared to sulphonylureas[29] • Increase ACE2 expression[30] • Therefore avoid in COVID-19
Glucagon like peptide-1 receptor agonists (GLP-1 RAs) [Liraglutide]	• Also increases ACE2 expression in lungs[31] • Best avoid
DPP 4 inhibitors	• In MERS—COV: Reduced viral entry • Increased upper respiratory infection with DPP 4 inhibitors known, but no increased risk of pneumonia • No evidence for or against use of DPP 4i in COVID-19
SGLT2 inhibitors	• Better to discontinue because of risk of dehydration and euglycemic ketosis
Sulphonylureas and insulin	• Dose may have to be adjusted based on blood glucose levels

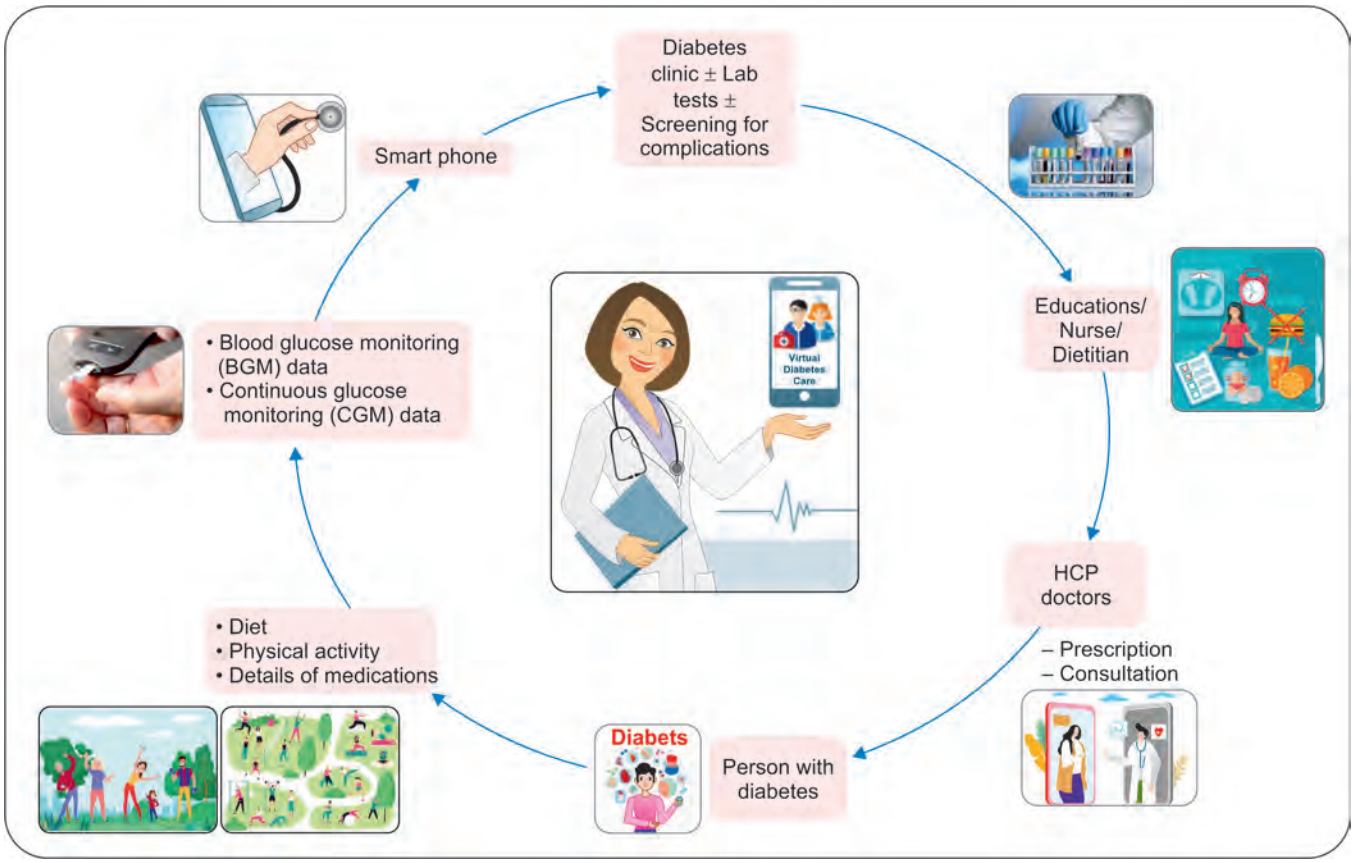

Fig. 1: Interaction of the person with diabetes and health-care providers using technologies

Telemedicine which was not legally permit until the COVID-19 set in was rapidly legalized by the Board of Directors of the National Medical Council of India and guidelines for the same were rapidly drawn.[32] With this, telemedicine for diabetes too off in India. Many government and private hospitals and clinics rapidly adopted telemedicine in India.

In a study conducted by us currently, it was seen that 82% of patients who availed the teleconsultation were happy with it.[33] However, only 58.1% stated that they would be keen to continue it in the future.

It is reasonable to assume that if the COVID-19 or similar pandemic arise in the future, telemedicine will become a most accepted method of diabetes treatment.

In the future, we could see the integration of the person with diabetes and the health-care provider (doctor/nurse/educator/dietitian), thanks to using technologies as shown in **Figure 1**.

Glycemic Control during COVID-19

There have been several predictions regarding the diabetes control during COVID-19. One school of thought believes that due to disruption of lifestyle (diet/exercise), there could be disastrous effects on glycemic control. There were even predictions that A1c could be worsen from around 8% to 12% or even 16%.[34] In a study of 2,500 persons with diabetes in India, it was seen that the reverse is also true. It was seen that glycemic control actually improved from 8.2% to 7.7% in this set of individuals. Reduced frequency of eating out (and eating healthier home meals), timing meals, less stress, better sleep, possibly lower exposure to pollution (because of working from home), and reduced smoking and alcohol (because of non-availability) could be some of the factors which contributed to the improved diabetes control in this study.[33]

Conclusion

In conclusion, the COVID-19 has taught us many things about diabetes. The worse outcomes and increased mortality points to the obviously need for tighter diabetes control. On the other hand, as a silver lining to the difficulties due to the lockdown, many people's health and lifestyle seem to have improved, resulting in better diabetes control and to the birth of telemedicine.

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CHAPTER

7 COVID-19-associated Renal Injury

Shashidhar Shree Niwas, Ramya Vedula, Prateek Kumar, Madhuri, Shashank Jain

Abstract

SARS-CoV-2 related renal disease is common in severe cases. Common presentations are proteinuria, hematuria, oliguria, and renal dysfunction. Emerging data from case reports and autopsy series of COVID-19 suggests that it causes acute kidney injury (AKI). Intrinsic renal pathology including viral mediated tubular cell injury, thrombotic vascular processes, and glomerulonephritis. Predominant pathways of renal injury are due to hemodynamic changes, direct cytopathic effect, and cytokine storm syndrome. The indications for RRT in AKI largely remain the same regardless of the COVID-19 status of any given patient.

Introduction

The Corona Virus Disease (COVID-19) pandemic which is rapidly evolving and expanding has infected a population of more than 77 million across the globe and around 10 Million in India as of 25th December, 2020.[1] This virus was first recognized in December 2019 in Wuhan of China when pneumonia of unknown origin came into limelight.[2] It was identified as COVID-19, a neovirus causing severe pneumonia that rapidly led to a major health crisis with devastating consequences not only in India but also in major developed countries of the world.[3,4]

Initially data from China and Italy, which was identified as caused by COVID-19, shows that death rate worsens in persons with increasing age more than 50 years and also leads to higher risk due to comorbidities like hypertension (HTN), cardiac disease, diabetes mellitus, chronic renal disease, cancer, etc.

Diagnosis

The diagnosis of COVID-19 is mainly based on epidemiological factors (history of contact), clinical manifestations, laboratory examination (hemogram), chest computed tomography, and virological investigations. Incubation period varies between 4–15 days. The virus is highly contagious and mode of transmission is respiratory droplet, contact, aerosol.

Infection has been reported in all ages, but lesser in children. The majority of infections are mild, presenting with a flu-like illness. The common clinical presentations of COVID-19 are fever (98%), cough (76%), myalgia and fatigue (18% each), loss of smell and taste, accompanying leukopenia (25%), and lymphopenia (63%). About 16–20% cases have been classified as severe which includes pneumonia, multiorgan dysfunction, and cytokine storm syndrome.[5,6]

Renal Manifestations of COVID-19

Data indicates SARS-CoV-2 has particular organotropism beyond the respiratory tract, including the kidneys, liver, heart, and brain, and this influences the course of COVID-19 disease and, possibly, aggravates preexisting conditions.[7] Emerging data from case reports and

autopsy series of COVID-19 suggests that it causes acute kidney injury (AKI). Intrinsic renal pathology including viral mediated tubular cell injury, thrombotic vascular processes, and glomerulonephritis have been reported. AKI also resulted from extrinsic factors such as fluid depletion, multiorgan failure, and rhabdomyolysis.[7,8] Clinical reports have emerged of proximal tubular injury, in association of Fanconi syndrome that manifests as hypokalemia, hypophosphatemia. It also has features of normal anion gap metabolic acidosis, hypovolemia due to salt wasting manifestation. The USA, France, and China reported incidence of AKI that varies from 3% to 37% of patients in retrospective, observational.[8-11]

Pathogenesis of Renal Injury

The incidence of renal manifestations and impact and outcome of COVID-19 on kidney is not completely known. Studies describe the clinical manifestations, associated risk factors, and course of acute renal injury in hospitalized patients with COVID-19.[7-12] The largest available published data was in 13 New York metropolitan city hospitals.[9] Total 5,449 patients got admission in these centers with COVID-19, AKI was diagnosed in 36.6% cases. Out of them, 14.3% needed kidney replacement therapy (KRT). Acute renal injury was mostly observed in conditions with respiratory failure. Renal injury was more common (89.7%) of patients on mechanical ventilation as compared to those of non-ventilated patients (21.7%).

Surprisingly 96.8% of patients requiring renal replacement therapy were on ventilators. The onset of AKI was observed within 24 hours of intubation in 52.2% of those who needed mechanical ventilation. Major factors for AKI were higher age, diabetes mellitus, cardiac disease, black race, HTN, and requirement of mechanical ventilation and inotropic agents.[6] Out of them 35% died, 26% discharged among all patients with AKI but 39% were still hospitalized. This study clearly shows AKI occurs early in course, and is in temporal association with respiratory failure and have a poor prognosis. Hematuria (46%) and proteinuria (42%) were documented which are mostly part of glomerulonephritis, AKI, thrombotic microangiopathy.

There are predominantly three pathways of renal injury:

- Renal impairment due to hemodynamic changes,
- direct cytotoxic effect, and
- cytokine storm syndrome.[9]

Expression of viral receptor ACE2 on tubular epithelial cells might suggest direct cytopathic effect in renal injury. There may be a role of immunological and prothrombotic factors, which may be triggered by infection. Angiotensin converting enzyme (ACE) both expressed on renal tubular cells was identified as binding partners for SARS-CoV.[9] Viral RNA has been identified in kidney tissue in infected persons. Higher plasma cytokine levels granulocyte-colony stimulating factor were present in patients requiring intensive care unit admission.[9]

Histopathology

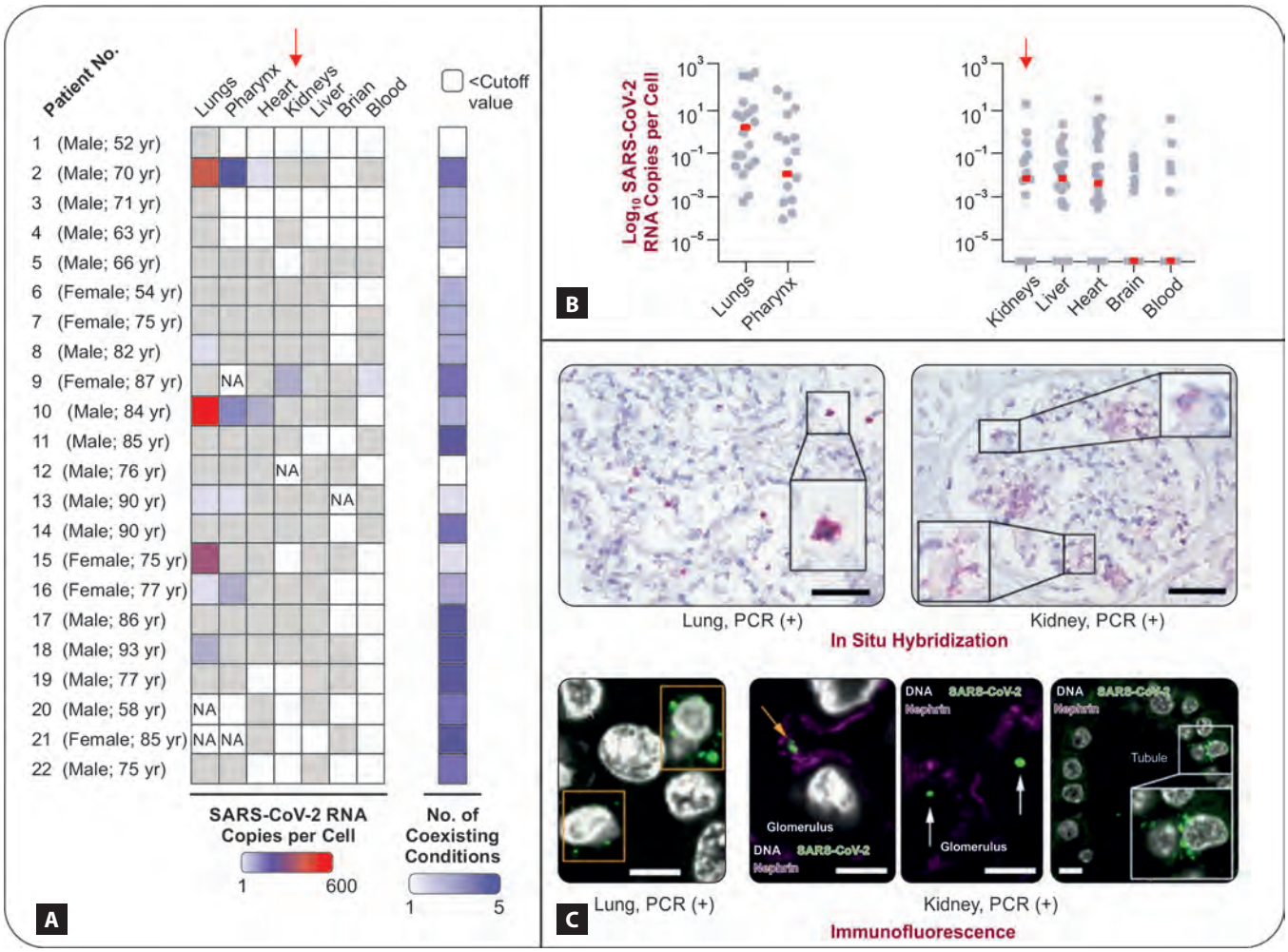
Largest series of 26 cases of postmortem renal biopsy samples were studied by light microscopy described proximal tubule injury, non-isometric vacuolar degeneration, and even frank tubular necrosis was observed.[13] There were red blood cells accumulation obstructing the capillary lumen in absence of platelets and fibrinoid material. There was no evidence of vasculitis, interstitial inflammation or hemorrhage **(Figs. 1A to C)**.

Assessment of Renal Injury in Suspected or Confirmed COVID-19

In patients with COVID-19, AKI is quiet common except in mild cases especially with high risk factors. Its incidence increases as severity increases further. Up to 31% on ventilators and 4% not on ventilator needed renal replacement therapy (RRT). AKI is an independent predictor of mortality.[9-12] Common causes may include volume depletion, hemodynamic changes, viral infection leading directly to kidney tubular injury, overzealous diuretics, thrombotic vascular processes, glomerular pathology, or rhabdomyolysis. In management of COVID-19, maintaining euvolemia is critical in prevention and management of AKI, overzealous diuretics, hyperpyrexia, and increased respiratory rate increases insensible fluid loss and hypovolemia may also increase risk of coagulopathy. Assessment of hemodynamics, volume status, monitoring intake output charts, identifying risk factors for AKI, history of pre-existing comorbidities in all patients is essential.

Patients with Dialysis-requiring AKI

COVID-19 infection presents particular challenges for patients on dialysis. The indications for RRT in AKI largely



Figs. 1A to C: (A) Clinical information of 1-26 patients affecting different organs. (B) SARS-CoV-2 RNA copies in different organs. (C) Expression of SARS-CoV nucleoprotein in renal tubules

remain the same regardless of the COVID-19 status of any given patient. Continuous variant of renal replacement therapy (CRRT) is modality of choice in providing dialysis wherever this facility is available among seriously ill patients with AKI.[14,15] Sustained low-efficiency dialysis or SLED may be performed in hemodynamically stable patients to rapidly changing hemodynamics, deteriorating clinical condition, multiorgan dysfunction, hyperkalemia, metabolic acidosis, shock, inotropic, and ventilator support, which depends upon facility and skilled staff.[14-16]

In resource constrained situation there are strategies to reduce cost and better utilization of available resources like: colocalization of desired dialysis patients on same floor/ICU and time, SLED instead of CRRT, extended tubing and putting dialysis machine outside of room.

Figure 2 shows a simple overview of continuous venovenous filtration (CVVH), which is a most commonly used form of CRRT.[17] A dialysis filter, which is used as a permeable membrane that filters patient's blood, and then the ultra-filtrate is removed, resulting in clearance of nitrogenous waste products; however, blood cellular components and large proteins like albumin are not removed. Isotonic fluid is used as replacement volume and provides base equivalents like bicarbonate or citrate. The replacement fluid is commonly given prefilter than postfilter to avoid hemoconcentration which can lead to clotting of the membrane.[15] To increase clearance of waste products during intermittent hemodialysis the rate of replacement fluid and filtrate turnover is increased.[16]

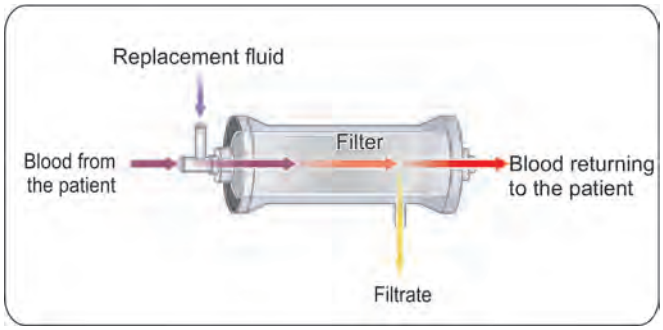


Fig. 2: Depicting simplified overview of continuous renal replacement therapy

Studies have suggested that circuit thrombosis is more common in COVID-19 than noncovid patients.[15] In the absence of major contraindications, patients with COVID-19 should receive anticoagulation during RRT. If available, remote monitoring with audio and video streams should be used to troubleshoot alarms.

When resource constrained setting or overburdened hemodialysis centers due to increasing COVID cases, peritoneal dialysis is a good alternative in AKI cases.[17] Patients with AKI who are treated with peritoneal dialysis have similar rates of all-cause mortality, kidney function recovery, and infectious complications compared with patients treated with other modalities.

Pharmacological Agents for COVID-19

High-quality evidence showing the effectiveness of treatments for COVID-19 is scarce, but over 400 studies are now registered in ClinicalTrails.gov testing a range of therapies.[18] Given the abundance of scientific research and clinical, clinicians require accurate evidence for effective medical treatment of COVID-19 infection.

Antiviral Agents

- *Remdesivir:* It is an enzyme inhibitor of RNA polymerase which acts against SARS-CoV-2. Randomized controlled trial has been performed of IV Remdesivir in patients admitted with COVID-19 with evidence of pneumonia. It has shown superior effect in reducing the time to recovery in admitted patients with COVID-19 and pneumonia.[19-20]
- *Hydroxychloroquine:* It has shown in vitro activity against SARS-CoV-2, an immunomodulatory benefit. However, several clinical trials have not shown very convincing data against COVID-19.[21,22]
- *Ivermectin:* This has been recently approved by FDA in COVID-19 infection. It also shows antiparasitic activity previously shown to have broad-spectrum antiviral activity in vitro.[23] It is an inhibitor of the causative virus (SARS-CoV-2). Ivermectin therefore warrants further investigation for possible benefits in humans.
- *Tocilizumab:* Disproportionate and excessive immune response to infection with the SARS-CoV-2 virus has been found to be part of cytokine storm in the ARDS and multiorgan failure in some patients. Cytokine IL-6 inhibitor, tocilizumab is part of several randomized, double-blind, placebo-controlled phase 3 clinical trials as well as uncontrolled trials to evaluate the safety and efficacy of tocilizumab plus standard of care in hospitalized adult patients with severe COVID-19 pneumonia with some promising initial results.[24,25]
- *Plasma therapy (convalescent plasma):* It is a type of passive antibody therapy in which blood plasma is isolated from people who have recovered from the COVID-19 infection and is administered to those with the disease to suppress viremia and improve clinical symptoms.[26]
- ICMR has regularly updated the clinical management of COVID-19 in India. Recently it has included the role of remdesivir, favipiravir, tocilizumab, and convalescent plasma on selected group of patients. The document states, "Remdesivir (under Emergency Use Authorization) may be considered in patients with *moderate* disease (those on oxygen)... tocilizumab (Off Label) may be considered in patients with moderate disease with progressively increasing oxygen requirements and in mechanically ventilated patients not improving despite the use of steroids. Long-term safety data in COVID-19 remains largely unknown... Convalescent plasma (Off Label) may be considered in patients with moderate disease who are not improving (oxygen requirement is progressively increasing) despite the use of steroids."
- Though the revised protocols allow hydroxychloroquine to be prescribed to patients in the *early* course of the disease, evidence for its use "remains limited."

Conclusion

The COVID-19 pandemic has posted major challenges around the globe. Renal clinical presentation ranging from mild proteinuria, hematuria to progressive AKI necessitating renal replacement therapy (RRT), thrombotic microangiopathy, and rhabdomyolysis. International collaboration and interdisciplinary research is needed to obtain adequate evidence to support current clinical approaches and to develop new approaches to management. Multiple pathways might play role in AKI including direct renal injury. AKI is independent predictor of mortality in COVID-19. Strategies to enhance the antiviral potency of antiviral agents, vaccine, and ways to mitigate immunopathological host responses contributing to COVID-19 severity require further research in patients of COVID-19.

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CHAPTER

8 Sahaja Yoga Meditation for Reduction of Stress during the Present Corona Pandemic

Sandeep Rai, Devdutt Rai, Madhur Rai

Abstract

The world is fighting against the COVID-19 outbreak, which is now spread to more than 200 countries worldwide. There has been a huge loss of life, drastic changes in our way of life, disrupted plans due to travel restrictions and social distancing. Health experts say, during this time of heightened stress, anxiety, and fear, finding ways to cope up and to create stability is the key to maintaining a healthy body and mind. Pandemic-related stressors may be difficult to change; nevertheless an enhancement in one's coping abilities to combat the deleterious effects of stress on the body and mind can be definitely brought about. In fact, new studies have now revealed that by practicing only 15–20 minutes of Sahaja Yoga meditation daily, you can remain stress-free.

Introduction

When stress does not let up and is paired with the feeling that we have very little or absolutely no control over the circumstances that are creating it, that's called chronic stress. Chronic stress zaps brain power by damaging neural pathways and hampering judgment. It damages the immune system and many other organs including the heart and the brain. Presently robust evidence exists for the Mind-Body medicine practices like meditation and yoga for improving one's psychological and physical health.

Sahaja Yoga is indeed a very unique meditation developed by Dr. Nirmala Devi Srivastava, popularly known as H.H. Shri Mataji Nirmala Devi in 1970. This meditation causes a transformation inside a person by which one becomes balanced and de-stressed. It offers a practically easy method of understanding one's own energy systems and harnessing the innate powerful energy, present in all human beings, for improving one's own health. Scientific researches have now clearly shown that Sahaja Yoga meditation acts by reducing the activity of the sympathetic system (*Stress*) and increasing the parasympathetic activity (*Relaxation*) in an individual.

Sahaja Yoga meditation practice for 12–16 weeks, in subjects who had never practiced any form of meditation before, has shown a slowing of the heart rate, decrease in the respiratory rate, decrease in both BP and in the production of urinary vanillymandelic acid (VMA), which is a breakdown product of stress hormone adrenalin and an increase of Galvanic Skin resistance.[1] Changes in all these parameters reflect a de-stressed state of body. These parameters indicate activation of a deep parasympathetic state, which in turn indicates a physiologically relaxed state of the body and mind, and this may play a very big role in the prevention of stress-related diseases.

Electrophysiological studies (EEG) and analysis, on SY meditators, have shown specific brain activation patterns, which indicate a relaxed state of mind, a subjective feeling of happiness, and an enhanced interconnectivity of different brain regions.[2,3] In an interesting study examining emotional reactions of Sahaja Yoga meditators compared to non meditators, a decreased electrophysiological,

physiological, and psychological reactions were seen in meditaors when exposed to stressful stimuli, compared to non meditators, thus showing for probably the first time in the world, the neurophysiologic proof, to support the hypothesis, that Sahaja Yoga meditation leads to development of greater resilience in an individual to deal with stressful life events.[4] Many other randomized trials on Sahaja Yoga meditation have demonstrated beneficial effects on depression and work-related stress.[5]

In other researches conducted on Sahaja Yoga meditation, very good results were achieved in patients suffering from anxiety and depression,[6] enhancing QOL[7] and significant improvement in psychological health of a mixed population consisting of subjects from different countries and of age groups **(Fig 1)**.[8] Encouraging results have also been recorded in patients with hypertension, asthma, and perceived stress, after a couple of weeks of Sahaja Yoga meditation practice. SY meditation practice also showed a significant reduction in epilepsy attacks, attacks of bronchial asthma. and improvements in the control of diabetes and blood pressure.[6,9-16]

Chronic stress in known to increase cortisol levels in body which in turn decreases immunity and consequently impairs a person's ability to fight infections. Two randomly controlled studies conducted in the Dept. of Medicine & the Dept. of Physiology at the MGM Institute of Health Sciences, Navi Mumbai by the authors of this article, on effects of Sahaja Yoga on perceived stress and serum cortisol levels recorded a very robust reduction in perceived stress and serum cortisol levels in Sahaja Yoga meditation practitioners as compared to non-meditating healthy population.[17] More over an exciting new research has shown that practice of Sahaja Yoga resulted in increase in gray matter volume of brain, in many cortical and sub-cortical brain regions of the right hemisphere. These regions are associated with self-control, compassion, and stress modulation.[18]

Modern medicine's understanding of the human immune system, as a complex multidimensional interaction among different organ systems, is slowly expanding, throwing its light on new facets like neuroendocrine and psychoemotional aspects governing its effective functioning. Chronic stress, although mental in origin, has many detrimental effects on the body as well as on the immunity by creating an imbalance in the neuroendocrine pathways. These chronic stressors overwhelm the immune system of our body thus weakening the immune system's ability to activate a strong immunological response to an infectious organism and thus making the individual susceptible to life threatening medical consequences. It is now amply proven that practice of meditation establishes moderation in the person's psychological and emotional spheres and corrects the imbalance in the neuroendocrine pathways.

Both health and yoga experts now firmly believe that meditating on a regular basis can help to improve the immunity of the body, thus creating a shield in a fight against the highly infectious diseases, like COVID-19. Scientific research has already shown that meditation produces remarkable effects on the brain and immune

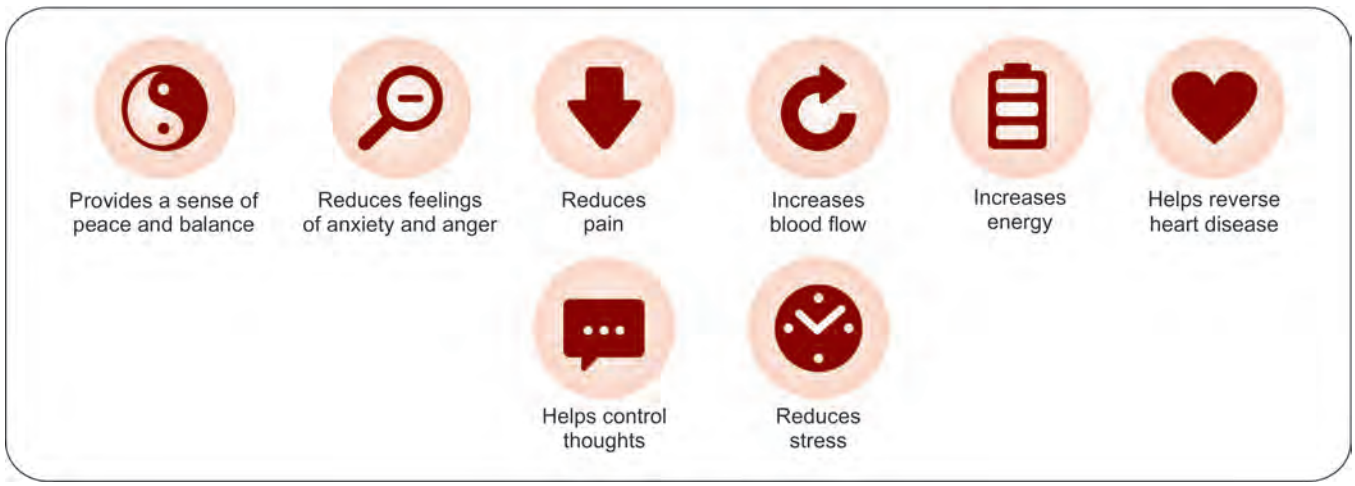

Fig. 1: Benefits of meditation

functions.[19-21] Recent studies have now shown that the relaxation produced after meditation reduces the levels of IL-6, a proinflammatory cytokine which plays a major role in the pathophysiology of several diseases including COVID-19.[22]

Meditation has shown to increase the telomerase activity of chromosomes and lengthens telomeres and thus promotes immune cell longevity.[23] Meditation has shown to reduce the activity of nuclear factor-kB (NF-kB), which is a known mediator in the pathogenesis of inflammation and in generating C-reactive protein which increases in inflammatory conditions including COVID-19.[24,25] Meditation has shown to boost the levels of salivary immunoglobulin A, which is an immune mediator at mucosal surfaces such as GI tract, respiratory tract, and genitourinary tract.[24,25] Meditation has also shown to increase the levels of antibody titer against influenza virus thus increasing immunity against some of the common viral infections.[23,26] Regular meditation practice has also shown an increase in the absolute lymphocyte count which is an important predictor of the risk of opportunistic infections and is now increasingly used to grade the severity of COVID-19 infections.[27] A very recent review analyzing various studies, for the effects of meditation and yoga on immune system has found the evidence of enhancement of immunity in an individual, by the practicing some forms of yoga and meditation.[28]

How Sahaja Yoga Meditation Reduces Stress?

The Possible Mechanisms: Mammals, including humans, have over millions of years evolved the ability to deal quickly and reflexively with perceived threats to their survival and this ability has conferred a robust survival advantage to this group of animals. In humans however, the same stress response can be triggered in situations which, while they do not necessarily threaten survival but occur fairly frequently over a prolonged period of time. Such a typical situation is in the present day stress of Corona pandemic which we all are facing on a daily basis. Repeated activation of the stress response is thought to result in dysregulation of the immune system which hampers the body's own survival mechanisms and this in turn damages health. The changes in mind and body achieved by Sahaja Yoga meditation are characterized by the relaxation response. Psychophysiological studies on Sahaja Yoga meditation, suggest that indeed it elicits a relaxation response. The hypothesis is that the innate energy, called Kundalini energy, described in detail in the ancient Indian scriptures, actualizes in limbic area of the brain and modulates the stress response of an individual through the limbic system **(Fig. 2)**. The limbic system has intricate connections with hypothalamus and via hypothalamus the autonomic nervous system is modulated. The limbic system by its action on the HPA axis modulates the release of various important hormones including cortisol which is secreted in response to stress. Practicing Sahaja Yoga meditation balances the energy systems of the body for its optimum functioning.

Sahaja Yoga is now a practiced in many corporate offices and is an integral part of wellness programs. It is also increasingly being incorporated in many youth development programs around the world. In this ongoing Corona pandemic, technology has enabled to teach and conduct online Sahaja Yoga collective meditation programs for lakhs of people in India and across the world, and these online programs have become hugely popular.

The Harvard Medical School also, in its latest health guideline released on COVID-19 pandemic, has said that, Yoga and meditation are "some tried and true ways to relax and to remain stress free in these difficult times." There have been numerous medical researches conducted in India and abroad on Sahaja Yoga. Sahaja Yoga is now available free of charge,on the various online platforms, to learn and practice, and it is also taught free at all the Centers of Sahaja Yoga which are present today in more than 150 countries of the world.

H.H. Shri Mataji Nirmala Devi ji has received numerous Prizes and recognitions from all over the world for her significant contribution to the understanding of subtle energy systems of the human body. She was conferred with the Honorary membership to the prestigious Presidium of Petroyaska's Academy of Art and Science, Russia (Einstein being one of the members). She has been conferred the United Nations Peace Prize and had been nominated for Nobel Peace Prize, twice. For any further information on Sahaja Yoga you may visit www.freemeditation.com or write to doctorsandeeprai@gmail.com.

Acknowledgments: We sincerely owe our gratitude to the Medical Director, Dr. S. N. Kadam, Respected Dean & Heads of Dept. Med. & Physio., MGMIHS, Mumbai;

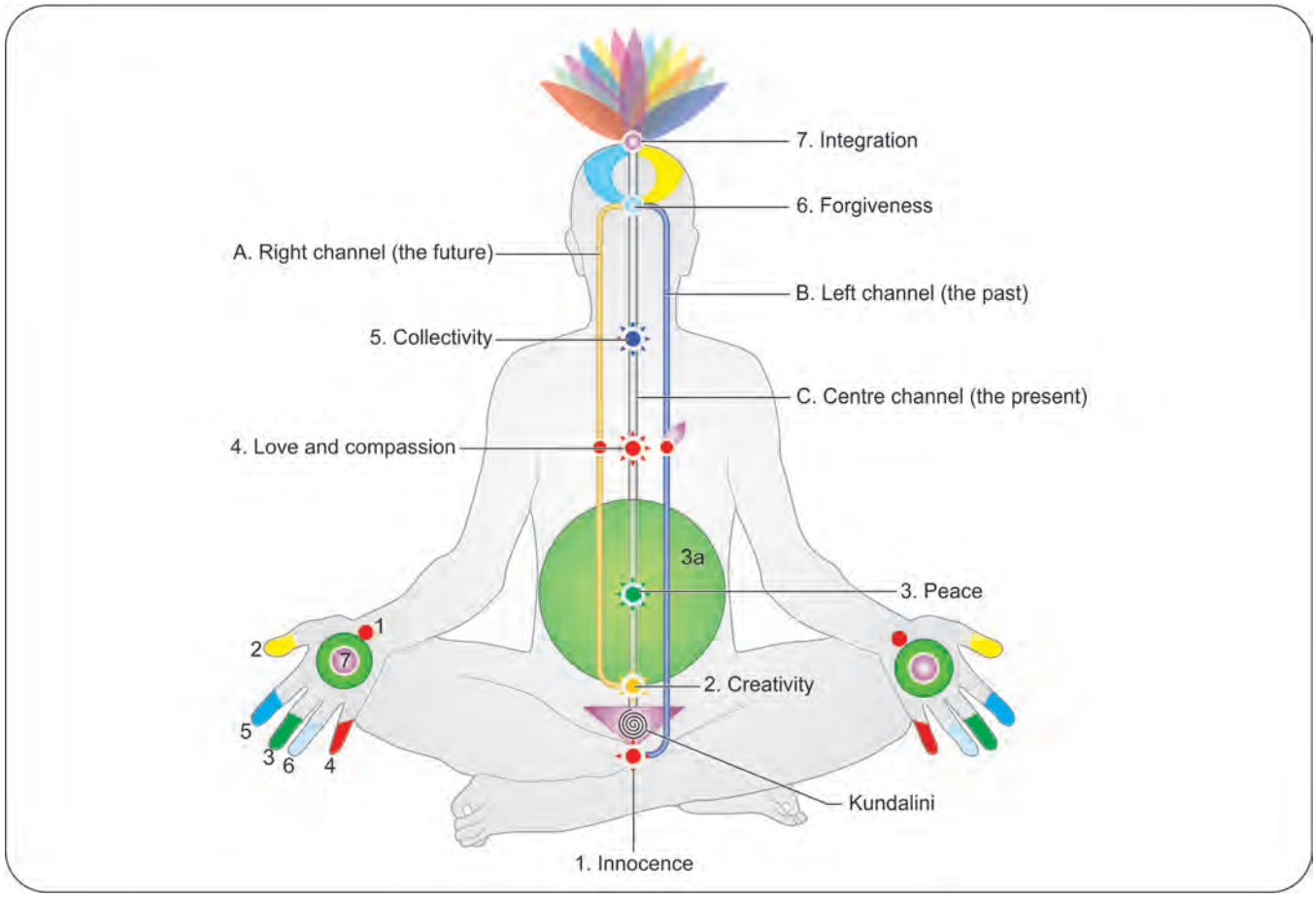

Fig. 2: The subtle system and chakras

Dr. Vishesh Agarwal, Consultant Physician, Nanavati Hospital, Mumbai; Dr. Yashoda Kattamani, Associate Prof. Physiology, MGMIHS; Dr. R. Manocha, Asst. Prof., Sydney Med School; Dr. Sheng Chia, Epidemiologist, London; Dr. Sergio Elias Hermandez, University de La Laguna, Tenerife, Spain; Prof. U. Panjwani, DIRDO, New Delhi; Dr. D. Chug, Neurologist, USA; Prof. K. Rubia, Kings College London; and all the doctors and subjects who participated voluntarily in research projects for their active participation, cooperation, and valuable contribution.

Conclusion

The world is fighting the COVID-19 pandemic and people are desperately looking for ways to cope up with this unrelenting stress. Chronic stress zaps brainpower by damaging neural pathways, compromises the immune system besides taxing many other organs of the body. It may not be an easy task to change the present day stressors, but coping abilities to combat negative effects of stress on health and disease can definitely be enhanced. In fact, new research reveals that simple 20 minutes of Sahaja Yoga meditation a day can keep stress away. By practicing this meditation, an inner transformation takes place by which one becomes energized and de- stressed. Studies show that Sahaja Yoga meditation acts by reducing sympathetic activity (Stress) and enhancing the parasympathetic activity (Relaxation). Rigorous researches on Sahaja Yoga meditation have demonstrated significant benefits on depressive mood, anxiety, and work stress and have shown improvement in Psychological health, Perceived Stress levels, and overall Quality of life. Sahaja Yoga meditation is taught free of charge in more than 150 countries around the world. The simple technique of Sahaja Yoga can be learnt free from internet and through online meditation programs also. For learning Sahaja Yoga meditation or for any more information please visit site -www.freemeditation.com or www.sahajayoga.org.in

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CHAPTER

9 Diagnosis and Management of Corona Infection

Sandeep Garg, Avishkar Agarwal, Sunita Aggarwal

Abstract

The current pandemic caused by SARS-CoV-2 (COVID-19) began in China and has taken over 4,00,000 lives, putting every country to a standstill. Its manifestations range from mild symptoms to respiratory failure and multi-organ damage in those with risk factors. Spreading mainly by person-to-person transmission, it reached every part of the world within 3 months. Management of the disease is based on case severity and symptomatic treatment. While several new drugs are being developed, many drugs have been repurposed for the same. Other than low dose steroids, no drug has shown proven benefit in preventing severe disease so far. As of now, prevention is the best strategy against this disease. There are universal preventive measures for everyone including health-care workers to be followed even outside health-care facilities. Certain vaccines are being developed all around the world, but that might be a long road ahead. Even after development of a specific drug/vaccine, this new disease is here to stay. Past experiences have taught us to learn to live with it and adjust our lifestyle accordingly.

Introduction

In 2019, a novel coronavirus disease 2019 (COVID-19) began in Wuhan, China, and spread worldwide and was declared a pandemic by WHO. It is caused by severe acute respiratory syndrome-coronavirus-2 also called as—SARS-CoV-2. As of the first week of June, 7 million reported cases and 400,000 deaths in more than 200 countries. In India, there is 250,000 reported case with approximately 6,000 deaths. This is a *Betacoronavirus* and is similar to Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV).

Clinical Features and Transmission

The spectrum of disease ranges from mild to critical:[1]

- Mild (no or mild pneumonia)—81%
- Severe disease (dyspnea, hypoxia, or >50% lung involvement on X-ray)—14%
- Critical disease (respiratory failure, shock, or multiorgan dysfunction)—5%

The median incubation period is 4 days (2–14 days). However, about half of the population seems to be asymptomatic. Clinical presentation is mostly of upper respiratory illness **(Table 1)**.[2]

There are certain risk factors and laboratory parameters, which predispose to severe or critical disease **(Box 1 and Table 2)**.[1]

Transmission

There are two main modes.

Person to Person

It is the predominant method that occurs via respiratory droplets spread through close-contacts. These respiratory droplets do not travel more than 6 feet. Although airborne precautions are recommended, the transmission via

TABLE 1 Clinical features

Typical clinical features		*Atypical clinical features*	
Dry cough	68%	Nausea & vomiting	5%
Fever*	44%	Nasal congestion	5%
Fatigue	38%	Diarrhea	4%
Sputum	34%	Tonsillar enlargement	2%
Dyspnea	19%	Conjunctival congestion	1%
Myalgia	15%	Hemoptysis	1%
Sore throat	14%	Lymphadenopathy	0.10%
Headache	14%		
Chills	12%		

*Low grade, about 88% developed during hospitalization
Some patients also reported of anosmia and dysgeusia

TABLE 2 Laboratory parameters in critically ill/severe cases

Increase in:	
Ferritin	>500 ug/L (normal: females 10-200 ug/L; males 30–300 ug/L)
CRP	>100 mg/L (normal: <8.0 mg/L)
D-dimer	>1000 ng/mL (normal: <500 ng/mL)
CPK	>2× ULN (normal range: 40–150 units/L)
Troponin	>2× ULN (normal: females 0–9 ng/L; males 0–14 ng/L)
LDH	>245 units/L (normal range: 110–210 units/L)
Decrease in:	
Absolute lymphocyte count	<800/uL (normal: 1800–7700/uL)

BOX 1 Risk factors for severe disease

- Age >65 years
- History of hypertension
- History of cardiovascular disease
- Diabetes mellitus
- Obesity (BMI ≥30)
- Biologics (eg, TNF inhibitors, interleukin inhibitors, anti-B cell agents)
- History of immunosuppression (e.g., Transplant)
- CD4 cell count <200 cells/microL (e.g., HIV)

BOX 2 List of Aerosol generating procedures

- Open suctioning of airway
- Sputum induction
- Tracheal intubation
- Noninvasive ventilation
- Tracheostomy
- Cardiopulmonary resuscitation
- Manual ventilation before intubation
- Bronchoscopy

this route is still unclear. Airborne precautions are recommended when high-risk aerosol-generating procedures are in place **(Box 2)**.

SARS-CoV-2 has been detected in other specimens as well, including stool, tear film, blood, semen. However, the role of these sites in the transmission is still not known. No feco-oral transmission has been detected as of yet.

Period of Infectivity

It can be transmitted 2–3 days before the onset of symptoms and then throughout the disease. Maximum transmission has been reported in the first 7 days. Infectivity peaks 1 day before the onset of symptoms.[3]

Environmental Contamination

If susceptible individuals come in contact with contaminated surfaces, then it serves as a potential source of contamination. The survival time of viral particles has been demonstrated to be different on different surfaces.

Diagnosis

Given the high transmission and prevalence of COVID-19, an efficacious strategy for quick diagnosis and prompt response is the need of the hour. An overview of the strategies is discussed below.

Whom to Test

In this time of the pandemic, a high clinical suspicion of the COVID-19 case is necessary. It should be suspected in any patient with new symptoms. ICMR has prioritized a certain group of symptomatic individuals to be tested and apart from this, testing of asymptomatic cases may be advocated in special circumstances **(Table 3)**.[4,5]

TABLE 3 Individuals to be tested

Symptomatic	*Asymptomatic*
• International travel in the last 14 days • Contacts of laboratory-confirmed cases • Health care workers involved in management of C0VID-19 • All patients of Severe Acute Respiratory Infection (SARI) • All symptomatic Influenza-Like-Illness (ILI) • All hospitalized patients who develop ILI symptoms • All symptomatic ILI migrants within 7 days of onset of illness	• Involved in public health monitoring, screening or sentinel surveillance • Immunocompromised who are admitted to hospitals • Before any immunosuppressive procedures • Undergoing major surgeries • High-risk contacts of a confirmed case to be tested once between day 5 and day 10 of coming into contact • Undergoing an aerosol-generating procedure

Testing Methods

There are two main testing methods approved:

RT-PCR

It is a confirmatory test based on the detection of unique sequences of virus RNA by NAAT polymerase chain reaction (RT-PCR).[6] The gene targets tested are: spike (S), nucleocapsid (N), envelope (E), and RNA-dependent RNA polymerase (RdRp), and certain regions in the first open reading frame.[7,8]

Specimen: Upper respiratory tract samples are collected usually (most commonly from nasopharynx or oropharynx). Lower respiratory tract specimens have higher viral load but are reserved for patients with initial negative test on an upper respiratory tract specimen but high clinical suspicion.[5] The specificity of most of the RT-PCR tests is about 100%.[9] The yield from these specimens is variable **(Table 4)**.

Timing of testing: In nasopharyngeal specimens, viral load becomes detectable earliest by first day of symptom-onset and peaks within the first 7 days. This positivity starts to decline by week 3 and subsequently becomes undetectable.[10] A "positive" PCR result indicates only the detection of viral RNA and it does not necessarily indicate the presence of viable virus.[6] PCR positivity remains longer in sputum and stool may remain positive even after nasopharyngeal samples; however, it is not related to the clinical severity of the disease.[11]

Truenat testing: Recently ICMR approved Truenat for screening. It was originally developed for the detection of tuberculosis. It has advantages of giving results in 30–60 mins. All positive results are confirmed with RTPCR.[12]

TABLE 4 Detection of COVID-19 in different samples

Bronchoalveolar lavage	93%
Sputum	72%
Nasal Swab	63%
Fibrobronchoscope biopsy	46%
Pharyngeal Swab	32%
Feces	29%
Blood	1.0%

Antibody Testing

Antibody against COVID-19 is likely to be reactive in the first several days to weeks of infection, and thus may have less utility for diagnosis in the acute setting. It is used mainly for screening purposes and those who present late, beyond the first 2 weeks of illness onset.[13] There are no data regarding the specificity of these serological tests. Cross-reactivity is a potential concern, and IgM tests are prone to false-positive results.

In India, ICMR has advocated the use of rapid antibody testing in hotspot areas **(Flowchart 1)**.[14]

Management

Case Severity and Level of Care

In India, ICMR has advised classifying the cases based on their severity into three groups, and further, the management of each group has been planned at a different level of care known as COVID dedicated facilities **(Table 5)**.

Treatment of Cases

Most of the cases of COVID-19 are mild and only a small proportion of them are severe. The management is mainly

Flowchart 1: The use of rapid antibody testing

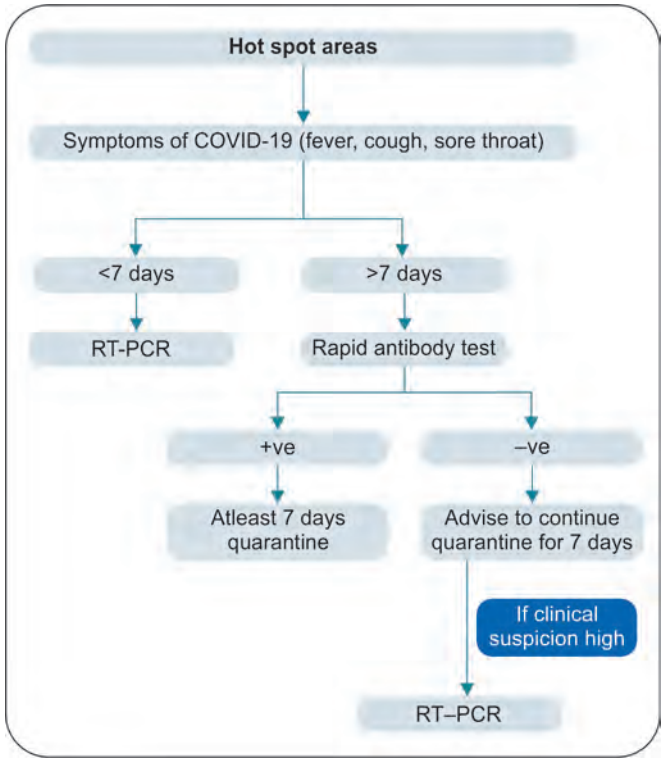

TABLE 5 Classification of cases and level of care

Severity of case	*Description*	*Level of care*
Mild and very mild case	All the cases presenting with fever and/or upper respiratory tract illness	COVID Care Centre (CCC)
Moderate case	All the cases who are confirmed to have pneumonia with **all** of the following: • Respiratory rate <30/min and/or SpO_2 >90% • Hemodynamically stable • <50% lung parenchymal involvement in X-ray	Dedicated COVID Health Centre (DCHC)
Severe case	All the cases with any of: • Respiratory rate >30/min and/or SpO_2 <90% • Acute respiratory distress syndrome (ARDS) • Septic Shock • >50% of lung parenchymal involvement in X-ray • Any other complication	Dedicated COVID Hospital (DCH)

symptomatic. The specific treatment consideration is as follows.[15]

Supplemental Oxygenation

Most of the severe cases require oxygenation. Oxygen can be given by nasal cannula or non-rebreathing mask. The target oxygen saturation is above 94%.[16]

The use of prone position can improve oxygenation. During prone positioning, there is relative recruitment of nondependent dorsal alveoli and because of a higher density of pulmonary vessels in the dorsal lung region, it results in improved $\dot{V}/\dot{Q}$ matching and oxygenation.[17]

Specific Pharmacotherapy

No specific drug therapy has been proven against COVID-19. Several therapies are being evaluated. Some of which are already clinically available for other indications. The potential treatment options in COVID-19 under consideration are given in **Table 6**.[15]

"Solidarity Trial" is an international clinical trial launched by the World Health Organization to find an effective treatment of COVID-19. It compares four treatment—chloroquine versus remdesivir versus lopinavir/ritonavir versus interferon beta 1a. Recently, India also became part of this trial.

Other Specific Issues

Hemodynamic stabilization: Patients with SARI with no evidence of shock should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation. If BP further falls, the use of inotropes and vasopressors should be considered.

Venous thromboembolism prophylaxis: COVID-19 is associated with profound inflammation and this can cause endothelial injury and subsequent thrombosis, a phenomenon also termed as thrombo-inflammation.[18] It is advised to use pharmacological (UFH, LMWH) in all hospitalized patients with d-dimer more than 1,000 ng/dL unless contraindicated.[26]

Steroid: The recent results from RECOVERY trial has shown remarkable improvements from low dose dexamethasone (6 mg/day), following which the use of same has been

TABLE 6 Specific pharmacotherapy against COVID-19 under consideration

Name	*Dose*	*Remark*
Chloroquine and Hydroxychloroquine (HCQS)	Chloroquine: 600 mg BD × 10 days *HCQS:* 400 mg BD on day 1 200 mg BD × 4 days	Inhibits endocytosis and blocks viral entry into cell HCQS is more effective than chloroquine[18] Latest studies have shown no benefit[19] Less in-hospital survival observed More chances of arrhythmia FDA has recommended against the use of this drug in COVID-19[20]
Azithromycin and HCQS	Azithromycin 500 mg OD × 5 days *HCQS:* 400 mg BD on day 1 200 mg BD × 4 days	The only drug approved by ICMR for severe cases A large multicentre cohort study observed no significant difference in in-hospital mortality[21] Both drugs associated with QTc prolongation and combined use may potentiate this. American College of Cardiology issued a warning and score-based approach to using these drugs[22]
Remdesivir	200 mg i.v on day 1 100 mg i.v × 10 days (for patients on mechanical ventilation) 100 mg i.v × 5 days (for other patients)	Nucleotide analogue which inhibits viral RNA dependent RNA polymerase Originally developed by company Gilead for EBOLA FDA has issued an approval for emergency use for hospitalized patients with severe disease[23] Not recommended in: • ALT >5x normal • eGFR <30 mL/min per 1.73 m^2 • Lactating or pregnant female • Children <12 years of age However, not available in the Indian market as of now
Lopinavir/Ritonavir	400 mg/100 mg BD × 14 days	Inhibits main viral protease Administration during early peak of viral replication has proven more efficacious[24] Drug-induced transaminitis is a major side effect. ICMR has approved off-label emergency use in:[25] • Severe patients • >60 years • With comorbidities
Convalescent Plasma	4 to 13 mL/kg (usually 200 mL single dose given slowly over not less than 2 hours)	Contains antibodies from the serum of patient who has recovered from COVID-19 Clinical trials undergoing (including in India) to prove efficacy May be considered in those who are not improving despite steroid therapy The early result showed an early time to recovery
Tocilizumab	8 mg/kg (up to a maximum of 800 mg per dose).	COVID-19 is characterized by a marked inflammatory response—the cytokine storm Markedly elevated inflammatory markers (e.g., D-dimer, ferritin) and elevated pro-inflammatory cytokines (including interleukin IL-6) are associated with poor outcome Studies from Wuhan showed clinical benefits and a decrease in C-reactive protein, D-dimer, and ferritin levels
Ivermectin + Doxycycline	Ivermectin – 200 ug/kg on day 1 Doxycycline- 200 mg stat on day 1 100 mg BD × 4 days	Both drugs inhibit viral replication and have proven efficacy in in-vitro studies Initial case reports from Bangladesh described promising results Clinical trials are undergoing to further evaluate the efficacy

recommended by all major societies including WHO and ICMR.

Use of ACE inhibitors: For patients already taking these drugs, it is advised to continue treatment, if there is no other reason for discontinuation.[27]

Critical Care and Other Complications

Acute respiratory distress syndrome (ARDS) and critical care: Among those who are critically ill, ARDS is the dominant finding. Age appears to be the major risk factor that predicts progression to ARDS.[28]

Oxygen target of 94% is preferred. Low flow via nasal cannula is appropriate (i.e., up to 6 L/min). Higher flows (up to 10–20 L/minute) may be administered using a simple face mask, venturi face mask, or non-rebreather mask. However, oxygenation at higher flow is associated with a higher risk of aerosolization.

Refractory hypoxemia is a major issue. Use of high-flow nasal cannula oxygen therapy (HFNO) or noninvasive ventilation (NIV) can be considered. No study is available regarding the comparative efficacy of the two.

The decision to intubate the patient against the risk of salvageability and risk of spread of infection is challenging. A low threshold for intubation in the following patients:

- Rapid progression over hours
- Lack of improvement on high flow oxygen >40 L/minute and FiO_2 >0.6
- Increasing work of breathing or tidal volume, worsening mental status or if developing hypercapnia
- Hemodynamic instability or multiorgan failure

However, given the high risk of aerosol generation, certain precautions must always be practiced **(Box 3)**.[29]

Septic shock: Sepsis, shock, and multiorgan failure occur but are less common than ARDS. The management of septic shock in COVID-19 is essentially in line with surviving sepsis guidelines.

Acute kidney injury (AKI) and dialysis: AKI among hospitalized patients with COVID-19 ranging from 5% to 23%. It usually manifests during the second week of infection.

Cardiac complications: The most common cardiac complications include myocardial injury leading to myocarditis, arrhythmia, and conduction system abnormalities, acute coronary syndromes, etc.

BOX 3 Precautions while intubating

- The most skilled person should perform the procedure
- Use of preoxygenation and rapid-sequence induction protocols
- An antiviral filter should be placed
- Use of video laryngoscopy
- ETCO2 measurement by continuous-wave capnography is the best method to confirm tracheal intubation

TABLE 7 Criteria for discharge

Mild/very mild/pre-symptomatic cases	• After 10 days from symptoms onset and afebrile for last 3 days • No need for repeat testing • Home isolation advised for further 7 days after discharge
Moderate cases	• After 10 days of symptoms onset and asymptomatic for last 3days • No need for repeat testing • Advised to follow home isolation for further 7days after discharge
Severe	• After clinical recovery, and • After the patient has been tested negative once by RT-PCR

Coagulopathy: Many studies have described hypercoagulability in COVID-19 and a low risk of bleeding in such patients.

Discharge of the Patients

In contrast to the initial "test-based strategy," the Govt. of India eventually shifted to "symptom-based strategy" or "time based strategy." The ICMR laboratory surveillance data also indicated that patients became negative after a mean duration of 10 days **(Table 7)**.

Prevention

Prevention is the best and the only proven strategy that can be adopted against COVID-19. Some of the preventive advises are enlisted in **Table 8**.

Future Perspective

Future of the COVID-19 management depends mainly on two pillars—discovery of an optimal drug and development of an efficacious vaccine. Many government agencies are funding researches in this field.

TABLE 8 Preventive measure against COVID-19

In healthcare setting	• For all patients/visitors: – Screening before entry – Universal use of masks • While dealing with suspect or confirm case: – Patient to be kept in a single occupancy room with a separate bathroom and no positive pressure. – Healthcare working entering the room should wear PPE comprising at least: ♦ Gowns and gloves ♦ Respirator or masks ♦ Eyes or face mask – Maintaining hand hygiene – Regularly Clean with sodium hypochlorite (for floor and surfaces) and 70% alcohol for metallic surfaces and doorknobs)
Personal preventive measures	• To practice social distancing • To maintain at least two meters distance • Proper hand washing • Respiratory hygiene (e.g., covering while coughing or sneezing) • Cleaning and disinfecting objects and surfaces

TABLE 9 Potential pharmacological therapies

Virus-based	
Main protease inhibitor	Lopinavir/ritonavir , Cinanserin, flavonoids
Papain-like protease(PL2pro) inhibitor	Disulfiram
RNA-dependent RNA polymerase inhibitor	Favipiravir, Ribavirin, Remdesivir, Galidesivir
Viral S spike protein inhibitor	Umifenovir
Viral Nucleic acid inhibitor	Mycophenolic acid
Other drugs	Loperamide
Host-based	
Viral endocytosis inhibitor	Chloroquine/Hydroxychloroquine
Host protease inhibitor	Camostat mesylate, Nafamostat
Inhibitor of viral nuclear transport	Ivermectin
Host immunity enhancer	Interferon alpha and interferon beta, Nitazoxanide
Host Matrix metalloproteinase(MMP) inhibitors	Tetracyclines (doxycycline, minocycline, etc.)
Immune-based	
Convalescent plasma	
IL-6 inhibitors	Sarilumab, Siltuximab, Tocilizumab
IL-1 inhibitors	Anakinra,
Anti CD6 monoclonal antibody	Itolizumab
JAK inhibitors	Baricitinib, Pacritinib Fedratinib, Ruxolitinib

Potential Pharmacological Therapies

Several treatments are being investigated for COVID-19. Some of these treatments are already available for other indications (repurposed drugs), while many new drugs are being developed specifically for COVID-19 **(Table 9)**.

Among the therapies mentioned in the table, the following are under trial in India:[30]

- Disulfiram
- Remdesivir
- Favipiravir
- Loperamide
- Convalescent plasma
- Tocilizumab (IL-6 inhibitor)
- Itolizumab
- Mycobacterium w

Potential Future Vaccines

Several vaccines are under development against COVID-19. As of May 2020, more than 150 vaccine candidates are under development.[31] The majority of these are in the preclinical or exploratory phase. Only a few have entered phase 1. Leading the race for a new vaccine, eight vaccine candidates have already entered human trials across the world **(Table 10)**.

In India, there are at least 30 attempts to develop an effective vaccine against the COVID-19 by six Indian companies.[32]

Recently, BCG vaccination has garnered a lot of interest. Studies have suggested that BCG immunization induces a non-specific immune response in the hosts that may have protective effects against non-mycobacterial, including viral, infections. However, more data is needed and this vaccine is under trial as of now.

TABLE 10 Vaccines

Name of vaccine	*Developing insitute*	*Country*	*Remark*
mRNA-1273	Moderna	US	Encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2
Adenovirus Type 5 Vector (Ad5-nCoV)	CanSino Biological Inc	China	Based on engineered replication-defective adenovirus type 5 vector to express the SARS-CoV-2 spike protein
ChAdOx1 nCoV-19	University of Oxford	UK	An engineered adenovirus-based vaccine to express the SARS-CoV-2 spike protein
PiCoVacc	Sinovac Biotech	China	Inactivated vaccine
Wuhan Institute of Biological Products Vaccine	Sinopharm	China	Inactivated vaccine
Beijing Institute of Biological Products	Sinopharm	China	Inactivated vaccine
INO-4800	Inovio Pharmaceuticals	US	DNA vaccine
BNT162 vaccine	Pfizer and BioNTech	Germany	mRNA-based vaccine to encode spike protein

Conclusion

The development of a vaccine or an efficacious drug is not reality as of now and seems to be a farfetched option. It is impossible to predict when the pandemic would be controlled. The new coronavirus might be here to stay. Moreover, it may take years to build up sufficient levels of immunity. Coronavirus is just another novel disease like HIV, which has not disappeared but measures have been developed by people to live by it. We need to learn to live with coronavirus and adjust ourselves to it.

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CHAPTER

10 Clinical Presentation and Systemic Manifestations of COVID-19 (Coronavirus Disease 2019)

Rajib Ratna Chaudhary, Sarda Mukund Shyam

Abstract

COVID-19 (Coronavirus Disease 2019) was reported in December, 2019, and the first case was reported in India on 30th January, 2020, in Kerala and declared pandemic on 11th March, 2020, by World Health Organization (WHO). SARS-CoV-2 virus is a single-stranded RNA virus and is the seventh member of the betacoronavirus family. SARS-CoV-2 virus is an airborne virus, spreads by an infected person on sneezing or coughing small droplets in the air so the person who inhales such droplets or touches the infected surfaces is infected. The incubation period of COVID-19 is 14 days and a median incubation period of 4–5 days (interquartile range 2–7 days). The clinical presentations of COVID-19 are cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia or ageusia. COVID-19 diagnosis is based on clinical features and to be confirmed by RT-PCR of nasopharyngeal or oropharyngeal swabs. Management of COVID-19 depends on the severity of disease; with mild disease by home isolation and moderate or severe disease, patients are hospitalized and supportive treatment given. Frequent hand washing with soap and water, face mask, social distancing, testing, and self isolation are important for prevention of COVID-19 until the vaccine becomes available.

Introduction

COVID-19 (Coronavirus Disease 2019) was reported in December 2019 and the first case was reported in India on 30th January, 2020, in Kerala. COVID-19 was declared pandemic on 11th March, 2020, due to its rapid spread in the world by World Health Organization (WHO).[1] India has now more than 88,72,203 infected cases, 4,43,794 active cases with more than 1,32,162 COVID-19 related death (20th November, 2020, MoHF, India).

The common symptoms of COVID-19 in mild cases are fever and cough, in moderate cases, shortness of breath, and in severe cases, the infection can cause pneumonia, multiorgan inflammatory failure, and death.

Frequent handwashing with soap and water, face mask, social distancing, and self-isolation are important for prevention of COVID-19 until the vaccine becomes available.

Transmission

SARS-CoV-2 virus is an airborne virus, spreads by an infected person on sneezing or coughing small droplets in the air so the person who inhales such droplets or touches the infected surfaces is infected.[2]

The transmission is high at the onset of symptom due to high quantity of viral shedding and low over the course of 7–10 days.

SARS-CoV-2 virus has been detected in the stool of COVID-19 patients and consumption of virus-contaminated food may cause infection and transmission is yet not confirmed.[3]

SARS-CoV-2 virus has also been found in semen, but sexual transmission is not yet confirmed.

Pathogenesis

SARS-CoV-2 virus is a single-stranded RNA virus and is the seventh member of the betacoronavirus family, subfamily orthocoronavirinae and sarbecovirus subgenus.

SARS-CoV-2 virus was isolated from epithelial cells of the human airway and its genome consists of ten open reading frames (ORFs), and consists of four structural proteins, that is, S (spike), E (envelope), M (membrane), and N (nucleocapsid) protein to make complete virus particle. SARS-CoV-2 virus virion is about 70–90 nm in size.[4]

SARS-CoV-2 virus enters the host target cell receptor, angiotensin-converting enzyme 2 (ACE2) by attaching with the S protein, which is expressed on alveolar epithelial cells type II (AECII), and on other tissues such as endothelium, heart, kidney, and intestine.[5]

SARS-CoV-2 virus has demonstrated novel glycosylation sites in the spike glycoprotein and the virus may utilize different glycosylation sites to interact with its receptors.[6]

The pathogenesis associated with hypercoagulability is not clear, but hypoxia and systemic inflammation may activate coagulation pathway due to high levels of inflammatory cytokines in COVID-19.

SARS-CoV-2 virus after entry in human system moves through replicative stage due to direct cytopathic effect and presents with mild symptoms and is followed by a stage of adaptive immunity in which virus level decreases as the immune system takes over and after that there will be sudden clinical deterioration in a stable patient due to tissue destruction because of inflammatory cytokine strom.[7,8]

Clinical Presentation and Systemic Manifestations

The incubation period of COVID-19 is 14 days and a median incubation period of 4–5 days (interquartile range 2–7 days).[9] COVID-19 patients reported symptoms in one study within 11.5 days of infection.[10]

Asymptomatic infection was reported in 50% of the Diamond Princess Cruise ship where out of the 619 people (17%) who were positive for SARS-CoV-2 virus.[11]

The most common presentation of COVID-19 is fever, headache, muscular pain, running nose, sore throat, breathlessness, tightness of chest, dry cough, hemoptysis, nausea/vomiting, and diarrhea. Loss of taste and smell precedes the onset of respiratory symptom.[9]

Delayed fever and respiratory symptoms may be atypical presentations in older adults and persons with medical comorbidities.

The systemic manifestations of COVID-19 are bilateral pneumonia (91.1%), which may progress to acute respiratory distress syndrome (ARDS) (3.4%), acute kidney injury (AKI) (0.5%), arrhythmias, heart failure, myocardial infarction, coagulopathy (0.1%), rhabdomyolysis, hyponatremia, acidosis, and septic shock (1.1%).[9]

Skin Manifestations

New onset pernio-like lesions of the feet and/or hands in the absence of any other clear cause (American Association Dermatology guidelines). They are usually asymmetrical.

Rashes of COVID-19 could be classified as:[12]

- Pseudo-chilblains (acral erythema with vesicles or pustules).[13] Pseudo-chilblains (COVID toes) occurs in warmer climate and presents with itching, burning, pain, and is more likely to ulcerate where a classic cold-induced chilblain is a benign and self-limited condition presenting with acral erythema of the toes and fingers with swelling.
- Vesicular (chicken pox-like) eruptions occur in middle-aged adults, which typically lasted for 10 days.
- Maculopapular eruptions are perifollicular in distribution and varying degrees of scaling. Some were described as like pityriasis rosea.
- Urticaria.
- Livedo or necrosis. Livedo and necrosis indicate severe illness and poor prognosis.

Ocular Manifestations

Nasal cavity and conjunctival sac are anatomically connected through nasolacrimal duct and most of the respiratory organism harbor inside nasal mucosa, so the patient of COVID-19 may present with conjunctivitis and SARS-CoV-2 virus was detected in conjunctival secretions but was absent in those without conjunctivitis. Tears sample may be used for diagnosing COVID-19.[14]

Hypercoagulability in COVID-19[15,16]

Hypercoagulable state developed in some patients of COVID-19 and small and large vessels were at increased risk of developing thrombosis. The patients may develop mild thrombocytopenia, prolonged prothrombin time, elevated D-dimer levels, myocardial injury, large vessel strokes, microvascular thrombosis in toes and clotting of catheters.

The high risk of death was strongly associated with elevated D-dimer levels. The thrombotic complications were most frequently reported venous thrombosis and pulmonary embolism.

The major comorbidities associated with COVID-19 are hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, hepatitis B, chronic kidney disease, malignancy, and immunodeficiency, which increase the severity of illness.[9]

Severity of Illness

The illness may range from mild to moderate, severe, and critical.[17]

- Mild to moderate 81% (mild symptoms to mild pneumonia).
- Severe 14% (shortness of breath, hypoxia, or >50% lung involvement with pneumonia on imaging).
- Critical 5% (acute respiratory failure, septic shock, or multiorgan inflammatory failure).

Psychoneural Manifestations

Psychoneural manifestations can be broadly classified in four categories.

Among General Population

The general population may develop fear and helplessness, depressive disorders, somatic symptoms, and even suicidal tendency.[18]

Among Covid Patients

Quarantined people feel loneliness, depression, insomnia, may cause self-harm, suicidality, and survivors are prone to develop Post Traumatic Stress Disorder (PTSD).[19,20]

Among Relatives of Covid Patient and Close Contact

Family member and close contact of patient generally develop psychological problem as they are isolated and quarantined. The patient's family member feels shame, guilt, or stigmatized and may suffer from PTSD.

Among Healthcare Workers

Healthcare workers may develop physical exhaustion, sleep disturbances, and emotional disturbances.[21,22]

Diagnosis

COVID-19 diagnosis is based on clinical features and to be confirmed by RT-PCR of nasopharyngeal or oropharyngeal swabs.

The RNA of SARS-CoV-2 virus has also been found in stool and blood and may be a marker of severe illness.

The routine investigations demonstrated lymphopenia, neutrophilia, elevated serum aspartate aminotransferase and serum alanine aminotransferase level, elevated lactate dehydrogenase, high C-reactive protein (CRP), and high-ferritin levels, which may be associated with severity of illness.[9,23]

Lymphopenia and elevated D-dimer indicate high mortality. Procalcitonin was elevated among those admitted in the ICU, but the level was normal at the time of admission.[24] Potential immune dysregulation was associated with high levels of plasma inflammatory markers.[23,25]

The X-ray chest and HRCT thorax may demonstrate patchy consolidation, extensive exudative infiltrates, and bilateral peripheral ground-glass opacities (GGOs), but may not be remarkable in the early stage of the disease.

Differential Diagnosis

The differential diagnosis of COVID-19 is another viral pneumonia caused by adenovirus, influenza, human metapneumovirus, parainfluenza, respiratory syncytial virus (RSV), rhinovirus, and bacterial pneumonia.[24]

Treatment and Prevention

There are investigational treatments for COVID-19 and treatment data is limited on hydroxychloroquine, azithromycin, remdesivir, and favipiravir on the course of disease, severities of illness and hydroxychloroquine as prophylaxis in exposed people.[26]

Frequent handwashing with soap and water, face mask, social distancing, and self-isolation is important for prevention of COVID-19 until the vaccine becomes available.

Prognosis

The predictors of high mortality are age 80 years and above, hypertension, diabetes mellitus, ischemic heart disease, chronic obstructive pulmonary disease, malignancy, severe lymphopenia, and elevated level of D-dimer.

Conclusion

- SARS-CoV-2 virus is a single-stranded RNA virus and is the seventh member of the betacoronavirus family, subfamily orthocoronavirinae and subgenus sarbecovirus infecting humans and was isolated from the epithelial cells of human airway.
- The clinical presentations of COVID-19 are cough, fever, malaise, myalgias, gastrointestinal symptoms, and anosmia or ageusia.
- Diagnosis of COVID-19 is usually confirmed on detection of SARS-CoV-2 virus by RT-PCR testing of a nasopharyngeal and oropharyngeal swab.
- Management of COVID-19 depends on the severity of disease; with mild disease by home isolation and moderate or severe COVID-19 patients are hospitalized and supportive treatment given.
- There is investigational treatment available for COVID-19 and so critical patients may be referred for investigational treatment.
- Frequent handwashing with soap and water, face mask, social distancing, testing, and self-isolation is important for prevention of COVID-19 until the vaccine becomes available.

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CHAPTER

11

Post-Acute COVID-19 Syndrome

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Abstract

Symptoms of acute-COVID-19 illness can persist for more than a couple of weeks, wherein we refer the syndrome as "post-acute COVID-19 syndrome." It may encompass symptoms localized to a single organ system or multiple organ systems. Post-COVID-19 fatigue, body aches, cough, lung fibrosis, bronchiectasis, myocarditis, coronary ischemia, pulmonary thromboembolism, stroke, microvascular coagulopathy, Guillain-Barré syndrome, cognitive dysfunction, anosmia, ageusia, gastrointestinal upset, psychological distress, depression, sleep disturbances, secondary infections (bacterial and fungal), rash, and asymptomatic liver and/or pancreatic enzyme elevations have been observed. The persistence of symptoms can be witnessed irrespective of the initial severity of COVID-19 illness, though "post-acute COVID-19 syndrome" is commoner subsequent to moderate and severe COVID-19 illness, compared to mild COVID-19 illness; and is commoner in at-risk groups (diabetes, hypertension, obesity, heart disease, and pre-existing pulmonary disease). Persistence of symptoms post-COVID-19 has been reported to be variable and can last for up to 6 months. The exact management is yet not known, but rest, gradual resumption of activity, nutritious diet, and symptomatic management form the mainstay. Specific therapies like steroids, antifibrotic agents (pirfenidone or nintedanib) for pulmonary fibrosis, and anticoagulants for elevated D-dimer levels to prevent coronary and cerebrovascular ischemia and pulmonary thromboembolism (post-ARDS) are being investigated and their role may be discernible in the times to come.

Introduction

COVID-19 is an acute infective illness. It was declared a pandemic in March 2020. Although the world has witnessed pandemics earlier too, but COVID-19 was like none before and it shook human beings out of their comfort levels. Man is a social animal, but the lockdowns, social distancing, wearing face mask, and restrictions on travel and social gatherings disturbed the social fabric of mankind. Managing COVID-19 illness in hospitals and isolation centers, by health-care personnel in personal protective equipment (PPE) or by video or teleconsultation became the order of the day, and resulted in a paradigm shift for the patients, who were so used to the "healing touch" of doctors and nurses. COVID-19 proved to be an acute mental distress to the patients, and also to the family members and the health-care workers involved in imparting care to the ill.

The Genesis and the Pathophysiology

To the patients, COVID-19 was largely asymptomatic in 80–90% of the cases, but 5–15% did have moderate or severe illness. The classification in to mild, moderate, and severe illness was based upon the presence of pneumonia manifesting as tachypnea and hypoxia.[1] However, COVID-19 proved to be a respiratory illness, inhalation of droplet nuclei being the primary mode of spread, but with systemic manifestations.

As the pandemic unfolded, several systemic manifestations were observed:[2,3]

- High CRP levels and elevated interleukin-6 and serum ferritin indicated a severe inflammatory state.
- Elevated D-dimer levels pointed towards presence of intravascular thrombosis, and this was evident in lungs in post-mortem of COVID-19 patients, and also stroke and coronary ischemia were seen in convalescent COVID-19 patients.
- Elevated liver functions and pancreatic enzymes were witnessed during the acute phase.
- Anosmia and ageusia were also witnessed as atypical manifestations.
- Lung involvement showed diffuse peripheral ground-glass opacities mimicking an acute respiratory distress syndrome (ARDS) like picture.

Most viral illnesses cause a self-limiting acute illness; however, acute COVID-19 illness was associated with significant morbidity and mortality among symptomatic patients, and more importantly, a sizable proportion of these reported delayed recovery and persistent symptoms. Risk factor groups for COVID-19 severity and associated mortality included higher age (>50 years), presence of diabetes, hypertension, obesity and cardiovascular disease, premorbid lung diseases, apart from factors like smoking, alcohol, and patients on immunosuppressive medications or suffering from immune-mediated disorders or cancers. These risk group patients are more prone to moderate and severe COVID-19 illness, and also to greater mortality including sudden deaths. Complications of COVID-19 especially the ARDS with worsening of hypoxia and surge in inflammatory markers akin to the cytokine storm were usually witnessed early in the 2nd week of illness, that is, 8th to 10th day of symptomatic illness. However, the deterioration in the form of respiratory failure was witnessed comparatively earlier, that is, in the latter half of 1st week of illness, in the presence of comorbidities like heart disease and/or diabetes, especially if uncontrolled.

A unique feature of acute COVID-19 illness is being witnessed, with the persistence of symptoms beyond the initial phase of 2 weeks, and at times taking months to resolve.[4] These patients have been variably called as "long-haulers" or suffering from "post-acute COVID-19 illness," "post-COVID illness," "long-COVID." Delayed recovery and greater persistence of symptoms are witnessed primarily in moderate or severe COVID-19 patients, and in those who have any of the aforementioned risk factors for COVID-19. However, this long-COVID syndrome has also been witnessed in mild COVID-19 patients.

The exact pathophysiology of the persistence of symptoms is yet not known. It is possible that some manifestations could be due to direct viral injury, or alternatively due to the systemic inflammatory response generated by the virus. Persistent viremia due to weak or absent antibody response, relapse or reinfection, inflammatory and other immune reactions, deconditioning, and mental factors such as post-traumatic stress singly or together contribute to the post-COVID syndrome. Long-term respiratory, musculoskeletal, and neuropsychiatric sequelae have been described with other coronaviruses (SARS and MERS). Apart from viral infiltration and inflammation, microthrombi and downregulation of ACE-2 receptors may be involved in the pathophysiology of cardiopulmonary complications.[5]

The severe inflammatory reaction witnessed in acute COVID-19 illness can lead to a dysregulated innate immune response, ciliary dysfunction, cytokine storm, thrombo-inflammation, microvascular coagulation, and immune exhaustion. This can lead to post-COVID-19 sepsis and predisposition to secondary bacterial and fungal infections, more so in diabetic patients and critically ill patients, who have anyway been administered steroids, anti-interleukin therapies, CRRT/ECMO, prolonged hospital stays with indwelling catheters and emergency procedures, mechanical ventilation, and, at times, breaches in asepsis. Covid-19 associated pulmonary aspergillosis (CAPA) has been reported, and recently, invasive mucormycosis (rhino-orbito-cerebral and pulmonary) has also been brought to the attention of physicians managing COVID-19 and post-acute COVID-19 patients.[6] Tuberculosis has also seen a resurgence in patients afflicted with COVID-19,[7] especially in the post-COVID immunosuppression phase.

The frequency of post-COVID-19 syndrome could vary from as low as 10% to as high as 70%. The exact frequency is difficult to state, as majority of the infections could have passed being asymptomatic, and so the true denominator is not known to calculate the true prevalence.

Clinical Features

Our own experience has shown a spectrum of findings, and **Table 1** outlines the manifestations seen in post-

TABLE 1 Symptomatology of "post-acute COVID-19 syndrome"

• Post-COVID myalgias, arthralgias, or body aches
• Post-COVID fatigue
• Anosmia/ageusia
• Chronic cough, pulmonary fibrosis, bronchiectasis, and reduction in pulmonary functions
• Gastrointestinal upset
• Transaminitis
• Asymptomatic elevation of pancreatic enzymes
• Thromboembolic conditions, viz. stroke and myocardial infarction/ischemia
• Asymptomatic elevation of D-dimer
• Guillain-Barré syndrome
• Other neurological syndromes, viz. seizures, encephalitis, PRES, delirium, cognitive dysfunction including difficulty in concentration
• Myocarditis, pericarditis, dysrhythmias, and pulmonary thromboembolism
• Metabolic disruption such as poor control of diabetes
• Psychological distress
• Psychiatric morbidity—depression
• Sleep disturbances
• Weight loss and malnutrition, including sarcopenia in elderly
• Low-grade fever
• Skin rashes—vesicular, maculopapular, urticarial or chilblain-like lesions on the extremities (COVID toes)
• Secondary infections (secondary to viral-illness induced immunosuppression), viz. post-COVID sepsis and mucormycosis
• Residual renal dysfunction (secondary to acute kidney injury)

acute COVID-19 illness. Post-COVID fatigue with or without myalgias/arthralgias is the commonest persistent symptom seen in clinical practice, and is associated with decreased capacity to perform activities of daily living. Many patients of mild COVID-19, who joined back after the mandatory 14–17 day isolation period, were unable to do even 6-hour desk work, and had to be advised rest again. Likewise, few patients did have severe myalgias or arthralgias and headache requiring prescription of potent analgesics to obtain relief. Persistent cough was seen across all severities including mild cases, while persistent dyspnea was more frequently encountered in moderate and severe COVID-19 patients. There were a couple of mild cases past middle-age, who were discharged after the requisite isolation period, but died during sleep around 3rd or 4th week of symptom onset. COVID-19 has been associated with a severe inflammatory process, and sudden cardiac deaths probably due to myocardial infarction or dysrhythmias, triggered by the inflammatory processes in the coronaries/myocardium could be the plausible mechanism. Similarly, most patients lost weight, indicating that COVID-19 is a severe catabolic stress on the body. Inflammatory mediators have taken weeks to months to revert back to normal. Transaminitis, pancreatic enzyme elevations, and D-dimer elevation have persisted for as long as 8–12 weeks, even in mild to moderate cases. Further, atypical symptoms like ageusia and anosmia have also been noted to persist for months together, taking their own sweet time to resolve. Psychological stress and sleep disturbances have been witnessed in many patients, and psychiatric mood disorders may be attributed to the illness, delayed return of normal health, loss of job, and financial losses incurred. Several other associated neurological syndromes are coming to light like headache, loss of concentration, cognitive dysfunction, Guillain-Barré syndrome, posterior reversible encephalopathy syndrome, apart from increase in cases of stroke.[4,8-10]

In a 6-day outcomes assessment of COVID-19 patients in Michigan, USA,[11] 488 telephonic contacts could be established, of which 159 patients (32.6%) reported cardiopulmonary symptoms such as cough or dyspnea, 92 (18.8%) of these had new onset cough or worsening of pre-existing cough, while 65 (13.3%) had persistent loss of smell or taste. 58% patients telephonically contacted reported new or worsening difficulty in the conduct of activities of daily living. In the study cohort, 195 patients were employed before hospitalization, 78 (40%) could not return to work because of health issues or loss of jobs. 30 (25.6%) of the remaining 117 who returned to work, reported reduced work hours due to health issues. Out of the 488 surveyed, 238 (48.8%) reported emotional impact, with 28 (5.7%) seeking consultation from mental health practitioner.

In another study[12] among 150 noncritical COVID-19 patients, two-thirds of patients had some or the other symptom at day 60 of symptom onset. The proportion of patients who still had asthenia, dyspnea, and anosmia/ageusia at day 30 respectively was 49.3%, 36.7%, and 28% and on day 60 respectively was 40%, 30%, and 23%. In a

telephonic survey[13] among French patients conducted at 3 months, the most common persistent symptoms were—fatigue (55%), dyspnea (42%), memory loss (34%), sleep disorders (30.8%), and difficulty in concentration (28%). 30% of the active workers could not join back because of their health issues. In an Italian study[14] on 143 patients, 87% of patients had persistent symptoms at 60 days after onset of first COVID-19 symptom—32% had 1 or 2 symptoms, while 55% had 3 or more symptoms. Fatigue (53.1%) was the commonest symptom followed by dyspnea (43.4%), arthralgias (27.3%), and chest pain (21.7%), with 44.1% reporting a deterioration in the quality of life.

Investigations

It is general consensus that asymptomatic patients may need not be investigated. Blood tests need to be ordered appropriately for specific clinical conditions. Anemia may need to be ruled out in patients having dyspnea, apart from a chest X-ray/CT scan and an echocardiography. C-reactive protein and leucocyte counts may be elevated suggesting infection or ongoing inflammation. Concomitant fever, especially if moderate to high grade should prompt rethink of a concurrent infection. Elevated troponin may suggest myocarditis or ischemia and needs to be correlated with the clinical picture, while elevated natriuretic peptides may indicate heart failure. Although troponin and D-dimer tests may be falsely positive, but negative test results can remove the clinical uncertainty from the minds of treating physicians. Serial chest radiographs and CT scans of the thoraces can aid in picking up pulmonary lesions, but at times indicate disproportionately greater severity compared to what the clinical picture suggests. The exact role will only be clear over a period of time.

Prognosis

As already stated, more the number of risk factors present, longer may be the persistence of the symptoms, and more number of symptoms are likely to persist. However, how long will the symptoms persist is difficult to state at the present moment. Some manifestations like stroke and myocardial infarction or sudden cardiac death are catastrophic or considered the end-points, while Guillain-Barré syndrome may go either way depending upon the extent of progression and responsiveness to management strategies. COVID-19 ARDS survivors are at risk of long-term impairment of lung function. Serious interstitial lung disease is rare in patients who are not hypoxic, but it may be too early to comment upon the pulmonary involvement and spontaneous reversibility of fibrosis. However, the experience with influenza-associated pulmonary fibrosis and the previous coronavirus illnesses (SARS and MERS) indicates that residual damage at 1 or 2 years may not be that alarming.[4,15] What sequelae will post-acute COVID-19 syndrome leave behind are yet not known, but symptoms do improve over time, and presently symptoms have been documented to persist for as long as 6 months.

Management

It is evident from the manifestations of COVID-19 and the universality of persistent symptoms, which can be attributable to virtually all the organ systems, that COVID-19 is a systemic illness. There is no definitive management for COVID-19, apart from oxygen therapy, steroids and awake proning in moderate and severe COVID-19 patients. Therefore, to talk about management of the persistent symptoms, that is, post-COVID syndrome is still very difficult. Several drugs are being tested for specific system abnormalities, and there is no specific management.

It was observed that moderate/severe COVID-19 patients, especially those suffering from diabetes, heart disease, or morbid obesity, continued to remain oxygen dependent even after 3–4 weeks of symptom onset. These patients had to be discharged on bed rest and domiciliary oxygen. Home pulse oximetry can be helpful in monitoring these patients with post-COVID lung fibrosis, and rate of oxygen flow may be accordingly adjusted. Prolonged course of steroids and antifibrotic agents like pirfenidone and nintedanib are being tried to reverse lung fibrosis in COVID-19 patients where CT scan has showed fibrotic changes. Deep breathing exercises and steam inhalation help tackle persistent cough in convalescent patients, although cough mixtures (with antitussives) may be prescribed in irritating cough conditions.

Rest, gradual increase in activity and good nutrition including a balanced diet with adequate micronutrient supplementation holds the key to improving fatigue, weight loss, and helps in reversing the catabolic process associated with COVID-19 illness.

Analgesics (non-steroidal anti-inflammatory drugs and paracetamol) can help get rid of body aches, headache, arthralgia, myalgia, and low-grade fever. However, antidepressant medications like amitriptyline, fluoxetine, and duloxetine may be very helpful to overcome depression and the body pain in patients who have associated psychological distress too. Sedatives hypnotics may be used for inducing sleep. Patients with diabetes, obesity, hypertension, and coronary heart disease who have persistent D-dimer elevation can be prescribed aspirin or alternative anticoagulants, although the duration of therapy in these patients is not yet defined.

Psychotherapy and counseling can be very helpful in tiding over the psychosocial issues related to the post-COVID syndrome. Fungal infections may add to the burden of COVID-19 management and contribute to increased morbidity and mortality. Treatment involves antifungal agents, surgical debridement, control of associated comorbidities, and withdrawing of treatments, which contribute to immune suppression. Amphotericin B is the drug of choice for invasive mucormycosis, but posaconazole or isavuconazole may be used in patients with concomitant renal dysfunction.

Conclusion

Post-acute COVID-19 syndrome requires attention to detail, and treating physicians should actively seek for the varied symptom profile that may be witnessed and comprise this syndrome. Physicians managing COVID-19 and following up these patients post-discharge need to be very attentive and carefully seek symptoms, so as to outline this syndrome and its behavior over time. This will help to determine the progression of individual symptoms and their subsidence over what period of time will be unraveled. Further, management options as part of various clinical trials and also as part of observational studies will guide us to devise management protocols for post-acute COVID-19 syndrome.

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Section 2

Section Editor: **BB Thakur**

Hypertension

CHAPTER

12 Home Blood Pressure Measurement

BR Bansode

Abstract

Home blood pressure measurement (HBPM) is self-measurement of blood pressure. Because easy technique, accepted by majority of people and awareness of complication of hypertension patient get adhere to treatment of hypertension.

The International Society of Hypertension also recognized usefulness of HBPM in the management of hypertension. HBPM improves adherence to drug treatment. HBPM helps treating doctors to modify or reduced the doses of antihypertensive drugs.

Introduction

Hypertension is major cause of morbidity and mortality worldwide.[1,2] Accurate and reproducible of blood pressure measurement by reliable and authentic blood pressure devices is an important clinical skill, which every clinician should acquire it. The correct diagnosis of hypertension is based on proper measurement of blood pressure **(Fig. 1)**. The complication of raised blood pressure if someone aware than he will be more adherence to the treatment of hypertension, and further hypertension management is easy and can avoid, delay the complication of hypertension.

Since 1960, the pioneering work by George Pickering and Maurice Sokolow, the several techniques developed to the measure blood pressure like clinic/office BP, 24-hr ambulatory blood pressure (ABPM), and home blood pressure. Out of these, home blood pressure is gaining important method because of easy technique, self-monitoring blood pressure, wider acceptance, and availability of HBPM devices also increasing awareness of importance of regular blood pressure monitoring and early recognition of morbidity due to hypertension **(Fig. 2)**

Why we should Know about Hypertension?

Hypertension is silent killer often patients are asymptomatic and when symptomatic it may be too late to revert the progress of disease process. Increased blood pressure may be leading cause of death globally.

Most guidelines recommended that when person's SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg then the condition termed as hypertension.

American College of Cardiology (ACC) and American Heart Association (AHA) recently gave guidelines[3] that when SBP > 120 mm Hg and DBP > 80 mm Hg have hypertension. White coat hypertension-office blood pressure more than home blood pressure. Mask hypertension when office or clinical blood pressure is normal and home blood pressure is more (10–15%).

Patients with hypertension are often asymptomatic and disease progress so much that complications slowly and silently develop like stroke, heart failure, CAD, and sudden death. Hence, every effort should be made to protect people at large by creating awareness of hypertension, educating them, train them in taking home blood pressure measurement (HBPM), aware them classification, and complication of hypertension.

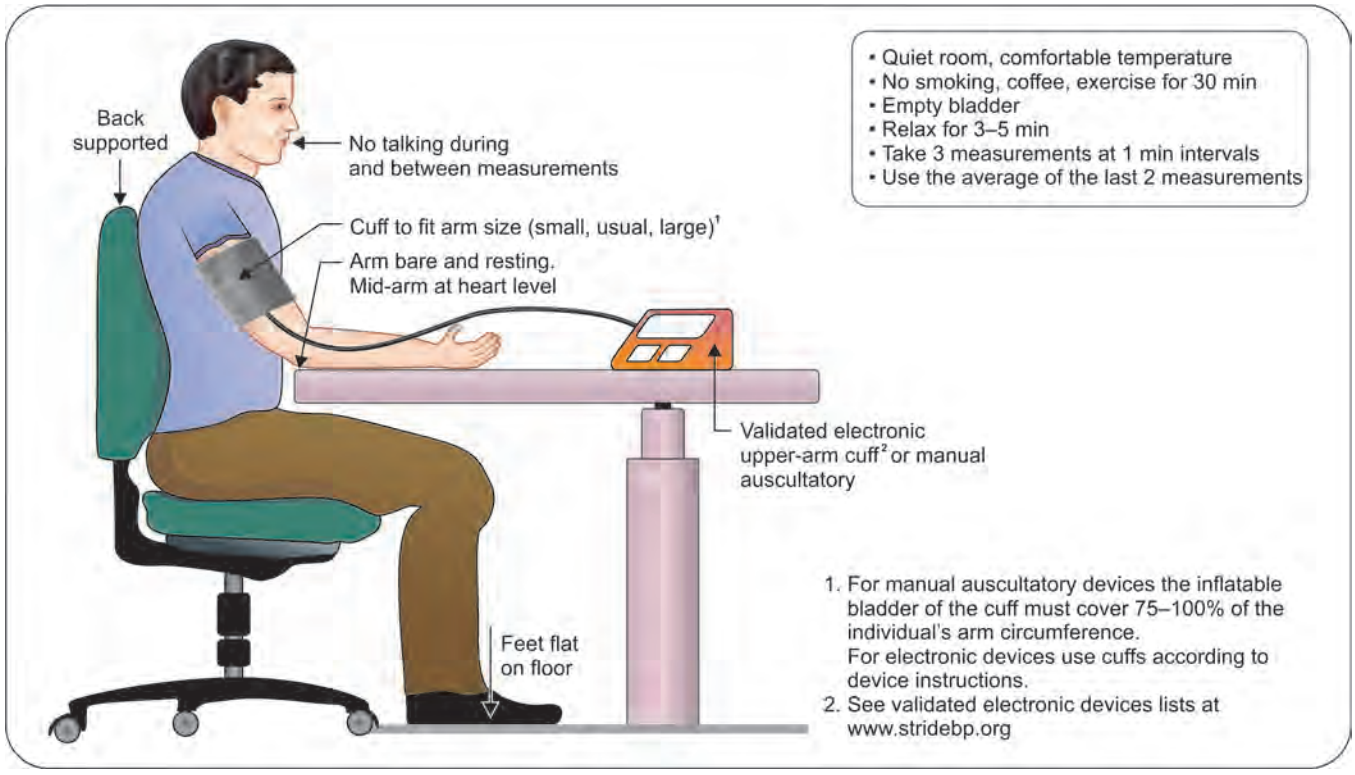

Fig. 1: Technique blood pressure measuring at home

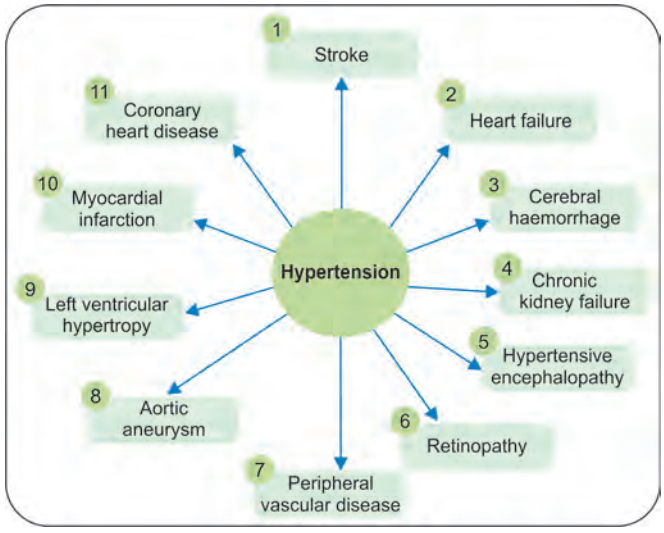

Fig. 2: Vascular complications of hypertension

Hypertension is major cause of morbidity and mortality globally account for 10.4 million death/year **(Fig. 3)**. There for (KSH) International Society of Hypertension has develop worldwide practice guidelines for clinician in 2020 for uniform and better management of hypertension in adult age 18 years and above.[4,5] There is clear shift of trend of hypertension from high income group to low income group[6,7] due to education, awareness improved living conditions, and following lifestyle measurement.

These large disparities in regional load of hypertension is due to low level of awareness, non-adherent to treatment and low control rates of hypertension in these groups. Therefore, the International Society of Hypertension launched the global campaign to increase awareness of hypertension mainly the May measurement month initiatives along with Hypertension Society India, Association of Physicians of India, and other hypertension societies took several initiative like lifestyle modification, home blood pressure monitoring, and meditation to reduce mental stress level and regular follow-up with appropriate lab investigation to treating physicians.

To describe hypertension and its complication and management is beyond the scope of this topic; therefore, we restrict our self to "Home Blood Pressure Measurement", that is, how to measure blood pressure, what is proper technique, how to create awareness of hypertension in

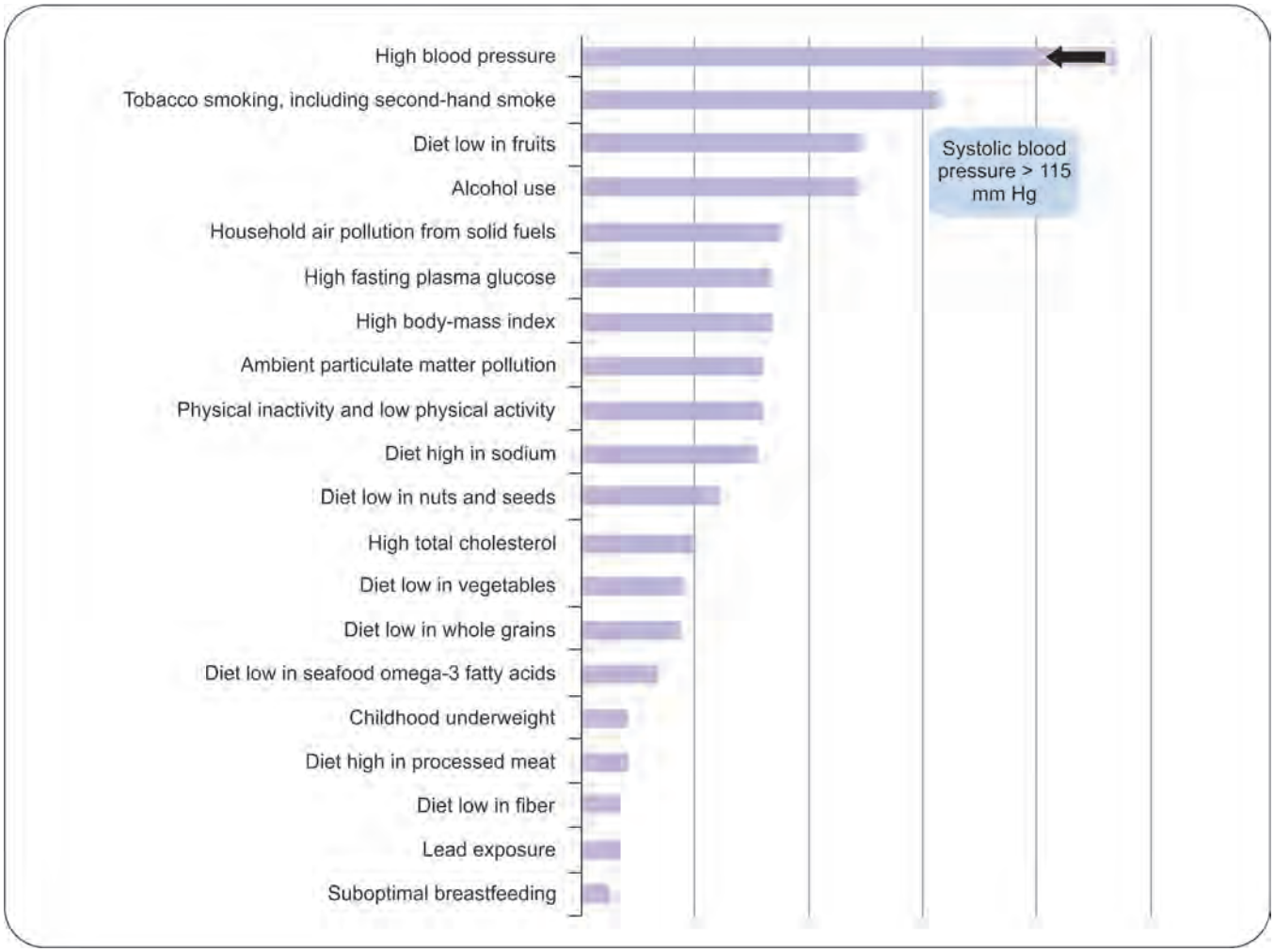

Fig. 3: Global leading risk for death

masses and high-risk populations, how the standard method should be applied for measuring blood pressure. The good equipment, appropriate blood pressure cuff and proper training of personnel are very important. Lastly, compare these HBPMs with other standard method like ambulatory blood pressure measurement. These devices should be calibrated regularly with mercury sphygmomanometer once in 6 months or 1 year.

The measurement of blood pressure is the clinical procedure of greatest important that is performed in the sloppiest manner (Norman Kaplan). Equipment for HBPM—the fully automatic with big screen should be used, brachial artery (arm) should be used for blood pressure measurement. Wrist or other Oscillometric devices may not work well with patient in atrial fibrillation.

Types of Blood Pressure Measurement

- Home blood pressure measurement
- Average blood pressure measurement
- White coat hypertension
- Mask hypertension

In some patient's non adherent to treatment, hypertension and diabetes mellitus, anxiety prone patients s/s hypotension, smoker, obese, hypercholesterolemia and non-dipper the ambulatory blood pressure measurement is more useful than HBPM.

High blood pressure is single major cause of death globally accept 10.4 million death/year.

In 2010 the estimated figure was 1.39 billion had high blood pressure.

In recent year raised blood pressure (hypertension) clearly shift from high income group to low income group[8,9]

- Checking blood pressure yourself at home is the first important step in managemet of hypertension which raised your confidence for correct diagnosis of hypertension.
- It is low cost, easy acceptance of techniques, and reproducible.
- Home blood pressure monitoring is more closely related to office blood pressure which induces target organ damage and better predictor of CV events.
- It detects mark hypertension, white coat hypertension.
- It improves adherence to antihypertensive therapy.
- It improves closing of antihypertensive drugs.

Guidelines for Home Blood Pressure Measurement

- Checking blood pressure yourself at home is the first important step in management of home blood pressure, which will help to raised your confidence, awareness, and help to consult your treating doctor early.
- Thirty minutes before taking home blood pressure avoid Tea, Coffee, Smoking, Tobacco, Alcohol Food, Physical exercise, and Medication.
- Sit 5 minutes in upright chair quietly with feet flat on floor before measuring blood pressure.

Once you know correct technique and choose proper device, it is early help you and your physician to control hypertension reduce cost and visit to clinical for measuring blood pressure.

Blood pressure reading should be taken twice daily. Two reading should be taken with a gap of 3–5 minutes. In irregular heart rate HBPM may not give correct Blood pressure measurement other method (tentative) or blood pressure true should be used for getting current blood pressure reading.

HBPM improve the patient's compliance adherence to treatment helps in preventing complications of hypertension.

In some patients non-adherence to treatment, hypertension, and diabetes mellitus anxiety prone patients e/o hypertensive s/s, smoker, abase, hypercholesterolemia and non-dipper average blood pressure measurement is more useful than HBPM.

What is the Value of Home Blood Pressure Monitoring?

It is inexpensive to monitor blood pressure of home, especially before and after changing the therapy. It is more accurate than office blood pressure monitoring. It helps to confirm the smooth control of blood pressure with therapy. It correlates more closely with ambulatory blood pressure monitoring than clinical blood pressure measurement. It helps to confirm diagnosis of hypertension in untreated patient.

Five prospective studies have compared home blood pressure monitoring, office blood pressure monitoring for predicting CVS outcome. All studies have found that home blood pressure monitor is significant predictor of CVS outcome, than office blood pressure monitoring. Home blood pressure monitor product is better TOD than office blood pressure monitoring. Home blood pressure monitoring is reproducible, it differentiate between White coat, sustained hypertension, and detect mask hypertension.

In older people where blood pressure variably is high and WCH is common and in DM, CKD blood pressure control is very important to reduce complication of hypertension home blood pressure monitoring is very helpful.

Home blood pressure is also helpful in pregnancy for early detection of pre-eclampsia, in CKD blood pressure fluctuation is very high; in patients with hpertension for early detection and diagnosis home blood pressure is helpful.

Despite of advances made in treatment of hypertension over last 60 years. There is still room for improvement in the management of hypertension.

Home blood pressure readings are very often lower than office blood pressure readings, that is, <135/85, or <130/80 mm Hg in high risk group.

Indications for ABPM

- Suspected White coat hypertension
- Suspected masked hypertension (normal clinic blood pressure and elevated ABPM)
- Suspected nocturnal hypertension or non-dippers
- Suspected episodic hypertension (e.g., pheochromocytoma)
- Resistant hypertension

- Titrating antihypertensive therapy
- Hypotensive symptoms while taking antihypertensive medications
- Autonomic dysfunction
- Hypertension detected early in pregnancy
- Suspected or confirmed sleep apnea

ABPM:

- Can be expensive
- Should be comfortable for patient to wear (light and quiet)
- Use of correct cuff size
- Need to be familiar with equipment
- Time to instruct patient, full explanation to patient of what is required
- Requires patient cooperation in order to obtain as many readings as possible
- Twenty-four-hour blood pressure correlates most closely with TOD (compared to clinic or casual blood pressure)
- Higher incidence of cardiovascular events when blood pressure remains elevated at night (non-dippers)
- Blood pressure variability is an independent determinant of TOD
- Highest incidence of cardiovascular events occurs in morning hours

The upper limit of normal for home blood pressure monitoring is 135/89 mm Hg. It corresponded to 140/90 mm Hg.

Equipment:

- Fully automated monitors that use the *Brachial Artery (Arm)* for measurements are the most reliable
- Wrist monitors are not recommended
- Proper documentation of reading by patient/automated by machine—*Date, Time,* and *blood pressure*
- Oscillometric devices may not work well with patients who have atrial fibrillation or other arrhythmias
- Patients HBP monitoring device should be calibrated against mercury sphygmomanometer every 6–12 months

Equipment cuff size: See **Table 1**.

Benefits:

- HBPM is easy to use, more reproducible, more accurate, and has higher prediction of target organ damage than clinic blood pressure (Class IIa LOE B)

TABLE 1 Equipment cuff size

Cuff name	*Bladder width*	*Bladder length*	*Mid arm circumference*
Small arm	10	24	22 to <27 cm
Average arm	13	30	27 to <33 cm
Large arm	16	38	33 to <41 cm
Extra large	17	43	41 to <52 cm

- Differentiates between White coat HT and Sustained HT
- In patients with prehypertension, detects masked HT
- Used to determine response to treatment
- Improves adherence (patients who use HBPM are more likely to take medications regularly)
- Improves quality of treatment and reducing the cost

Benefits in special subsets:

- Elderly: Blood pressure variability tends to be high, and White coat hypertension is common.
- Diabetics: Tight blood pressure control is important and home monitoring may help achieve this.
- Pregnancy: The early detection of pre-eclampsia might be facilitated by HBPM.
- Chronic kidney disease: Blood pressure may fluctuate a lot and home monitors help with management.
- Children: White coat hypertension occurs in children, and there are some data on normal home blood pressure levels at different ages.

Support for Home Blood Pressure Measurement

- Measurements taken by patients at home are often lower than readings taken in the office and closer to the average blood pressure recorded by 24-hour ambulatory monitors.
- Home blood pressure reading predicts risk better than office blood pressure
- In a 2005 Gallop poll:
  - 35% of hypertensive patients now check their blood pressure at least once per week.
  - 86% of patients who had been advised to purchase a blood pressure monitor had done so.
  - 55% of patients were monitoring their blood pressure an increase of 17% from 2000.

Conclusion

- Home blood pressure monitoring is very important for controlling the hypertension in masses. Therefore, the education of masses and training of taking home blood pressure to individual are also essential. The treating physician is also getting help for changing therapy for hypertension.
- ABPM can be regarded as the gold standard for the prediction of risk related to blood pressure.
- ABPM predicts clinical outcome better than clinic blood-pressure measurements.
- It is recommended that HBPM should become a Routine Component of blood pressure measurement in the majority of patients with known or suspected hypertension.
- HBPM has minimal cost, enhances self-confidence and compliance.
- HBPM can *improve blood pressure control.*
- HBPM *Correlates More Closely* with the results of Ambulatory blood pressure monitoring than clinic blood pressure.
- HBPM is more *Predictive of Adverse Outcomes* [e.g., stroke, end-stage renal disease (ESRD)] than clinic blood pressure.

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CHAPTER

13 Orthostatic Hypotension

Priti Gupta, Ankur Gupta, Sunita Aggarwal, Bhawna Mastebhakti, Pritam Gupta

Abstract

Orthostatic hypotension (OH) is an important but underrecognized entity. It is associated with an increased risk of cardiovascular diseases, and contributes to recurrent falls, syncope, and mortality, more so in the elderly population. A fall of 20 mm Hg or more in systolic blood pressure and/or 10 mm Hg or more in diastolic blood pressure is termed as Orthostatic hypotension. It can be a sign of autonomic dysfunction (neurogenic OH) or intravascular volume depletion (non-neurogenic OH). Orthostatic hypotension may also be classified in to initial, classic, and delayed. Diagnosis of OH can be made using the bedside standing test, head-up tilt table test, and the 24-hour ambulatory blood pressure measurements. Management of OH can be difficult, and constitutes both pharmacologic (midodrine, droxidopa, and fludrocortisone) and non-pharmacologic measures.

Introduction

Orthostatic hypotension (OH) or postural hypotension is an important, though an underrecognized entity in clinical practice. Its importance is evident because of its association with increased risk of cardiovascular diseases, recurrent falls, syncope, and mortality. Besides, it is also associated with prothrombotic state, chronic kidney disease, fragility fractures, and cognitive decline. However, in the SPRINT trial, OH was not found to be associated with a higher risk of CVD events, falls, or syncope.

A recent meta-analysis demonstrates that OH affects nearly one in five older persons living in the community, and almost one in four persons living in long-term residential care facilities. It is common in patients with diabetes, affecting an estimated 30% of individuals with type 1 diabetes and 25–30% of individuals with type 2 diabetes. In the in-patient setting, prevalence as high as 64% can be observed.

Definition of OH

It is defined as a fall of at least 20 mm Hg in systolic blood pressure (BP) and/or of at least 10 mm Hg in diastolic BP within 3 minutes of active standing or head-up tilt table testing (HUTT) at an angle of at least 60°. However, this traditional definition of OH is recommended for normotensive persons. In hypertensive individuals, a reduction in systolic BP of 30 mm Hg is required to define OH. In addition, European Society of Cardiology proposed an additional criterion for OH: a fall in systolic BP to <90 mm Hg irrespective of magnitude of the BP drop.

Clinical Features

The inability to tolerate the upright posture because of signs and symptoms, which are relieved by recumbency is termed orthostatic intolerance (OI). OI generally results from either ineffective regulatory mechanisms or environmental conditions that exceed the ability of these

homeostatic mechanisms to compensate appropriately for the environmental stress. The clinical manifestations can be:

- Light-headedness or woozy sensation
- Visual (blurring/dimming) and hearing difficulties
- Syncope/presyncope
- Deficits in memory, reasoning, information-processing speed, and concentration
- Fatigue
- Headache
- Tremulousness
- Sweating
- Weakness
- Neck cramping or "coat-hanger headache," due to hypoperfusion of the trapezius and shoulder girdle muscles
- Nausea and chest/abdominal pain
- Exercise intolerance

OH Classification

According to the period of occurrence, OH is classified as initial, classic, and delayed.

Initial OH is defined as a transient drop of >40 mm Hg in systolic BP and/or >20 mm Hg in diastolic BP within 15 seconds of active standing. The proposed underlying pathophysiologic mechanism is a temporal and abrupt mismatch between cardiac output and total peripheral resistance. Initial OH is frequently symptomatic and a common cause of situational syncope, which may be underrecognized.

Classic OH is the most common and typical variant of OH. It is defined as a sustained decline in systolic and/or diastolic BP (according to the current criteria for OH) within 30–180 seconds of active standing or HUTT. Classic OH is caused by decreased total peripheral resistance and/or an excessive fall of cardiac output, such that compensatory vasoconstrictor mechanisms are not sufficient to restore postural BP decline.

Delayed OH is defined as a sustained fall in BP (according to the current criteria for classic OH) occurring after 3–45 minutes of active standing or HUTT. The possible pathophysiologic mechanisms of delayed OH include increased pooling in the lower body capacitance vessels and gradual impairment of compensatory mechanisms during prolonged orthostatic stress, resulting in slow progressive declines in venous return to the heart, cardiac output, and BP. Delayed OH is considered a mild form of classic OH and may progress to classic OH.

OH can also be classified based on underlying pathophysiological mechanisms as neurogenic or non-neurogenic.

Neurogenic OH is due to primary neurological disorders like Parkinson's disease, multisystem atrophy, pure autonomic failure, Lewy body dementia or secondary polyneuropathies like endocrine disorders (diabetes mellitus, adrenal insufficiency, and hypothyroidism), malignant diseases (amyloidosis, multiple myeloma, and paraneoplastic syndromes), autoimmune diseases (lupus, Sjogren's syndrome, rheumatoid arthritis, celiac disease, Guillain-Barré syndrome and multiple sclerosis), toxins (alcoholism, chemotherapy, and poisoning by industrial chemicals), nutritional deficiencies (vitamins B1, B6, B12, and E), infections (herpes zoster, human immunodeficiency virus), uremia, and cirrhosis.

The causes of *non-neurogenic OH* are aging, volume depletion (blood loss, dehydration), venous pooling (prolonged immobility, deconditioning, postprandial, exposure to hot and humid environment, varicose veins), cardiovascular disorders (hypertension, heart failure, cardiac arrhythmias, aortic stenosis, hypertrophic obstructive cardiomyopathy), renal failure, medications like diuretics, vasodilators (alpha-receptor blockers, calcium channel blockers, hydralazine, nitrates, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), central sympatholytics, beta-receptor blockers, psychotropic agents (antidepressants, tranquilizers, antipsychotics), and anti-Parkinsonian agents.

Diagnosis of OH

The clinician should have a high degree of suspicion and careful history should always be obtained. The three recommended methods to evaluate OH are explained below.

- *Schellong test or bedside standing test:* The test is named after Fritz Schellong, a European pioneer of cardiovascular autonomic neuroscience. Active standing-up from the supine position is the "gold standard" method for initial evaluation of OH. There is no universal standardized protocol for performing a standing test, although this usually consists of a supine phase of 5–10 minutes, followed by an active standing phase of at least 3 minutes, ideally 5–10 minutes.

Blood pressure and heart rate are measured at the end of the supine phase and at 1-minute intervals during the orthostatic challenge. If the patient is unable to stand up from the supine position, a sitting-to-standing protocol is acceptable, although less sensitive than the supine-to-standing one. A sustained decrease of at least 20 mm Hg in systolic blood pressure or at least 10 mm Hg in diastolic or an absolute systolic blood pressure below 90 mm Hg after 3 minutes standing qualifies for OH.

- *Head-up tilt table test (HUTT):* It is a specialized method which largely depends on an expert to interpret the findings. It is performed if bedside standing test is negative in presence of strong clinical suspicion of OH. Moreover, its methodology is not standardized, and it is a less sensitive test. Protocols for performing HUTT vary in the durations of the supine pre-tilt and the passive head-up tilt, the tilt angle, and the monitoring of hemodynamic parameters.
- *24-hour ambulatory blood pressure measurements (ABPM):* Diagnosis of OH by ABPM is based on diurnal variation of systolic and diastolic BP. Reduced dipping (night/day fall 10% in mean values of BP) and reverse dipping (night/day increase in average BP levels) are patterns of diurnal BP variation that associate strongly with OH. ABPM may be helpful for diagnosing masked OH (OH that is not detected in the office) and postprandial OH. In addition, ABPM is recommended for patients with established OH, for assessment of nocturnal hypertension, drug induced OH and OH severity, and for tailoring treatment and diagnosing of additional comorbidities such as obstructive sleep apnea.

Treatment

It consists of both pharmacological and non-pharmacological measures.

Non-pharmacologic Measures

Patient education is the cornerstone of the management of neurogenic OH. The provocative factors that might precipitate or exacerbate OH [e.g., warm ambient temperatures; hot baths or showers; straining, especially with breath holding (the Valsalva maneuver); sudden moves from the supine or seated position to the upright position; and ingestion of large meals] should be sought for. Physical activity and exercise should be encouraged to avoid deconditioning. Simple activities like leg-crossing; stooping; squatting; and tensing of the muscles of the legs, arms, abdomen, buttocks, or whole body reduce venous pooling and thereby increase central blood volume and cardiac filling, with resultant increases in cardiac output, BP, and cerebral perfusion. Additional non-pharmacologic measures include increased salt and water intake, slow rising, raising the head of the bed during sleeping, and the use of compression garments on the abdomen or lower extremities. Rapid ingestion of approximately 500 mL of tap water (e.g., over 3–4 minutes) elicits a marked press or response and improvement in symptoms in patients with neurogenic and non-neurogenic OH. In fact, acute water ingestion is the only class I recommended treatment for OH. All other measures (including pharmacologic treatment as well) have class II recommendations.

Pharmacologic Measures

Midodrine (class IIA): Patients with neurogenic OH report improvement in symptoms after taking midodrine. A dose-dependent effect is seen, usually corresponding to an increase in standing blood pressure. Though an important drug, several side effects may limit its use. Some of them are supine hypertension, scalp tingling, piloerection, and urinary retention. The dose usually used ranges from 5 to 10 mg per oral three times a day (the last dose at least 3 hours before bedtime).

Droxidopa(class IIA): It is mainly used for neurogenic OH that occurs in patients suffering from Parkinson's disease, pure autonomic failure, and multiple system atrophy. According to some small studies droxidopa might reduce falls. Concomitant use of carbidopa in patients with Parkinson's disease may decrease the effectiveness of droxidopa. Some side effects such as supine hypertension, headache, dizziness, and nausea may limit its use and titration. Usual dose is 100 mg per oral three times a day slowly increased to 600 mg three times a day over 3–7 days.

Fludrocortisone (class IIA): The improvement of symptoms of OH is primarily seen due to increases in plasma volume. If taken regularly, at least in astronauts after space flight, fludrocortisone may prevent OH. Since supine hypertension is a limiting factor for its use, other medications should be used before fludrocortisone. Commonly seen side effects

include edema, hypokalemia, and headache. Adrenal suppression and immunosuppression, which are serious side effects can also occur with doses >0.3 mg daily. The starting dose is 0.1 mg per oral daily, maximum being 0.3 mg daily.

Pyridostigmine (class IIB) and octreotide (Class IIB) may be beneficial in certain refractory cases.

Conclusion

OH is an important diagnosis, which is likely to be missed in day-to-day clinical practice. A high index of suspicion, with good history and evaluation, is helpful in confirming the diagnosis. Apart from patient education and other non-pharmacological strategies, acute water ingestion is the recommended Class I treatment. Certain medications (Class IIA) like midodrine, droxidopa, and fludrocortisone form the basis of adjunct therapies in managing OH.

Suggested Readings

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CHAPTER

14 Cooking Oil: Making the Right Choice

Rudrajit Paul, Shibendu Ghosh

Abstract

Edible oil is an essential component of daily Indian food. However, there are a lot of wrong notions about the relative health benefits of different cooking oils. In a culturally diverse country like India, people in different communities have been using different sources of vegetable oil for hundreds of years and it is very difficult to come to a consensus for 1.4 billion people. In this article, the authors have discussed the biochemistry of edible oils including smoke point, the Omega 3:6 ratio, presence of phytosterols and the merits and demerits of refining these oils. Without selecting any particular oil, the authors have tried to discuss the health benefits and risks of various types of vegetable oil with special emphasis on the PUFA and MUFA content, the importance of omega-3 fat and the presence of saturated fat. The scientific basis of health risks associated with saturated fat and trans-fat has also been touched upon. The authors have also discussed the harmful effects of the commonly used cooking medium, Vanaspati. Finally, the authors have also discussed in brief, the problem of edible oil adulteration in India. There is no one correct option when it comes to choosing cooking oil. Sometimes, mixing two oils or using particular varieties of oil on particular weekdays may be the answer.

Introduction

The daily diet in India usually has curries as an indispensable component. Boiled, grilled, or steamed food, although popular for occasional feasts, is not preferred as daily food in India and most Indians prefer cooked items.

But India is a land of diversity. There are many tribes of Northeast India who prefer boiled food. In their cuisine, there is often very little oil. We must be aware of this culinary tradition of our country too. Thus, generally, the cooking medium, viz. oil, is an integral component of quotidian Indian diet. This is one of the main sources of fat in Indian food.

However, there is almost no scientific study or rational discussion on this indispensable dietary element and most Indians get their half-baked ideas on cooking oil either from family tradition or from the so-called "diet experts" online. The void left by the lack of proper scientific discourse is filled by pseudoscientific gibberish or advertisement gimmicks released by the processed food industry. The Indian cuisine varies radically throughout the length and breadth of this incredibly diverse country and any discussion on the "Indian" diet must be aware of this diversity. Otherwise, making just one dietary recommendation for the entire country is likely to be eschewed by various cultural groups and will never be acceptable for all sections of the population. The authors of this article recognize this dietary multiplicity of the country and will shape their discussion in an inclusive manner.

The Indian Culinary Culture

First of all, the authors will describe the prevailing culinary culture of the country with reference to cooking oil. But

it must be remembered that the choice of cooking oil is shaped by a lot of factors like family tradition, education level, socioeconomic status, place of residence, and accessibility. The Indian media or movies have a harmful tendency of clubbing various cultures of this country together as "North India" or "South India". But clubbing such diverse cultures as Malayali, Konkani, or Tamil together under the broad heading of "South Indian culture" is like describing British, French, and Italian cultures together. In the southern part of the country, in Kerala, coconut oil is the most popular cooking oil. They would never think of using mustard oil. But in the eastern part of the country, in Bengal, mustard oil is the oil for popular fish or meat dishes.[1] Again, in Tamil Nadu, the state bordering Kerala and having a lot of cultural similarities, they prefer sunflower oil, groundnut, and sesame oil, but not coconut oil. If you go to Gujarat, you encounter sunflower oil and ghee for cooking. In Kerala or Tamil Nadu, mustard oil is used for pickles only, not for cooking. Similarly, in Bengal or Gujarat, coconut oil is used for applying on hair, not for preparation of food. Ghee is popular in Punjab, Haryana, and Madhya Pradesh for cooking. Groundnut oil is also used in Karnataka. In Goa, for the traditional dishes, they use coconut oil but for daily cooking, sunflower oil is preferred.

However, the cooking habit of urban Indians is radically changing with time. All across India, the upwardly mobile middle class is now shifting toward safflower oil, olive oil, rice bran oil, or soyabean oil. The earlier popularity of cottonseed oil or rapeseed oil is now dwindling. This is not specific to any culture and mainly reflects Western influence. Especially, the use of olive oil is seen as a status symbol by many Indians; but as subsequent discussions will show, this really does not have much health benefit to justify the cost. Over the last two decades, India has been importing millions of tons of palm oil as a cheap vegetable oil. This oil is used for making roadside food, biscuits, and many packaged food items. Millions of Indians are unknowingly consuming palm oil every day, although they don't buy it for their home. Vanaspati, hydrogenated vegetable oil, is used in many hotels or restaurants of India. This is mainly prepared by processing palm oil. *Thus, while discussing the cooking oil of Indians, not only the domestic food but also the outdoor food items must be discussed.*

The discussion below is designed to be a scientific discourse on the pros and cons of various cooking oils and is not intended to be judgmental on any culture.

Some Important Physical and Chemical Properties

If the reader wants to make an informed choice about his/her cooking oil, then some preliminary knowledge on the biochemistry of this product is needed.[2] Some important terms are discussed first.

Smoke Point

This is the temperature at which oil starts to emit smoke or starts to burn. If the smoke point is low, that oil will burn in the frying pan easily. This gives a bad smell, bad taste, and also can generate free radicals. Thus, if the reader wants to deep fry something, obviously oil with high smoke point will be needed. Otherwise, the oil will burn and the frying will be half-done. **Table 1** gives the smoke point of some commonly used cooking oils.

The authors would like to discuss two points on this table. Firstly, as seen here, butter is not a good frying medium. It has low smoke point and will burn easily. On the other hand, ghee has smoke point of 480°F. Thus, ghee can be used safely for frying. Secondly, the term "refined" is very important while discussing the smoke point.[2] Unrefined safflower oil has smoke point of 225°F, while refined one has smoke point of 510. Thus, the final smoke point is also dependent on the degree of refining of the oil. This is one of the advantages of refining oil, although the disadvantages of refining will be discussed later.

PUFA

These are organic acids with more than one double bond in their backbone. Many of them are essential in nutrition. These acids are further divided into Ω-3 and Ω-6 acids.

TABLE 1 Smoke point (in Fahrenheit) of some cooking oils

Oil/Fat	*Smoke point*
Mustard Oil	480
Butter	302
Coconut oil	450
Virgin olive oil	410
Refined safflower	510
Refined sunflower	450
Sesame oil	450

They will be described later. In high temperature cooking, the polyunsaturated fatty acids (PUFA) in cooking oil can degrade into hydroperoxide and other harmful products.

Some studies have found cardiovascular benefit with consumption of some varieties of PUFA, like the Ω-3 variety. This is thought to be due to the antiatherogenic effect of long chain Ω-3 PUFA.[3] Also, it raises HDL and lowers triglyceride in blood. The LDL particles in blood are also modified with alteration in their apolipoprotein levels, which make them less atherogenic. It is also thought that these varieties of PUFA may alter gene expression in the early stages of atherosclerosis.[3]

In the website of the American Heart Association, three oils are mentioned as good sources of PUFA: soybean oil, sunflower oil, corn oil. Of these, corn oil is not found in India till now. But in the future, it may be imported and sold here. Also, the AHA recommends nuts like Walnut and soybean as sources of good PUFA. *But there is a problem with PUFA-rich vegetable oils. During the process of refining, the PUFA in these oils may be oxidized, which may be harmful for the body.*[4]

MUFA

These are fatty acids that have only one double bond in their carbon skeleton. Some studies have shown decrease in blood LDL levels with monounsaturated fatty acids (MUFA) intake. But studies on diet are at best imperfect and it is often impossible to separate the relative benefits of each dietary component. The Mediterranean diet is rich in MUFA.[4] Some studies have found that high MUFA intake may be associated with decreased risk of malignancy, diabetes, and neurodegenerative diseases.

Food rich in MUFA: Olive, Avocado, Cashew nut, tea-oil, whole grain wheat.

Cholesterol

Cholesterol is a compound which is found only in animal sources of food. *Any plant product is expected to be free of cholesterol. Thus, the advertising gimmick of brandishing vegetable oil as "cholesterol-free" is basically a redundant message.* Rather, if vegetable oil was not cholesterol free, it would be abnormal and we would suspect contamination with some animal fat!!

Saturated Fat

Saturated fat is the type of lipid which contains no double bond in the carbon skeleton. Usually, these are solid at room temperature (although this is not universally true). Animal products like ghee are usually high in saturated fat. Saturated fat is considered to be bad for the vascular system. A Cochrane database review, published in May, 2020 found that cutting down on saturated fat led to a significant reduction in cardiovascular events.

Food high in saturated fat: butter, ghee, coconut oil (87%), palm oil (50%), sausage. All the commonly used vegetable oils contain very little saturated fat except rice bran oil, which has 25% saturated lipids.

Interesting fact: Ghee, constituted of 62% saturated fat, has a very long shelf life. That is why, in the Ayurvedic system of medicine, old Ghee was considered a valuable component. In India, two types of Ghee are in use: Cow and Buffalo products. Both are similar in fat content and only difference is the high carotene content in Cow milk Ghee.

Trans-fat[5]

A trans-fatty acid is an unsaturated fatty acid in trans-geometric configuration. Trans-fatty acids have no known metabolic function in human body. They increase LDL in blood. This is produced mainly as a result of hydrogenation of vegetable oil. In the USA, the government has issued a guideline that there is no safe limit of consumption of trans-fat. It is to be completely eliminated from diet. Studies have shown that the concentration of trans-fat in adipose tissues of individuals who died of IHD were 8–10% higher compared to others. *Studies in New York have shown that restriction of trans-fat in food industry led to significant reductions in the incidence of AMI and CVD mortality*. The effects of trans-fat are shown in **Figure 1**.

Common food with trans-fat: Margarine, butter, some cake products. In Indian context, trans-fat is mainly found in foods that are cooked with reused oil. *In roadside eateries of India, it is very common to find the same oil being used to fry a variety of products throughout the day. Constant reheating of oil produces trans-fat.* Vanaspati, hydrogenated vegetable oil, is used commonly in India as a cheap substitute of ghee. This product contains trans-fat and is harmful. *The reader of this article should be aware that Vanaspati is the commonest cooking medium in hotels and cafes and thus many Indians are unknowingly consuming the trans-fat of Vanaspati every day in canteens.* Deep fried commercial food also contains trans-fat. For large multinational food companies, the quality of food is improved by regulation. But in the small scale industries

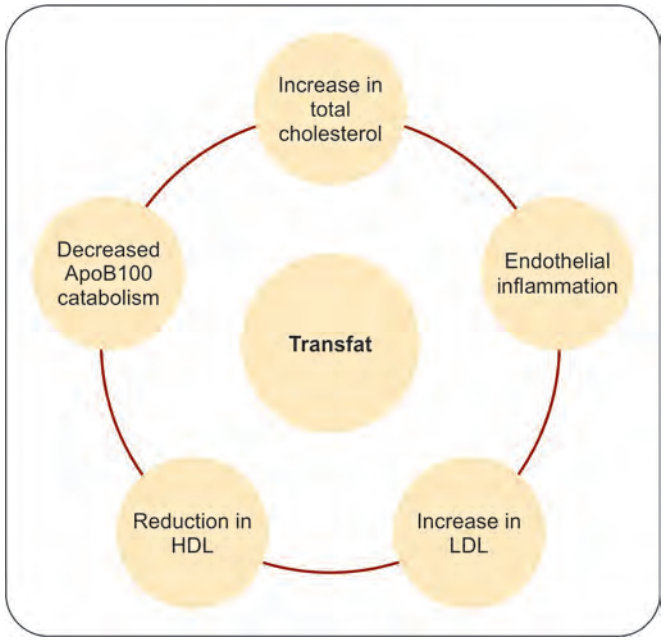

Fig. 1: The metabolic effects of trans-fat

in remote parts of the country, the quality of local food industry is largely unregulated and those items may have trans-fat.

Oryzanol

This is a product of rice bran. Thus, Oryzanol is available only in rice bran oil. This is sometimes marketed as a health supplement but benefits are doubtful. It may have some antioxidant action.

Ω-3 and Ω-6 Ratio

As discussed earlier, these are varieties of PUFA. A particular specimen of oil (any oil) contains various types of PUFA. The nomenclature is based on the position of the double bond in the carbon skeleton. For example, Ω-3 acids are those where the double bond is three atoms away from the terminal methyl group.

Ω-3 acids include DHA, EPA, and alpha linolenic acid (ALA). Common sources are flaxseed oil, hemp oil, fish oil, and eggs. Animal sources are the sole supplier of EPA and DHA, while plant sources supply ALA. ALA can be converted into the other forms. Thus, vegetarian diet is enough to get the required Ω-3 acids. *The enzymes required for conversion of ALA to other PUFA are δ6 desaturase and elongase in the liver endoplasmic reticulum.*

Ω-6 acids include linoleic acid, calendic acid, etc. Most of the vegetable oil contain Ω-6 acids.

Ω-9 acids include oleic acid, erucic acid. *These are MUFA, not PUFA like the two previous ones.* Sources include mustard, olive, and rapeseed.

The reader must not assume that one particular oil contains one type of PUFA or MUFA. Usually, it is a combination and the relative percentages vary with processing. For example, mustard oil contains 60% MUFA (erucic acid etc.), 21% PUFA (Ω-6 more than Ω-3), and the rest saturated fat.

Ω-3 fatty acids are considered to be better for our health. Oil like hemp oil is rich in this variety, but it is not popular for cooking due to low smoke point. So, some authors have suggested blending two or more varieties of oil to make a more nutritionally healthy mixture. This can also overcome the problem of low smoke point.

The main aim is to increase the proportion of Ω-3 acids in our diet. Some cooking oil with good Ω-3 content are: canola oil and ghee. Fish oil, like cod liver oil, contains excess Ω-3 fraction. But fish oil is not used for cooking in India. Fish oil, like cod liver oil, is also a rich source of vitamins A and D. *But in India, fish oil is not popular due to its smell and also due to vegetarian culture of many communities in the country.* Coconut oil does not contain any Ω-3 acid. Sunflower oil, the most popular oil in urban India, has very high Ω-6 to Ω-3 ratio. Ω-6 acids are proinflammatory and thus, may have adverse effects on the blood vessels. But they don't act in isolation. Other dietary factors are also responsible in tandem for the cardiovascular morbidities. Thus, it may be a suggestion to mix sunflower oil with some other oil like canola oil to improve Ω-3 content.

Tocotrienols

When oil is extracted from seeds, along with the lipids, some other compounds also get extracted. One of them is tocotrienols, a type of tocols (which also include tocopherols). It is mainly found in palm oil, rice bran oil, wheat germ oil and soybean oil. These are one of the most important antioxidants in vegetable oil. If a sample of oil is high in tocols, then the PUFA in that oil will resist oxidative damages. α-tocopherols are the major tocols in most oils like almond, olive or sunflower. In some varieties like soybean and canola oil, γ-Tocopherol is higher. Palm oil, although considered a cheap and inferior quality of edible

TABLE 2 Tocopherol content of some common edible oil

Oil	*Tocopherol (mg/100 g)*
Wheat germ oil	150–190
Sunflower	33–60
Safflower	37–50
Coconut	0.2–2

oil, contains high quantity of all types of tocopherols. The α-tocopherol content of some common oils that are given in **Table 2**.

Tocols have neuroprotective and anti-cancer properties and also prevents vascular changes in diabetes. However, during the refining process of vegetable oil and the deodorizing process, tocopherols are lost. The only exception being extra-virgin olive oil, which is prepared by a separate method without heat application. This retains the tocopherol content. Physical refining of oil reduces phenolic compounds more than chemical refining.

Phytosterol

Phytosterols are plant compounds which are analogous to animal cholesterol. It has beneficial effect on blood cholesterol and reduces LDL levels. It is a good antioxidant and may also be beneficial in reducing the incidence of cancers. During lipid extraction from plant seeds, phytosterols are also added to the oil.

Rich sources of phytosterol include corn oil (990 mg/100 g), rapeseed oil (893 mg/100 g) and sunflower oil (253 mg/100 g). Prolonged cooking and high temperature food processing reduces the phytosterol content in oil.

Carotenoids

These are another group of important compounds in edible oil. Cold-pressed oil is a better source of carotenoids than heat-extracted variety. Palm oil is a good source of carotenoids. There is a variety called red palm oil, which has particularly high carotene content. But it is costly due to its rarity. Carotenoids are good antioxidant and have a role in diet complementary to tocopherols.

In a recent study, it was found that only cold-pressed oils contain appreciable amount of carotenoids. The oils with higher carotene content are rapeseed oil, soybean oil and linseed oil.

Cold Pressing

Cold pressing is the process of extracting oil from plant seeds like olive by pressing at room temperature, without applying any extra heat. This prevents thermal degradation of phenolic and other useful compounds. However, the yield of oil is less and thus, for a burgeoning consumer market of India, quicker heat extraction method is preferred. Some consumers also prefer the better smell and taste of heat-pressed oil. Only olive oil and sesame oil are suitable for cold press production on a large scale.

Making the Right Choice

So, in the preceding discussion, the reader has been introduced to the essential principles based on which edible oils should be chosen. There is no single correct answer for this topic. *Besides the scientific points mentioned above, the other important factors in the choice of any food are cultural, tradition, smell, taste, etc.* Those issues cannot be neglected because they influence human behavior to a large extent. It must be remembered that any oil or ghee is 100% lipid by chemical composition and yields 9 kcal/g when metabolized. So, there is no "low-fat" oil and all varieties of oil, whether high in PUFA or high in saturated fat, yields the same number of calories.

Mustard oil is preferred in parts of Eastern India due to its distinctive smell and taste. This pungent smell is due to allyl isothiocyanate. This compound has no nutritional value. Mustard oil has about 21% PUFA, which is higher than coconut oil (2%). But mustard oil has high erucic acid, which is not digested by human intestine. This can also cause other metabolic problems**.** *That is why the USFDA has banned the import of mustard oil in their country*. Coconut oil, on the other hand, contains medium chain triglycerides, which have better absorption and metabolism. Also, these MCTs are less likely to be stored as fat and there is less weight gain.

Olive oil is the staple component of Mediterranean diet. It has high MUFA, which is good for the heart. Also, it contains other beneficial compounds like tocopherols. But Ω-3:Ω-6 ratio of olive oil is not optimal. Soybean oil has good PUFA content. But one disadvantage is that it gets rancid very quickly. *Mustard oil also has high PUFA but due to presence of other antioxidants, it can be stored without rancidity for long.* Safflower oil has high smoke point which is good for frying. But it contains high PUFA

and this can be oxidized to toxic compounds in prolonged cooking. Also, high PUFA content means that it gets rancid very easily. In this context, coconut oil is better for frying as it has high saturated fat and is thus, less prone to oxidation.

Palm oil has high saturated fat. But it also has high levels of tocopherols which are essential for human body. Avocado oil and peanut oil are high in MUFA content but these are not popular in India till now.

So, how should a consumer make the choice? It is often a delicate balancing act. For example, ghee is high in saturated fat, which is bad for the cardiovascular system. But at the same time, ghee has long shelf life, high smoke point and Vitamins A and D, which are points in its favor. Similarly, mustard oil has high smoke point, contains 21% PUFA but it has erucic acid, which is not digested in our intestine. Again, the Ω-3:Ω-6 ratio in mustard oil is better than most other oils. This is how a consumer will have to make the choice. If a consumer cannot make a single choice, then it may be advisable to mix two or three oils. For example, 3 days a week the cooking may be done with mustard oil and the rest 4 days, olive oil can be used. Or if the vitamin content of ghee is considered important, occasional ghee products may be consumed. This is how a diet plan is made.

Last but not the Least: The Problem of Adulteration

In India, one major problem is food adulteration.[1] Consumers here have very little say over the quality of food items they get, especially outside the metro cities. Some common adulterants used in edible oil in India are:

- Since palm oil is cheaper, it is often added to costlier oils like groundnut oil or sunflower oil
- Liquid paraffin in coconut oil
- Argemone to mustard oil
- TOCP (an incident of TOCP addition to rapeseed oil led to mass paralysis in west Bengal in the 1980s, this is one reason why rapeseed oil is not popular in India)
- Coloring chemicals

Thus, a consumer of India, while selecting edible oil, has to remember not only the chemical properties or cultural factors, but also the problem of adulteration.

Conclusion

The choice of oil for cooking is a contentious issue. A lot of considerations like cultural acceptability, cost, availability, and health effects are taken into account while making the choice. Some people consider mixing a variety of oils for the optimum health benefit. Some people also consider opting for exotic varieties like olive oil or peanut oil. The final decision should be based on informed choice and scientific judgment.

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CHAPTER

15 Expanding Role of Combination Therapy in Hypertension

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Abstract

Hypertension is a major risk factor for cardiovascular (CV) disease, cerebrovascular accidents, chronic kidney disease, peripheral vascular disease, and heart failure. As per the recommendation of latest guidelines, monotherapy may not work in most patients, and to achieve optimal BP targets, most of the hypertensive patients eventually require a combination of two or more antihypertensive drugs. The combination therapy looks like a lucrative option than increasing the dose of single agent and offers several advantages over high dose monotherapy to treat hypertension. The aim of a physician treating hypertension should always be a cost-effective, long-term therapy to control BP with drugs that are effective, safe, well tolerated, and must also actually reduce the CV risk.

Introduction

Hypertension is a tremendous public health burden globally affecting millions of patients. It is estimated that 26% of the world's population suffer from hypertension, and the prevalence is expected to increase to 29% by 2025, mainly attributed to increase in economically developing countries.[1] Hypertension is a major risk factor for cardiovascular (CV) disease, cerebrovascular accidents, chronic kidney disease, peripheral vascular disease, and heart failure.[2] Significant reduction in clinical CV end points can be achieved with meticulous control of blood pressure (BP) in hypertensive patients, more importantly in the presence of comorbidities like diabetes mellitus, chronic kidney disease, etc. In recent times, newer antihypertensive agents have come on the scene and there has been a rise in awareness among both patients and physicians, but a significant percentage of hypertensive patients continue to have suboptimal BP control.[3]

Recently, evidence suggests that for control of hypertension, monotherapy may not work in most patients, and to achieve optimal BP targets as per the recommendation of various guidelines, most of the hypertensive patients eventually need a combination of two or more antihypertensive drugs. The fact that multiple factors are involved in etiology of hypertension also favors the use of combination drugs acting through different mechanisms to control the BP. Latest international guidelines also recommend to initiate a double-drug combination therapy for patients with a systolic BP (SBP) more than 20 mm Hg and/or a diastolic BP (DBP) more than 10 mm Hg above the target BP and also for those patients who are at increased CV risk.[4,5]

Combination Therapy: Need of the Hour

The rise in BP is controlled by diverse mechanisms. The three factors that primarily determine the BP are: renal sodium excretion and resultant plasma and total body volume, cardiac output, and vascular tone.[6] The sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) chiefly control these parameters on a real-time basis. Apart from that BP in

individual patients is also influenced by diet, genetic, and environmental factors. Due to this multifactorial etiology involved in genesis of hypertension, many a times it is very difficult, if not impossible, to control the BP by using a single antihypertensive drug. On the other hand, combination of two drugs with different mechanisms of action can provide two to five times greater antihypertensive effect than with monotherapy.[7]

Various clinical trials report that achieving BP goals is usually not possible with monotherapy. *As per the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 26% of the patients could achieve target BP with a single drug*—despite the fact that the goal BP for diabetics (36% of the patient population) was <140/90 mm Hg rather than <130/80 mm Hg as per recommendations of latest guidelines.[8]

In the Losartan Intervention for Endpoints Reduction (LIFE) trial, more than 90% patients with left ventricular hypertrophy needed at least two antihypertensive drugs to achieve target BP of <140/90 mm Hg.[9] In the Hypertension Optimal Treatment (HOT) trial, the target BP (diastolic only) with a single drug was achieved by only 33% patients, 45% needed two drugs, and 22% required three agents.[10] The average SBP at the end of the study was 141 mm Hg, indicating that even a greater number of patients would have required combination therapy as per current treatment guidelines.

Apart from achieving target BP control, time taken to achieve it is also important in patients having hypertension with high CV risk. As demonstrated in a post hoc analysis of the Valsartan Antihypertensive Long Term Use Evaluation (VALUE) trial, patients who reached their BP goals at 6 months had lesser subsequent CV events.[11] In a randomized controlled trial in patients with hypertension and metabolic syndrome, starting treatment with a combination of valsartan and amlodipine achieved BP goal more rapidly than initiating with a high dose of valsartan monotherapy.[12] In a cohort study of hypertensive patients 34% risk reduction in CV events was mainly attributed to the more rapid achievement of BP target with combination therapy.[13] Combination therapy can even be effective in hard-to-treat patients in achieving normal BP. This early normalization of BP also motivates the patients to be more compliant to lifelong treatment. Single pill combinations (SPCs) containing two or three drugs in the same tablet offer additional advantage by improving adherence and potentially reducing the cost of therapy.

Theoretical Considerations of Combination Therapy

Efficacy

By combining drugs that either effectively block the counter-regulatory responses or interfere with clearly different pressor mechanisms, BP lowering is possible to a greater extent than with monotherapy. Usually combining agents from harmonious classes is about 5 times more effective in reducing BP than increasing the dose of one agent. Another important need to make a good combination is that the combined-drug administration should produce additive and continuous BP reduction throughout the dosing interval.[14]

The beta-blocker/calcium channel blocker (CCB) combination is a good example to show the harmonious action of two agents where on one side beta-blocker attenuates the CCB-induced activation of the sympathetic nervous system, and on the other hand, the vasodilatory effect of CCB weakens the alpha-mediated reflex vasoconstriction induced by beta-blockers.

Tolerability

Most drug combinations are designed so as to improve the tolerability of therapy by neutralizing the dose dependent side effects (that occur due to use of higher doses) of a single agent, by the pharmacologic effects of an added drug. For example, hypokalemia produced by thiazide diuretic can be counter-balanced by addition of a potassium-sparing diuretic, such as amiloride, triamterene, or spironolactone, or a RAAS inhibitor.

Adherence

Combination therapy can improve the adherence and compliance to treatment by simplifying regimen in terms of reducing the number of medications, frequency of dosing, and also being cost effective most of the times. This definitely helps in control of BP. In a meta-analysis of nine studies, the adherence rate was improved by 26% in patients receiving SPCs in comparison to those taking their components separately.[15] **Table 1** summarizes

TABLE 1 Comparison of various hypertension treatment strategies[7]

	Low-dose monotherapy	*High-dose monotherapy*	*Free combination therapy*	*Single-pill combination therapy*
Effectiveness	×	✓	✓✓	✓✓
Tolerability	✓	×	✓	✓✓
Adherence	✓	✓	×	✓
Convenience	✓	✓	×	✓
BP variability	×	×	✓	✓
Flexibility	✓	✓	✓	✓
Fast attainment of target BP	×	✓	✓✓	✓✓

the benefits and drawbacks of various drug prescribing strategies in hypertension management.

Indications of Combination Therapy[16]

- Unable to achieve the target BP with monotherapy.
- Presence of adverse effects of single drug that may be improved by the addition of a second agent (e.g., adding an angiotensin-converting enzyme inhibitor to a CCB to reduce peripheral edema).
- The SBP is ≥20 mm Hg and/or DBP is ≥10 mm Hg above the target BP.
- Presence of convincing indications that may get benefitted from different mechanisms of action of multiple antihypertensives.

Advantages of the Combination of Antihypertensive Drugs

The combination therapy looks like a lucrative option than increasing the dose of single agent. The advantages of combination therapy are summarized in **Box 1**.

Specific Drug Combinations Available

Various trials have been used and studied different classes of drugs in combination for treatment of hypertension. Angiotensin receptor blockers (ARBs), thiazide diuretics, alpha and beta-blockers, calcium channel blockers (CCBs), and angiotensin-converting enzyme inhibitors (ACEIs) are the most commonly used classes of antihypertensive agents for combination therapy. On the basis of these large, result oriented trials, various international guidelines have classified the different available combinations as preferred, acceptable, or not acceptable **(Box 2)**.[17,18]

BOX 1 Advantages of combination therapy

- Rapid and sustained control of blood pressure due to additive effect of combined drugs
- Minimization of the dose dependent side effects that occur due to use of higher doses of a single agent thus improving the tolerability of therapy
- Many other pathophysiological mechanisms of increased blood pressure are simultaneously blocked
- Much better protection to target organs
- Other beneficial effects independent of antihypertensive action of drugs:
  - Anti-inflammatory action
  - Metabolic anti-counter regulatory actions
  - Nephro- and cardiovascular protection
- Homologous blood pressure lowering and good safety profile
- Reduced pill burden and most of the times economically effective

RAAS Inhibitors (ACEI/ARB/DRI) + CCB

The addition of RAAS inhibitors to a DHP-CCB leads to greater degree of BP reduction and increased tolerability by significantly reducing the incidence of tachycardia and peripheral edema observed with CCB monotherapy. In the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, the ACE inhibitor/CCB combination was found to reduce the CV complications and stroke incidence by 20% as compared to the ACE inhibitor/diuretic combination.[19]

RAAS Inhibitors (ACEI/ARB/DRI) + Diuretics

The RAAS inhibitor reduces the incidence of diuretic induced hypokalemia and new onset glucose intolerance. Most outcome trials have shown the thiazide-like

BOX 2 Specific drug combinations used in hypertension[17,18]

Preferred:
- ACEI/DHP (dihydropyridine) CCB
- ARB/DHP CCB
- ACEI/Diuretic
- ARB/Diuretic

Acceptable:
- Beta-blocker/Diuretic
- DHP CCB/Diuretic
- DHP CCB/Beta-blocker
- Thiazide diuretic/Potassium-sparing diuretic
- Direct renin inhibitor (DRI)/DHP CCB
- DRI/Diuretic

Not acceptable:
- Centrally acting agent/Beta-blocker
- CCB (non-dihydropyridine)/Beta-blocker
- ARB/Beta-blocker
- ACEI/Beta-blocker
- ACEI/ARB

diuretic chlorthalidone to be more effective than hydrochlorothiazide (HCTZ) in controlling 24-hour BP along with better night time protection.[20]

Beta-blockers/Diuretics

Although various outcome studies have shown reduction in morbidity and mortality with this combination but due to increased incidence of new onset diabetes, erectile dysfunction and fatigue with both beta-blockers and diuretics this combination is not recommended for use in patients with metabolic syndrome or in those who are at increased risk for developing diabetes.[17]

CCBs + Diuretics

Due to the natriuretic effect of CCBs, this combination of a CCB leads to a partially additive BP reducing effect. However, the combination does not have a favorable effect on either drug's adverse effect profile. So, this combination is classified as an acceptable combination.

CCBs + beta-blockers

The combination of a beta-blocker and a dihydropyridine CCB is acceptable and results in additive BP reduction. In the HOT study a beta-blocker added to felodipine was the second combination used to achieve BP goals.[10]

Other Combinations

Other drug combinations like Centrally acting agent + Beta-blocker, CCB (non-dihydropyridine) + Beta-blocker, ARB + Beta-blocker, ACEI + Beta-blocker, and ACEI + ARB are considered as non-acceptable or ineffective either because of increased incidence of some serious side effects or inability to produce significant additive BP reduction when they were used in various clinical studies.

Single Pill Combinations

Single pill combinations (SPCs) offer several potential advantages, including simplification of the treatment regimen, convenience, and sometimes decreased cost of therapy. The choice of combined agents can be used to minimize the adverse effects of each individual agent. The disadvantage like the risk of causing orthostatic hypotension is mainly observed in older patients and patients with diabetic autonomic neuropathy.

After the success of two drug combinations, researchers are moving toward three-drug therapy at a lower dose. In a 2018 study in Sri Lanka, treatment with a three-drug SPC in mild hypertensive patients resulted in 15% better BP control in the combination group without any statistically significant difference in adverse effects after 6 months of therapy.[21]

In the TRINITY (triple therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in hypertensive patients study) trial, at 12 weeks, the triple-combination therapy resulted in significantly more BP reduction when compared with three different dual combinations, made by using two of these three drugs, with no significant difference in adverse events in patients with moderate to severe hypertension.[22]

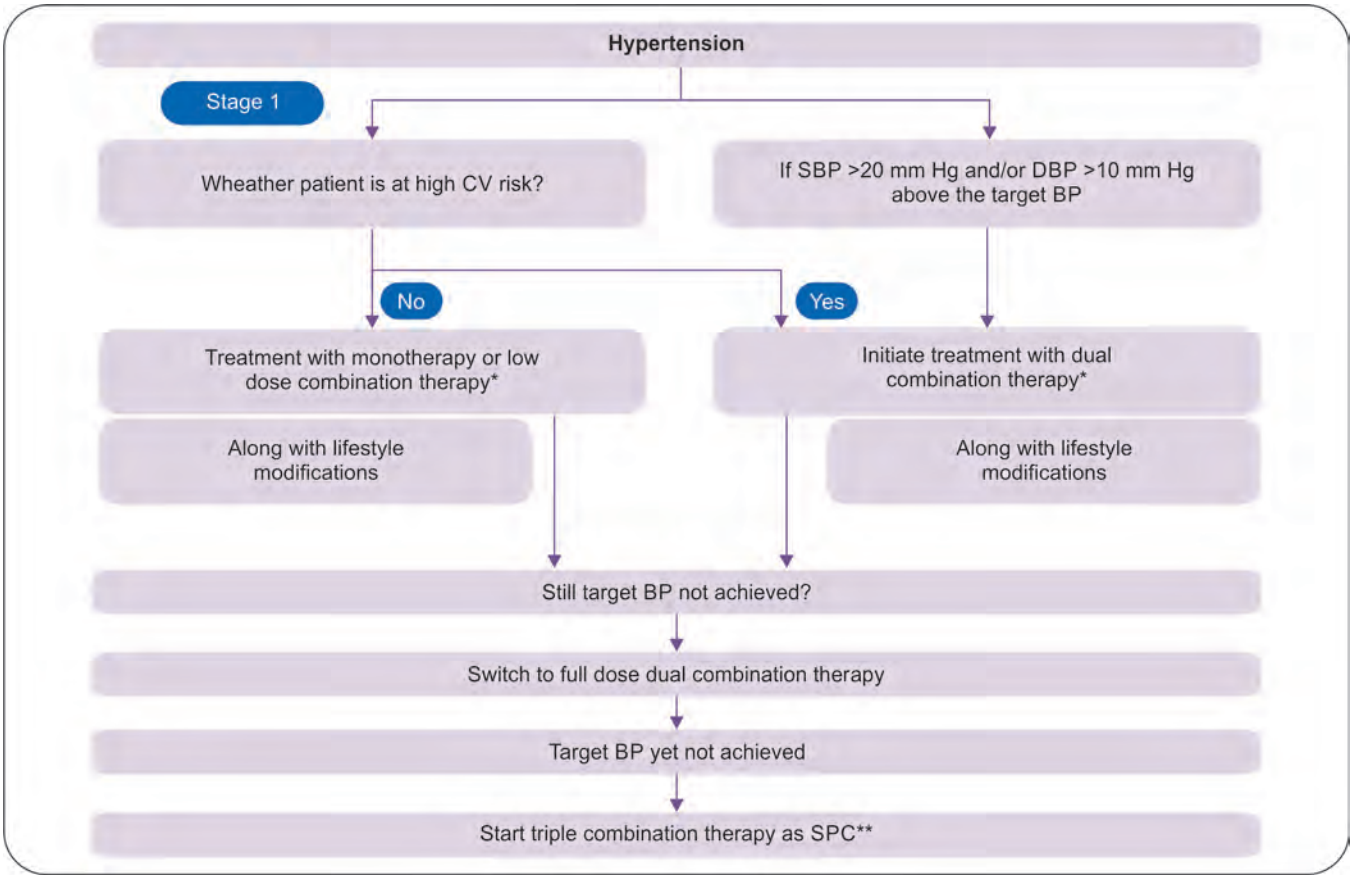
A simple algorithm for the use of monotherapy and combination therapy has been depicted in **Flowchart 1**.

Effects of Combination Therapy Independent of Antihypertensive Action

Anti-inflammatory Effects

Studies have shown that combination of an ACEI with a CCB is more protective than monotherapy in decreasing the various inflammatory mediators such as interleukins, tumor necrosis factor, etc.[23]

Flowchart 1: Algorithm for management of hypertension using combination therapy



*Preferred and acceptable dual-combination should be used only **(Box 2)**.
**If BP goal is not reached on triple SPC, consider secondary causes of hypertension and add a fourth BP-reducing drug if required.

Hemodynamic Effects

Matsui et al. in their study showed that the combination of the ARB plus CCB reduced the central aortic pressure to a greater extent than the combination with the diuretic agent.[24]

Nephroprotective Effect

Studies have found that the combination of an ACEI with a CCB was better than ACEI monotherapy in reducing proteinuria and taper down rate of renal deterioration in hypertensive patients who do not respond to monotherapy.[25]

Uricosuric Effect

It has been consistently shown in studies that the combination of losartan plus a CCB more significantly reduce uric acid levels than the combination of losartan plus HCTZ providing additional benefits in hypertensive patients with hyperuricemia.[26]

Metabolic Effects

Among the various antihypertensive agents, ACEIs and ARBs improve insulin resistance whereas beta-blockers and diuretics are associated with insulin resistance and increased glucose intolerance. CCBs increase high-density lipoprotein levels while beta-blockers and thiazides raise triglyceride levels.[27] These pleiotropic effects were also observed when these drugs were used in combination therapy.

Vascular Effects

In a study, combination of benazepril plus amlodipine more effectively resulted in improved arterial compliance,

reduced arterial stiffness, and decreased left ventricular mass than high doses monotherapies of both drugs.[28]

Conclusion

The goal of a physician treating hypertension should always be a cost-effective, long-term therapy that controls BP with drugs that are effective, safe, and well tolerated and should also actually reduce the CV risk. All major current guidelines suggest that ≥1 antihypertensive agent is needed in most hypertensive patients to reach desired BP targets. *Summarized recommendations are as follows:*

- Combination therapy must be routinely used to achieve BP goals.
- Initiate combination therapy in patients who require ≥20/10 mm Hg decrease in BP to achieve desired BP.
- Preferred or acceptable drug combinations should be maximally used.
- Combination therapy in stage 1 patients should be started, especially when the second drug improves the tolerability of initial therapy along with additive BP reduction.
- Use SPCs rather than separate individual agents to improve convenience and compliance of treatment.
- Triple therapy including a RAAS inhibitor, a CCB, and a natriuretic should be initiated in those patients who do not respond to dual therapy in 6–8 weeks.

Although the basis of treatment is guideline recommended medical therapy, still individualized treatment and expert advice should be preferred because each and every patient is a unique subject with a specific CV profile and not merely a statistically derived number in clinical trials.

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CHAPTER

16 Management of Hypertension with Increased Sympathetic Activity—A New Way Forward

BB Thakur, Smita Thakur

Abstract

Hypertension is one of the most important preventable causes of morbidity and mortality across the globe. It is estimated that 25–35% of modern population suffer from hypertension and is estimated to cause over seven million deaths each year. Evidence from randomized controlled trials (RCTs) has shown benefit of antihypertensive drug treatment in improving outcomes in persons with hypertension. Since hypertension does not have any specific symptom and most of the time, the symptoms do not cause any inconvenience, it remains an insufficiently treated disease with only 10–20% patients having controlled blood pressure in spite of availability of so many drugs.

It has long been known that Sympathetic Nervous system plays a crucial role in blood pressure control through several reflex and non-reflex mechanisms including its effect on renal sympathetic outflow. It plays an important role in the development and progression of the essential and all grades of hypertensive state and end-organ damage. We now know conclusively that Sympathetic over activity is the leading cause of stroke, chronic kidney failure, left ventricular hypertrophy, and sudden cardiac death.

Some pharmacologic classes of antihypertensive drugs (such as beta-blockers, ACE-inhibitors, and angiotensin II receptor blockers) may elicit profound sympathoinhibitory effects, while long-acting CCBs have no effect on it and diuretics and short-acting calcium antagonists further increase the adrenergic cardiovascular drive.

The unmet need of controlling blood pressure in those patients whose pressure is not controlled to target with usual drugs may be addressed, in part, by developing new drugs and devices/procedures to treat hypertension and its comorbidities.

Alongside pharmacological therapy, device-based approaches to modulate SNS have demonstrated beneficial effects on BP control. In the past few years, two new procedures have been developed for the treatment of resistant hypertension by modulating SNS: catheter-based renal denervation and electrical stimulation of carotid baroreceptors. However, the interventional procedures are still in experimental stage.

Introduction

Hypertension is a complex and progressive cardiovascular syndrome of multiple etiologies that result in functional and structural changes in the heart and vascular system and it remains one of the most important preventable contributors to disease and death in the world.[1,2]

Most patients with hypertension have other risk factors including lipid abnormalities, glucose intolerance and diabetes, family history of early cardiovascular events, obesity, and tobacco use with or without alcohol excess.

There is unholy alliance between obesity, type 2 diabetes, the sympathetic nervous system (SNS), and hypertension in young/middle-aged subjects.

It is estimated that one-fourth to one-third of the population is afflicted with this condition[3-5] and is estimated to cause over seven million deaths each year, which is about 13% of the total number of deaths worldwide.[6] According to a review on "The Global Burden of Hypertension," the estimated prevalence of hypertension (in people aged 20 years and over) in India

in the year 2000 was 20.6% among males and 20.9% among females and is projected to increase to 22.9% and 23.6% respectively by year 2025. These trends are increasingly been seen with aging populations.[7]

Evidence from randomized controlled trials (RCTs) has shown benefit of antihypertensive drug treatment in improving outcomes in persons with hypertension.[8-10] Since hypertension does not have any specific symptoms, and most of the time, the symptoms do not cause any inconvenience, it remains an insufficiently treated disease with only 10–20% patients having controlled blood pressure levels.[5]

SNS has always been implicated in causation of hypertension, but there has been a renewed interest because of:

- Sympathetic abnormalities influence the development and progression of TOD;
- New therapeutic approaches for control of blood pressure have been developed by modulating SNS; and
- SNS overdrive has impact on morbidity and mortality in CVD.

Sympathetic overactivity is presently recognized as a major contributor to development and sustenance of hypertension.[11] Several pathophysiological changes lead to increased vascular tone and resistance, tachycardia, compromised central and peripheral hemodynamics, renal vasoconstriction, oxidative stress, metabolic abnormalities, and adverse remodeling of cardiac and vascular smooth muscle. Notably, many antihypertensives result in reflex SNS activation, which can result in elevated resting heart rate, and this is one of the newly recognized cardiovascular risk factors. Secondary causes of hypertension can also increase sympathetic activity.

It is well acknowledged that sympathetic overactivity is the leading cause of stroke, chronic kidney failure, left ventricular hypertrophy, and sudden cardiac death.

Understanding the mechanisms involved in the regulation of the SNS has currently lead to novel approaches in hypertension treatment **(Fig. 1)**.

A distinct feature of the SNS is the immediate regulation of peripheral vascular resistance through modulation of the vascular tone. In addition, the release of sympathetic neurotransmitters contributes to adaptive mechanisms through regulation of cell proliferation, transformation, and apoptosis, and these are all blood pressure independent.[12-15]

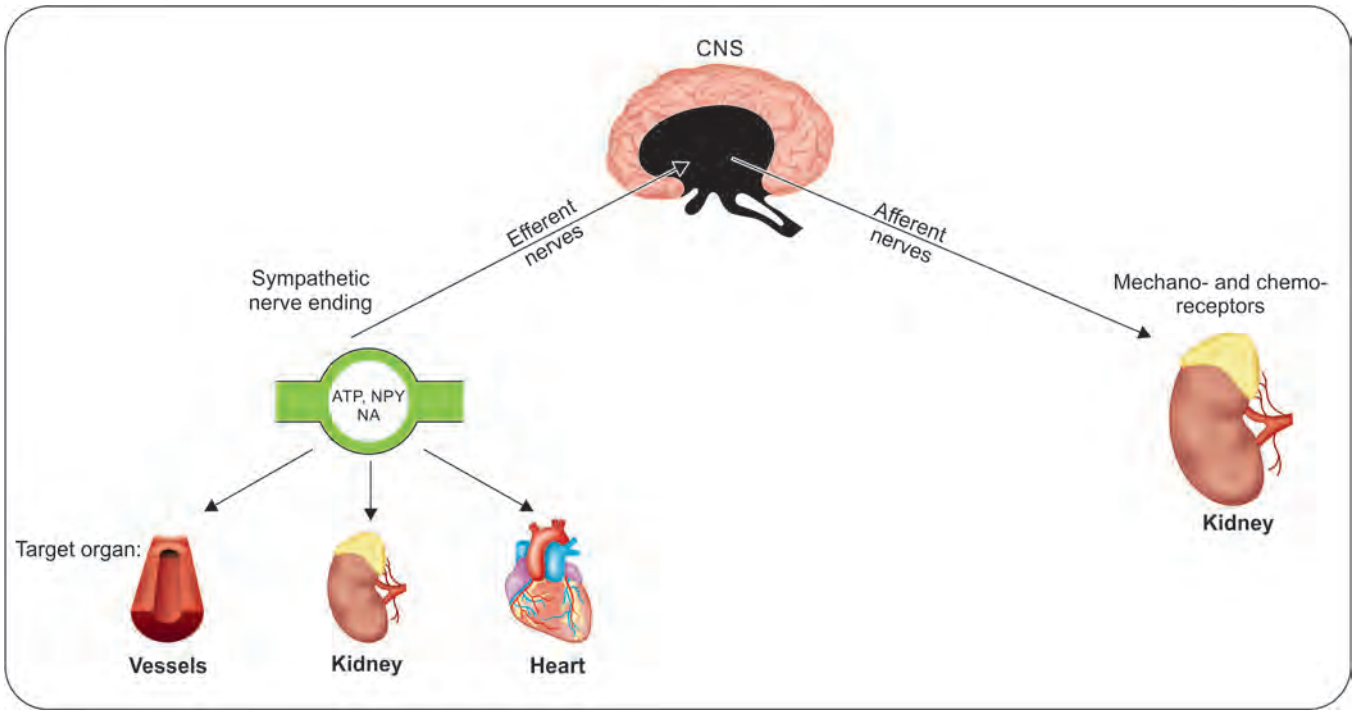


Fig. 1: Schematic of sensory, afferent and sympathetic efferent neurons, and target organ innervations

The renin-angiotensin-aldosterone system (RAAS) is responsible for the central nervous feedback in sympathetic activation, angiotensin II and nitric oxide (NO) are important effectors of this system.[16] In chronic kidney disease, RAAS inhibition leads to decrease in efferent sympathetic activity.[17] All RAAS inhibitors do not have the capability to penetrate through the blood-brain barrier; therefore, it is likely that peripheral actions of angiotensin II modulate afferent signal transduction.

Renal ischemia releases adenosine as a paracrine transmitter, leading to potent activation of afferent neurons.[18] Severing afferent and efferent sympathetic nerve fibers prevent no hypertension in animal model with chronic kidney injury.[19] Independent from CNS-effects, chronic kidney injury leads to a neither increase of presynaptic or epinephrine release in the heart and kidney. This might be due to an increase in angiotensin II through RAAS activation.[20-22]

Multiunit sympathetic nerve activity (MSNA) is equivalent to the sympathetic activity. This can be measured as "bursts" per minute, and helps establish the concept of kidney as a pacemaker of sympathetic activity. Converse et al. analyzed the sympathetic activity in dialysis patients versus healthy controls.[23] Interestingly, in kidney transplant patients with normal serum levels of creatinine and urea, the sympathetic overactivity persisted. Only bilateral nephrectomy was able to abolish the pathologic sympathetic overactivity.[24]

Sympathetic Overactivity

The SNS plays a pivotal role in rapid adaptation of the body to ongoing events, orthostatic reaction is a glorious example of its instant activation.[25] However, it is the long-term gradual modification in the sympathetic activity, which contributes to development of hypertension. There is an increase in sympathetic activity with an increase of MSNA of 1 burst/min per year, with advancing age.[26] Female subjects have a lower MSNA, but they exhibit more significant annual increase, compared to their male counterparts.[27] A good correlation between blood pressure and MSNA has been observed above 40 years of age, which does not exist in younger patients.[27] Diminished compensatory mechanisms in the elderly population (endothelial dysfunction, diminished baroreflex, etc.) could be the reasons. Sympathetic overactivity could be the underlying factor linking heart failure, sleep apnea, metabolic syndrome, and hypertension.

Sympathetic Overactivity in Sleep Apnea

Sleep-related respiratory dysfunction is much more common in patients with hypertension compared to the common population.[17] Sleep apnea patients demonstrate an increased blood pressure. Apnea causes an immediate rise in sympathetic activity that leads to increase in blood pressure.[28] In chronic sleep apnea, this activation of the SNS persists during daytime also which results in increased MSNA and norepinephrine release.[29] Denervation of the carotid body abolishes the blood pressure increase after hypoxia.[30] Desensitizing chemoreceptors through respiration of 100% oxygen lead to a decrease in sympathetic activity, heart rate, and blood pressure in wake sleep apnea patients but not in healthy controls.[31] Dysfunction of baroreceptors also exists in sleep apnea patients, similar to what is observed in chronic heart failure patients.

Sympathetic Overactivity in Metabolic Syndrome

Baroreflex dysfunction could be the cause of sympathetic overactivity in overweight patients.[32] Accumulation of visceral fat is associated with an increase in MSNA and greater cardiovascular risk.[33] An increase in MSNA is often observed in type 2 diabetes patients.[34] Overweight people suffer more from hypertension and type 2 diabetes, thus interlinking together to manifest as metabolic syndrome. Administration of an increasing dose of insulin increased MSNA in euglycemic individuals, suggesting that hyperinsulinemia plays an important role.[35]

Sympathetic Overactivity in Hypertension

Almost all studies measuring microneurographic sympathetic nerve activity in hypertensive patients could demonstrate the central role of sympathetic overactivity.[36] MSNA increase is more pronounced in patients with observable target organ damage[37] **(Fig. 2)**.

The associated conditions with hypertension like chronic kidney disease, heart failure, obesity, and sleep apnea are all associated with increased sympathetic overactivity and tend to coexist. It is postulated that sympathetic reactivity might be genetically determined. Children of hypertensive individuals show normal MSNA levels, but when subjected to mental stress show

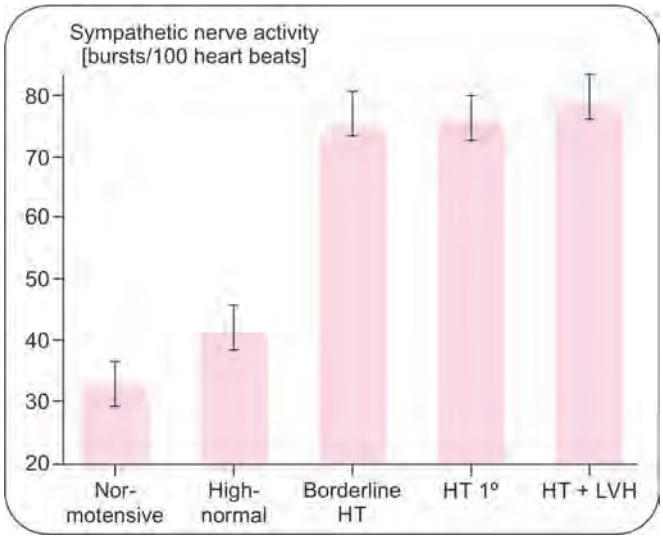


Fig. 2: Microneurographic measurements confirm a significant increase in sympathetic nerve activity (MSNA) in patients with hypertension (HT) compared to healthy individuals. An increased MSNA can already be found in high-normal blood pressure patients (130–139/85–89 mm Hg)[37]

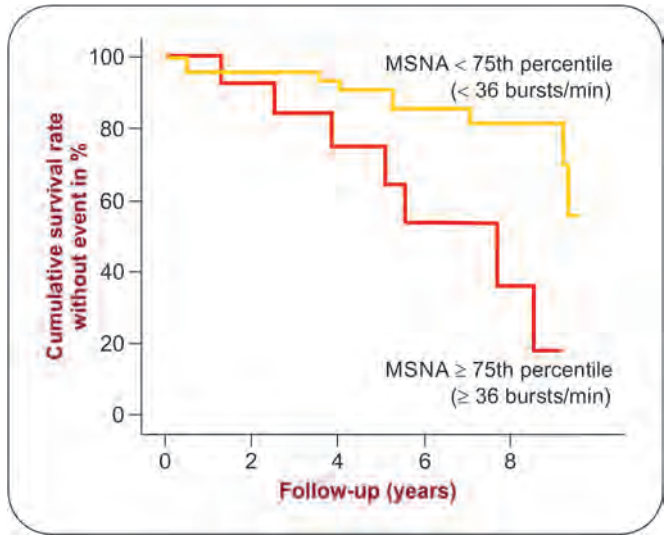


Fig. 3: Kaplan-Meier curve for adverse cardiovascular events in dependence of MSNA above (≥ 36 bursts/min) and below (< 36 bursts/min) the 75th percentile (modified)[47]

a significantly increased MSNA, compared to children of non-affected parents.[38]

Diastolic (± systolic) hypertension in young/middle-age is accompanied by increased sympathetic nerve activity, particularly in presence of metabolic syndrome or type 2 diabetes. Hypertension in preeclampsia[39] or pulmonary arterial hypertension[39] also shows an increased activity in microneurography.

Currently chronic kidney injury is conclusively linked to pathogenesis of hypertension. As seen in Figure 1, activation of afferent neurons in the injured kidney leads to increased sympathetic activity through central nervous mechanisms. It is well established that there is reduced norepinephrine clearance and an increase of serum norepinephrine levels in chronic kidney failure.[40] Kidney through release of a soluble monoamine-oxidase (Renalse) degrades circulating catecholamines and thereby might regulate blood pressure.[41]

Therapeutic Approach

Non-pharmacological Treatment

Aerobic exercise training and calorie restriction both inhibit SNS activity, and are the two most commonly applied and effective non-pharmacological therapies for hypertension. This is especially important for metabolic syndrome and obesity-related hypertension, where there is a contribution of sympathetic inhibition for reductions in both blood pressure and insulin resistance.[42] Another non-pharmacological approach with an antiadrenergic component is the regular application of continuous positive air pressure (CPAP) ventilation in patients with obstructive sleep-apnea-related resistant hypertension at night. This therapeutic approach has been shown to prevent nocturnal obstruction of upper airways, reduce sympathetic activity, and favor blood pressure reduction.[43-46]

Pharmaceutical Approach

In patients with chronic renal failure, the severity of disease correlates very well with sympathetic activity.[47] An increase of MSNA of 10 bursts/min increases the event rate by 60%. Adverse cardiovascular events are also increased in these patients **(Fig. 3)**.

Some pharmacologic classes of antihypertensive drugs (such as beta-blockers, ACE-inhibitors, and angiotensin II receptor blockers) may elicit profound sympathoinhibitory effects, while long-acting CCBs have no effect on it and diuretics and short-acting calcium antagonists further increase the adrenergic cardiovascular drive.

Pharmacological intervention can be achieved with RAAS-blockade (Renin- or ACE-inhibitors, or AT1-blockers), which leads to a reduction in the efferent sympathetic activity.[48,49] However, normalization of sympathetic activity can only be achieved if a central sympatholytic drug (moxonidine) is added to this treatment.[50]

The initial antihypertensive drugs had antiadrenergic effects and were potent, but their side effects made them fall out of favor. Beta- and alpha-adrenergic blocking drugs are similar and effective. Centrally acting sympathetic suppressants, imidazoline-binding agents, such as moxonidine and rilmenidine can be prescribed in patients with essential hypertension as both produce the desired sympathetic inhibition in the sympathetic outflows to the heart, kidneys, and skeletal muscle vasculature.[51] Moxonidine also has renoprotective properties in chronic renal failure and reduces MSNA,[52,53] independent of blood pressure reduction. These are largely free of the side effects witnessed with clonidine, most notably rebound hypertension seen with clonidine when doses were missed.

In patients with resistant hypertension, target goal of <140/90 mm Hg cannot always be achieved using oral antihypertensive medication. Therefore, alternative approaches for blood pressure control have been researched, especially concentrating on novel treatment strategies to alter sympathetic overactivity.

Antiadrenergic Devices

Alongside pharmacological therapy, device-based approaches to modulate SNS have demonstrated beneficial effects on BP control.

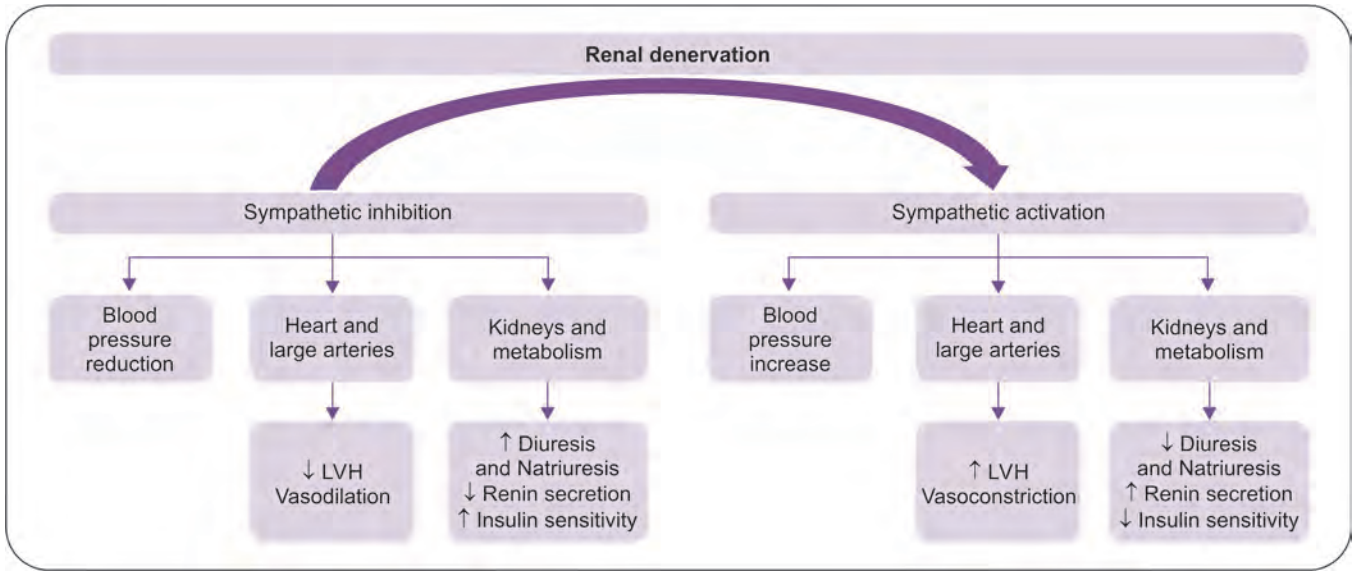
In the past few years two new procedures have been developed for the treatment of resistant hypertension: catheter-based renal denervation and electrical stimulation of carotid baroreceptors.[54-57]

Renal Denervation Therapy

Traditional surgical sympathectomy proposed in early forties has been discarded due to unacceptable severe side effects like voiding dysfunction, intestinal dysfunction, impotence and orthostatic dysregulation, and operative risks.[58,59] Due to pharmaceutical alternatives, surgical sympathicolysis was replaced by antihypertensive drugs.

This novel and recently introduced therapeutic approach **(Flowchart 1)** to RH involves bilateral destruction of the renal nerves travelling along the renal artery, using percutaneous catheter-based radiofrequency ablation **(Fig. 4)** via femoral artery.[60-64] The basis for renal denervation lies in the importance of sympathetic influences on renal vascular resistance, renin release, and

Flowchart 1: Scheme illustrating the possible mechanisms through which renal denervation may exert blood pressure-lowering effects: increase (up arrow) and reduction (down arrow)



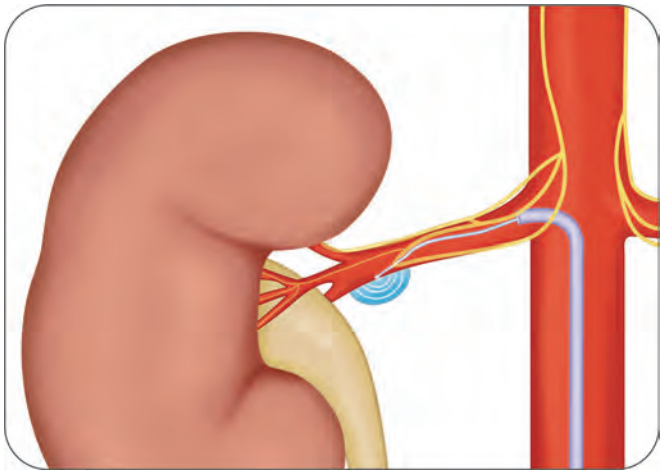


Fig. 4: Catheter-based renal denervation. The tip of the catheter is placed in the distal renal artery via vascular access through the femoral artery. Radiofrequency energy is applied via the top of the catheter to target the renal nerves in the surrounding adventitia. Four to six radiofrequency ablations are performed in each artery and separated both longitudinally and rotationally to achieve circumferential coverage

sodium reabsorption, the increased sympathetic tone to the kidney and other organs displayed by hypertensive patients[65-67] and the pressor effect of renal afferent fibers, seen in experimental animals.[68,69]

The Symplicity HTN-1 and HTN-2 trials have shown substantial blood pressure reductions in response to renal denervation,[70] in the order of 30/15 mm Hg, maintained beyond 2 years. Although renal denervation resulted in improved blood pressure control, the patients continued to take antihypertensive drugs at a reduced number or dose.

However, surprisingly, the very recently reported Symplicity HTN-3[71] has failed to achieve its primary efficacy endpoint and has not found favor on merit and it is still under scrutiny.[72] Following the initial hype[73] on the basis of initial results of Symplicity HTN-1 and HTN-2, the Symplicity HTN-3 study[74] was terminated in February 2014 by Medronic, because the primary endpoint that is lowering of the systolic occasional blood pressure by ≥5 mm Hg—was not achieved after 6 months compared with a control arm. The study, published online in March 2014, showed only a difference of 2 mm Hg for office and 24-hour ambulatory systolic blood pressure.[75] The European Society of Hypertension and national expert teams have not come out so far regarding the indication for this interventional method.[76-79] A subsequent position paper statement by the European Society of Hypertension Working group[80] has very elegantly summarized the current status of this therapy and ways forward. Currently one should refrain from referring further patients for treatment with this method. As there is no safety concerns except for vascular issues and no major complications (impairment of renal function, renal artery stenosis/thrombosis) have been reported,[75] the method may be useful for the small patient population with true treatment resistance, provided all contraindications are observed and after rigorous investigations and treatment.

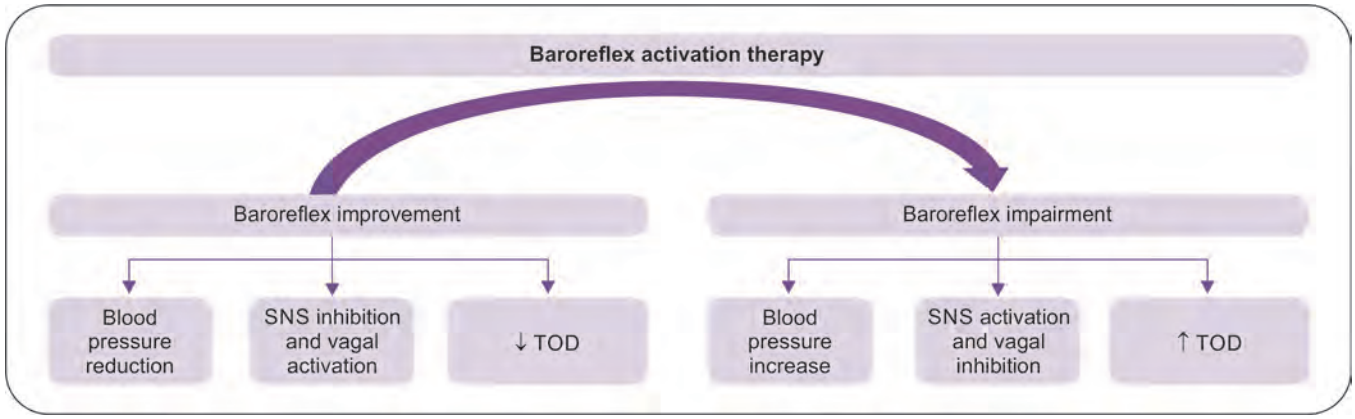
Although there remain many questions to be answered regarding its long-term success, clinical outcomes, and technical issues, further renal denervation therapy trials are very likely to be conducted with new devices at various stages of development.

Carotid Baroreceptor Stimulation

Another invasive method is baroreflex stimulation (electrical stimulation of the carotid sinus nerve), which underwent a revival based on two studies.[3,82]

Dysfunction of the baroreceptor reflex causes an increase in sympathetic activity in a variety of diseases such as sleep apnea and chronic heart failure. This option **(Flowchart 2)** allows appropriate physiologic adaptation to elevated SNS activation and reduced parasympathetic activation by electrically stimulating the carotid baroreflex, the carotid sinus nerves via implanted devices (baroreflex activation therapy—BAT). This device-based therapy **(Fig. 5)** has proved very effective in lowering blood pressure[56] and recently been reported to reduce SBP and DBP in resistant hypertensive individuals also[56,81,82] the reduction was quite marked when initial BP values were very high and the effect included ambulatory BP and persisted for up to 53 months. However, long-term observations have so far involved only a restricted number of patients and further data on larger numbers of individuals with an elevation of BP unresponsive to multiple drug treatments are necessary to confirm the persistent efficacy of this procedure. It seems to be safe with only a few remediable and local side-effects (infection, nerve damage, pain of glossopharyngeal nerve origin) and no effect on renal function[83] and even a positive effect on structural and functional cardiac parameters was demonstrated.[84] Previously, baroreflex activation therapy

Flowchart 2: Possible mechanisms by which electrical stimulation of carotid baroreceptors might help lower blood pressure



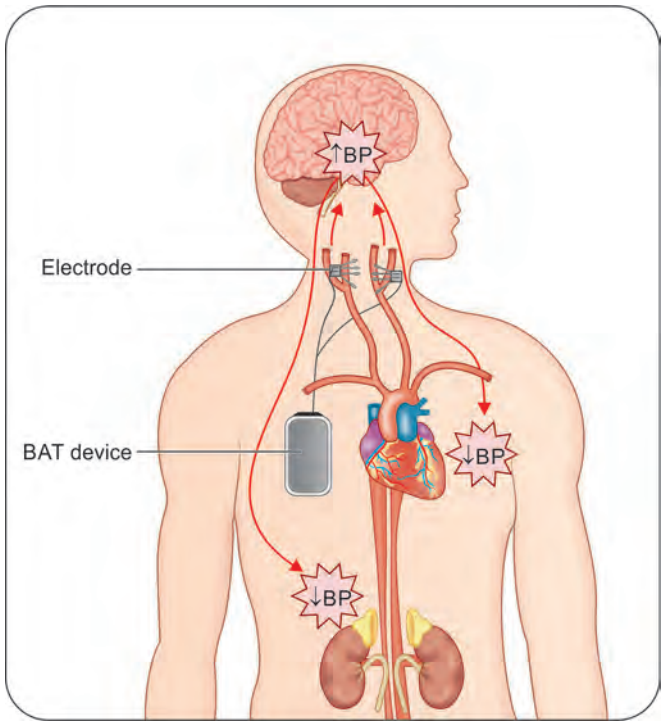


Fig. 5: This device-based treatment consists of an implantable pulse generator; bilateral carotid sinus leads to stimulate the area of greatest response. There is an external programmable device for noninvasive control of the pulse generator. Carotid sinus stimulation acts via a negative loop mechanism via central nervous system, leading to reflex blood pressure lowering

required bilateral carotid preparation and implantation of electrodes and the corresponding pacemaker aggregate. Due to the approach of bilateral activation, battery power of pacemakers lasts only for 2 years with the need of replacement after this period. Ongoing technical innovations to reduce the inconvenience caused by the surgical implantation of the stimulating devices, and to prolong the duration of the battery providing the stimulation, are being studied.

Baroreflex stimulation has been approved in Europe for the treatment of patients with resistant hypertension and a high-cardiovascular risk;[85] however, it should be applied in selected centers with great expertise in the treatment of hypertension and undertaken in close collaboration with vascular surgeons.

In contrast to renal sympathetic denervation, baroreflex stimulation is a reversible procedure; the system can be switched off in the event of hypotension or shock and be adapted to the requirements of a circadian blood pressure rhythm by external programming via radiofrequency telemetry.[82,86]

Slow Breathing Technique

Non-pharmacological approaches are recommended for all individuals with hypertension, regardless of drug therapy. Among several behavioral interventions, the device-guided slow breathing (SLOWB) exercise using RESPeRATE (Intercure, Ltd. Northern Industrial Area, Israel) has been introduced as a non-pharmacological approach in the prevention or treatment of elevated BP. It has been suggested that a decrease in breathing frequency may have beneficial effects on BP and autonomic CV regulation through the modulation of central mechanisms at the brainstem integrating cardiopulmonary receptors, arterial baroreceptors, and efferent sympathetic outflow.[26]

RESPeRATE aims to lower BP with ad hoc regular paced therapeutic breathing (slow and deep breathing) below 10 breaths per minute accumulating ≥40 minute of therapeutic breathing training per week. Madanmohan et al. (1983) studied the effect of shavasan and savitri pranayam (a yoga-breathing technique characterized by slow, rhythmical and deep breathing cycles) in trained subjects (yoga training >1 year) and found significant decrease in oxygen consumption, heart rate, and diastolic blood pressure. They attributed it to the ability of the subjects to achieve a state of deep psychosomatic relaxation. Shavasan alone has been shown to be effective in the treatment of hypertension (Datey et al., 1969; Patel and North, 1975). This was attributed to a decrease in the frequency and intensity of proprioceptive and enteroceptive impulse traffic reaching the hypothalamus. Practice of yoga has been found to be beneficial in many current trials.

Whether the device-paced breathing represents an adjunctive treatment to state-of-the-art drug therapy for hypertension requires further clinical investigation in a larger patient cohort. However, this method appears unlikely to reduce sympathetic activity alone over the longer term.

Deep Brain Stimulation

Deep brain stimulation (DBS) is an exciting interventional therapy designed to modify pathological activity within the SNS. This approach has gained significant recognition in the treatment of Parkinson's disease, recently entering clinical practice. Besides the promising therapeutic effects in a wide range of neurological disorders, DBS of the ventrolateral periadeuquotal grey/periventricular grey matter has been successfully demonstrated in refractory hypertension.[36,37,87] While this approach was primarily performed to treat chronic central pain syndrome that was unresponsive to pain-relief drugs, there was also an unexpected effect of sustained BP lowering. While costly, and associated with a 1% stroke risk, DBS appears to be an attractive approach for treating severe forms of uncontrolled hypertension in patients unresponsive to device-based interventional strategies. Whether DBS may be offered widely as a therapeutic tool for RH to improve CV outcomes merits further investigation.

Conclusion

Hypertension is one of the most significant health burdens in present day societies, affecting 25–35% of the population. Due to increasing life expectancy, incidence of hypertension is likely to increase in the future. The associated diseases (obesity, diabetes, and CKD) are also on rise. Despite the wide range of available non-pharmacological and pharmacological BP lowering approaches, hypertension is poorly controlled worldwide with a substantial impact on morbidity and mortality.

There is a distinct correlation between sympathetic activity, stage of disease, and hypertension. Almost every hypertensive subject shows sympathetic overactivity that correlates well with the adverse cardiovascular event rates (heart failure, myocardial infarction, and stroke).

Kidney plays an important role in the control of sympathetic nerve activity. There is increased sympathetic nerve activity in chronic heart failure, sleep apnea, and obesity also that can be measured by microneurography.

The well established contribution of sympathetic overactivity to human hypertension has led to the development of novel device-based and procedural interventions that favorably modulate autonomic neural mechanisms underlying hypertension. An additional approach currently being investigated to attain BP control in patients with RH is carotid body removal. Given the invasiveness, the cost of device-based strategies, and the different responsiveness of different patients, pre-procedural markers to stratify patients for the specific approach need to be identified. Future large scale clinical trials will determine the long-term safety and effectiveness of these various antihypertensive approaches in terms of BP control, hypertension-related end organ damage, and hard CV endpoints including death, myocardial infarction, and stroke.

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CHAPTER

17 Morning Surge Hypertension: A Treatable Hypertensive Variability

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Abstract

Morning surge hypertension (MSH) is among one of the most important hypertensive variabilities and its attenuation is very important. It is a short-term hypertensive variability. It is mainly controlled by the sympathetic neural output to the cardiovascular system, which is influenced by circadian rhythm. It seems like MSH is the main culprit behind the highest occurrence of cardiovascular and cerebrovascular events in the morning hours. For diagnosing MSH, ambulatory BP monitoring (ABPM) is the most appropriate method. Home blood pressure monitoring (HBPM) 2 hours after awakening is the practically available and largely affordable means in our country for MSH. Morning HBP recording in standing posture is a better predictor of MSH than morning HBP recording in sitting posture. For managing MSH, long acting antihypertensive a better choice. Long acting CCBs (especially amlodipine) are better than all other drugs. Long acting ACEIs, ARBs, β-blockers like nebivolol, etc. are good alternatives. For better management of MSH antihypertensives should be given in evening.

Introduction

Hypertension is a well known cause of cardiovascular, cerebrovascular, and all cause mortality and target organ damage (TOD). It is also among one of the most important preventable causes of death globally.[1] Blood pressure is not always the same rather it varies from time to time. This hypertensive variability is an independent risk factor for TOD and cardiovascular and cerebrovascular events. Thus, while choosing antihypertensive therapy, attenuation of hypertensive variability must be kept in mind. Morning surge hypertension (MSH) is among one of the most important hypertensive variabilities and its attenuation is very promising.

Blood Pressure Variability

We all diagnose and treat hypertension on the basis of clinic blood pressure measurement, but researchers showed that assessment and quantification of blood pressure variability (BPV) is of paramount importance. Ample evidences are there which show that increased BPV is independently associated with increased risk of TOD, cardiovascular events, and mortality.[2,3] Hence, for reducing hypertensive complications (e.g., cardiovascular and cerebrovascular events and TOD), attenuation of BPV is also required with reduction in average blood pressure values. BPV is directly proportional to mean BP values, and hence it is more in higher stages of hypertension as compared to lower stages of hypertension. White-coat hypertension and masked hypertension are well known BPV and there clinical and prognostic significance are well recognized.

On the basis of timing of changes in blood pressure, BPV can be divided into three types:

- Very short-term BPV (beat to beat oscillations in blood pressure)
- Short-term BPV (oscillations in BP within a day)
- Long-term BPV (oscillations in BP on day to day, visit to visit, or seasonal variation).

Causes and prognostic significance of all types of BPV differ with each other. According to definition MSH is a short-term hypertensive variability. Other short-term hypertensive variabilities are morning hypertension, nocturnal dipping, and nocturnal hypertension.

The circadian pattern in BP is well recognized. In night time during sleeping, BP values are usually low, which rise in early morning post-awakening period and usually coincides with transition period from sleep to wakefulness.[4] A moderate rise in BP in morning hours is physiological, but if it became much more then it is pathological and is termed as MSH, morning blood pressure surge (MBPS), or morning hypertension.

In the normal individuals, BP usually falls by 10–20% during sleep and this phenomenon is known as nocturnal dipping. In hypertensives this dipping status differs and on the basis of this difference they are categorized into four different groups namely:

- Dippers—in whom BP falls in the range of 10–20% during sleep
- Extreme dippers—in whom fall in BP is more than 20% during sleep
- Non-dippers—in whom fall in BP is less than 10% during sleep
- Reverse dippers or risers—in whom instead of falling BP rises during sleep.[1]

The suprachiasmatic nucleus (SCN) situated is hypothalamus is the master body clock. It has direct control over peripheral molecular clocks present in almost every cell of our body.[5] Due to a complex interaction of SCN with environmental and behavioral factors, a definite circadian pattern occurs in almost all physiological functions of our body.[4] The SCN receives inputs from our body (behavioral factors) from environment (temperature and light) and from cerebral cortex and then synchronizes autonomic output, hormone secretion, and behavior. At the morning hours or arousal time certain neurohormonal changes occur in our body. The most important among them are the activation of sympathetic nervous system. The MSH is mainly controlled by the sympathetic neural output to the cardiovascular system, which is influenced by circadian rhythm.[6] The occurrence of major cardiovascular and cerebrovascular events, e.g., myocardial infarction (MI), angina, stroke, transient ischemia attack (TIA), and sudden cardiac deaths are more common in morning as compared to other parts of the day. The exaggerated morning BP surge further increases the existing TOD in hypertensives. This might be the reason behind increased cardiovascular and cerebrovascular events in the morning.[7] It seems like MSH is the main culprit behind the highest occurrence of cardiovascular and cerebrovascular events in the morning hours.

The most widely accepted definition of MBPS is given by Kario et al.,[8] which can be calculated as follows:

- Sleep-trough MBPS—For getting it we have to take two values. First one is an average of the mean SBP of 2 hours after awakening and second one is an average of 3 lowest SBPs in the night. The difference is the sleep-trough MBPS.
- Prewaking MBPS—Here we again take two values. Fist one is a mean of SBP of 2 hours after awakening and second is mean SBP of 2 hours before awakening. The difference is prewaking MBPS.

For diagnosing MSH, ambulatory BP monitoring (ABPM) is the most appropriate method. Unfortunately, ABPM is neither available at every corner of our country nor is affordable by everyone. Home blood pressure monitoring (HBPM) 2 hours after awakening is the practically available and largely affordable means in our country for MSH.[4]

We can diagnose morning hypertension if the clinic BP values are more than or equal to 140/90 mm Hg in the morning or HBP values are more than or equal to 135/85 mm Hg in the morning.[9] One can also diagnose MSH, if the difference in morning and evening BP is more than 15 mm Hg, or if the difference in morning and nocturnal BP is between 35 and 55 mm Hg.[9-11] Nocturnal hypertension is diagnosed if average nocturnal BP is more than or equal to 120/70 mm Hg.[11] Usually it is found in non-dippers or reverse-dippers due to failure of nocturnal dipping.[11] In the beginning, night BP or BP during sleep could only be recorded by ABPM but now, with the development of newer home BP monitoring devices, which can intermittently (2, 3, and 4 AM) record nocturnal BP accurately during sleep, it is possible to get nocturnal hypertension by home BP monitoring also.[11]

According to consensus statement of the Asian expert panel, BP should be recorded two or three times every morning for 5–7 days and then average of these values should be used for evaluations.[9] According to the Japanese Society of Hypertension guidelines, morning HBP should be recorded within 1 hour after awakening and passing urine but before doing exercise or taking medicine or meal and evening HBP should be recorded just before going

to bed.[12] Morning HBP recording in standing posture is a better predictor of MSH than morning HBP recording in sitting posture.[13]

Pathophysiology of MSH

Many physiological changes occur in the morning but they themselves only are not capable of producing MSH or increased incidence of cardiovascular and cerebrovascular events in the morning. MSH and increased incidence of cardiovascular and cerebrovascular events in the morning occur due to a complex interaction among physiological, environmental, and behavioral factors.

Physiological Factors

These include hemodynamic, vascular, and hemato-rrheological changes.

Hemodynamic changes: In the morning, the most important hemodynamic changes are increase in heart rate and BP. Morning hours are also associated with increased cortisol secretion, activation of renin-angiotensin-aldosterone system (RAAS), and enhanced systemic vascular resistance. In the morning atherosclerotic plaques become more vulnerable to rapture and may cause thrombosis due to decreased vagal tone, increased catecholamine levels, and activation of RAAS. This may be the reason behind increased incidence of cardiovascular and cerebrovascular events in the morning.

Vascular changes: The main vascular changes in the morning are increased vascular tone and increase in the sensitivity of vascular receptors.[14,15]

Hematorrheologic changes: In the morning platelet aggregability is increased. According to Brezinski et al.[16] assumption of upright posture itself in the morning after sleep is responsible for increase in platelet aggregability. Other important hematorrheologic changes in the morning are increase in blood viscosity and decrease in fibrinolytic activity. These physiological changes all together make early morning prothrombotic state.

So, in the morning hours, physiologically there is

- early morning prothrombotic state
- the existing atherosclerotic plaques are more vulnerable to rupture, which may lead to thrombosis, and
- there is increase in vascular tone and vascular receptor sensitivity, which further increases the danger.

The physiological changes in the morning are like fuel ready to burn out, which needs only egniter (behavioral and environmental factors) to kindle the fire (producing cardiovascular or cerebrovascular events).

Behavioral and Environmental Factors

The most important factors are start of activity, heavy physical exertion, psychological stress, bursts of anger, smoking, alcohol consumption or salt intake, and cold temperature. Preexisting cardiovascular risk factors like aging, hypertension, dyslipidemia, and glucose abnormality further increases the risk. Increase in sympathetic nervous system activation and endothelial dysfunction, which may lead to increased surge in morning BP, may also be caused by poor sleep quality, sleep apnea or nocturnal hypoxia. Otto et al.[17] reported impaired endothelial function in morning hours in normal individuals. This impaired endothelial function reduces capacity for vasodilation, which further increases the risk.

According to Kario[18] vascular damages like small artery disease (increased vascular tone) and endothelial dysfunction and large artery disease (arterial stiffening) and baroreflex dysfunction are not only the consequence of exaggerated BP but are also the leading cause of exaggerated surge in morning BP and produces a vicious cycle of further damage. If BP is increased in normal individuals then vasodilation of small arteries occur which counter-balance the rise in BP, but in hypertensives this buffering capacity is reduced due to remodeling of small arteries, and hence lead to exaggerated surge in morning BP.[19] In response to any surge in BP in normal individuals baroreceptor-reflex, due to stretching of arterial baroreceptors situated in aortic arch and carotid arteries, occur which reduces BP but in cases of arterial stiffening this baroreceptor-reflex is impaired due to reduced stretching of baroreceptors, and hence will not be able to reduce surge in BP. Okada et al. observed an association between morning BP surge and arterial stiffening in elderly hypertensives.[20]

As most of the hypertensives take their drugs just after breakfast, so its effect is minimal in the morning and may lead to MSH. If the person is taking short-acting or intermediate-acting antihypertensive drug after breakfast then on next morning the effect will be lost and result in MSH.

The concept of morning hours is different in our country as compared to western world due to differences in climatic, geographical, and sociocultural factors. Most of the western researchers of circadian pattern divided the whole day into 4, 6 hourly quadrants and inferred that maximum cardiovascular and cerebrovascular events occur in second quadrant of the day (0600–1200 hours). This pattern is not suitable for our country. For circadian pattern study in our country the whole day should be divided into 6, 4 hourly intervals from 0000 to 2400 hours.[21] The factors responsible for morning events depend upon timing of awakening rather than on any hour or quadrant of the day. Ridker et al. observed that the risk of MI is twice more common within 3 hours after awakening than any other time of the day.[22] Rocco et al. found maximum number of transient myocardial ischemic attacks in 1–4 hours after awakening than any other comparable part of the day.[23] Above studies show importance of time of awakening. In our country, the time of awakening is in between 4 and 5 AM in rural and in between 5 and 6 AM in urban areas as compared to late awakening in western world. Most of the cardiovascular and cerebrovascular events in our country occur in between 6 and 7 AM (4 and 8 AM), that is, in between 2 and 3 hours after awakening.

Management

If we keep a target of morning HBP values less than 135/85 mm Hg then it will produce a strict 24-hour BP control and also provide a better effective protection than clinic BP values with same target.[24]

For managing MSH long-acting antihypertensives are better choice. Long-acting CCBs (especially amlodipine) are better than all other drugs. CCBs have a unique BP reducing property. It reduces higher BP values more than lower BP values, hence reduction in morning BP values is more as compared to night BP values, which results in higher reduction in surge in morning BP. Long-acting ACEIs, ARBs, β-blockers, like nebivolol etc. are good alternatives. As diuretics predominantly reduce night BP more than morning BP, hence they are not suitable for control of MSH. Timing of antihypertensive drug is also very important. For better management of MSH antihypertensives should be given in evening. Kario et al. observed a significant reduction in morning BP values and albuminuria by adding bed time doxazosin (α-blocker) on the top of base line antihypertensive therapy.[25]

Conclusion

Cardiovascular and cerebrovascular events occur more commonly in morning, which may be due to MSH. Proper management of MSH is essential to prevent these complications and TOD. Long-acting CCBs (especially amlodipine) is best among all drugs. Others are long-acting ACEIs, ARBs, Nebivolol, etc. For better results antihypertensives should be given in evening.

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CHAPTER

18 Hypertension in Elderly

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Abstract

The most rapid section is the elderly population and for the development of hypertension, age is a major risk factor. Variations in SBP/PP depend on various factors like arterial aging, frailty, multimorbidity, and polypharmacy.

Evaluation: Diagnosis of hypertension depends on various ways in assessment of blood pressure, cardiovascular (CV) risk factors, secondary causes, comprehensive geriatric assessment (CGA), etc.

Therapy: Lifestyle modifications and pharmacological treatment.

Conclusion: Elderly patient is the most rapidly increasing section in the society and age is a major risk factor for the development of hypertension. These population are associated with multiple comorbidities, frailty, cognitive decline, and loss of autonomic functions and has to be managed from a life-course perspective with proper investigations and timely treatment of high BP as compared with younger age groups.

Introduction

Elderly patients represent the most rapid increasing section of the population. For the development of hypertension (mainly systolic), age is a major risk factor. The rising number of older population (especially over 80 years) also leads to elevated blood pressure (BP) as well as at the same time they are more prone to multimorbidity, frailty, cognitive dysfunction, multiple medications, and partial/complete loss of autonomic functions.[1,2]

During aging, high BP (mainly systolic) is a clinical expression of arterial stiffness[3,4] and some studies have also indicated the association of neurocognitive disorders, like Alzheimer and vascular types, with elevated BP.[5]

According to some data, risks and benefits of correction of high BP are obtained in younger as well as selected older individuals.[6]

There are two major differences between these two age groups:

- The incidence and prevalence of comorbidities, frailty, and loss of autonomy increases mostly after 80 years; and
- In the "younger" old patients (60–70 years), evidence supports benefits of reducing BP, while there are limited evidence in patients (over 80 years).

Therefore, the management of older patients with high BP must be the following differences as compared with younger age groups.

Elevation in Systolic BP in Older Age Groups: Due to Arterial Aging

Both (systolic blood pressure) SBP and (diastolic blood pressure) DBP are independent predictors of cardiovascular disease (CVD) in younger age groups (<50 years), epidemiological studies suggest that SBP is a strong risk factor and DBP is inversely related with the risk in age group of 50 years or more.[4]

Increase in Pulse Pressure with Age

Both SBP and DBP increase as individual gets older. In the majority of cases, SBP and pulse pressure (PP) increase disproportionally to DBP with age and the most common cause is progressive stiffening of arterial wall.[3,7]

Causes like hypertrophy of wall, deposits of calcium, changes in the extracellular matrix, which include increase in collagen, fibronectin, fragmentation, disorganization of the elastin network, nonenzymatic crosslinks, and cell-matrix interactions, are responsible for decrease in elastic properties as well as the development of artery wall stiffness.[8] The duration of the diastolic interval and the rate at which pressure falls helps in determination of the DBP.

The speed of propagation of the pressure wave of artery (pulse wave velocity-PWV) and the timing of the reflections of the wave also depend on the viscoelastic properties of the arterial walls.

So the stiffening of the arteries increases PWV and there is an early return of the waves which are reflected, and then overlap with the incidental pressure wave, which further contributes to the increment in SBP and PP.[3,7]

Diabetes is also responsible for accelerated aging of arteries (due to increase in arterial stiffness) leading to an increase in PP as compared with nondiabetics.[9,10]

Increase of SBP/PP in Old Age

As SBP and PP better reflect the CVD risk in older age, whereas DBP better reflects the risk in younger age.[4] DBP in young patients is mostly depends on peripheral resistance (PR), and hence low DBP reflects low PR. In addition to this, there is hyperkinetic circulation in young age, so, DBP is less variable than SBP, thus reflects better CV risk.

In old age groups, a low DBP may reflect high arterial stiffness (major manifestations as compared to low PR).[3,7]

Few Terms: Frailty, Multimorbidity, and Polypharmacy

Frailty is a syndrome (biological) of decrease in reserve and resistance to stress factors, which result from collective decline across multiple physiological systems and cause adverse outcomes.[1]

It increases mostly after the age of 80 years. Susceptibility to stress factors is also influenced by behavioral, environmental, social, and biological risks, consequently resulting in an increase in multiple adverse health outcomes.

Few studies have indicated that there is increase in morbidity and mortality in very old frail subjects and are mainly observed in treated hypertensives (mostly on several antihypertensives) and not in normotensives.[11,12]

Polypharmacy (taking more than 4 drugs) and side effects related to drugs are major problems in this age group that may contribute to morbidity, increased rates of hospital admissions, as well as mortality.

Clinical Evaluation

- Diagnosis of hypertension should be based on:
  - At least three different BP measurements, which should be taken on two visits of office separately.
  - At least two measurements, which should be obtained while the patient is sitting comfortably for 5 minutes with the support of back, feet on the floor, arm in horizontal position, and the BP cuff (of adequate size) at the level of heart.
  - Assessment of BP by self at home and 24-hour ambulatory BP measurements, if needed, can contribute in detection of white coat hypertension and recognition of CV risk related to high BP levels.
  - White coat hypertension (exaggerated BP measurements) in the office is more common in older subjects.
- Secondary hypertension is uncommon; therefore, extensive workup for every old patient with hypertension is not needed. But if there is, sudden deterioration of hypertension (previously well controlled), resistant hypertension, etc., then the causes which are reversible should be investigated.
- CV risk factors and target organ damage should be assessed to check the overall risks of CVD.
- Physical examination, which includes fundus examination, abdominal bruits auscultation, peripheral pulses, and palpation of abdomen, should be done thoroughly.
- BP should be taken in supine position in older hypertensives (independent of the symptoms suggestive of orthostatic hypotension).
- An ECG should be done (to look for LVH, IHD, arrhythmias, and conduction disturbances) and urine examination for determination of concentration of albumin should be done.

- Comprehensive geriatric assessment (CGA), a proposed methodology to provide an approach (globally) to complex older age groups and their related problems, and allowing a specific and organized plan of care, which should be implemented for each and every patient.
- CGA permits for a complete assessment of drugs, which recognize and prevent drug-related problems and improve the quality of prescription.

Antihypertensive Therapy

Lifestyle Modifications

- Changes in lifestyle are beneficial for older patients who are being treated for hypertension.
- In obese patients, reduction in weight is the most effective intervention for lowering of BP.
- As older patients are more prone to have salt-sensitive hypertension; so sodium restriction is recommended.
- The Dietary Approaches to Stop Hypertension (DASH), reduction in alcohol intake (as it can lead to increased risk of falls and confusion), and increase in physical activity should be recommended. Weight reduction alone without exercise should not be recommended as it could induce loss of muscle mass and even can lead to cachexia.[13]

Pharmacological Treatment

Few Trials

Clinical trials (meta-analysis) as shown in **Table 1**, indicated that antihypertensive treatment in patients (>65 years) produces similar proportional reductions in the CV risk as that of in young patients,[14] but in older patients, the immediate benefits of treatment were more pronounced (because of a more average risk).

Target BP

In European-2013 guidelines, which stated higher SBP (>160 mm Hg), a definite evidence for reduction of SBP between 150–140 mm Hg is present.[15]

Later these were challenged by SPRINT Trial,[16] which was conducted in patients (with high CV risk and using antihypertensive drugs already), showed that keeping SBP of 120 mm Hg resulted in lowering of CV events and the total mortality as compared with patients with the target SBP of 140 mm Hg.[17]

Further it indicated that keeping a target of 120 mm Hg showed a significant rise in adverse effects in very old patients and frail patients like hypotension, syncope, dyselectrolytemia, failure of kidney, etc.

A group of experts on hypertension and geriatric medicine proposed few rules for the hypertension management in very old patients with partial/complete loss of autonomy.[18] It suggested that decisions regarding therapy should be taken after proper information of cognitive status, functional capacity, multi drug intake, frailty status, etc. of the patient. It also suggested keeping SBP (on treatment) between 150–130 mm Hg is safe range.

Older Hypertensives: Any Specific Drugs?

- JNC-7 recommended five drug classes (thiazides/thiazide-type diuretics, ACEIs, beta-blockers, CCBs, and ARBs) to be used initially.
- JNC-8 recommended four drug classes specifically (ACEIs, ARBs, CCBs, and diuretics).
- Additionally, the JNC-8 recommended these classes based on the evidences like race, CKD, and diabetics. So, the change between these two (JNC-7 & JNC-8) was the non-inclusion of beta-blockers in the 1st list treatment of JNC-8 with the exception like presence of associated indications (history of MI, chronic angina, or heart failure). It suggested that the beta-blockers may not be as beneficial as compared to other classes in the reduction of stroke, mostly in older patients.[19]
- Majority of older patients require dual antihypertensives but it is preferable to initiate with a single drug.[18]
- Increased risks of adverse effects are there with combination drug therapy, mostly among very older age patients with comorbidities.
- Cautious addition and titration of drugs are important, especially in the groups of older age, renal failure, or associated with hypotension and falls.

Other Issues in Older Hypertensives

Postural Hypotension and Nocturnal Dipping of BP

Older individuals are more prone to orthostatic hypotension, which is frequent with increasing age, and is associated with increased risk of death, CV events, and falls.[20-22]

TABLE 1 Design and main results of placebo-controlled trials designed to evaluate the benefits of treatment in individuals 60 years and older with systolic-diastolic hypertension or isolated systolic hypertension

	EWPHE	*MRC*	*STOP*	*SHEP*	*SYSTEUR*	*HYVET*
Number of subjects and age at enrollment	n = 840 Age > 60	n = 4396 Age = 65–74	n = 1627 Age = 70–184	n = 4736 Age > 60	n = 4695 Age > 60	n = 3845 Age > 80
Inclusion BP criteria (mm Hg)	SBP: 160–239 and DBP: 100–119	SBP: 160–209 and DBP < 115	SBP: 180–230 DBP > 90 or DBP 105–120	160–219/<90	160–219/<95	160–199/<110
Active treatment medication	HCTZ + triamterene	Atenolol or HCTZ + amiloride	Beta-blockers or diuretics	Chlorthalidone ± atenolol	Nitrendipine ± enalapril	Indapamide ± perindopril
Goal SBP levels (mm Hg)		SBP < 150 or SBP < 160	< 160/95	>20 from BL or SBP < 160	>20 from BL or SBP < 150	<150/80
BP reduction (mm Hg) with active tt compared with BL	30/15	33/15	28/15	27/9	23/7	29.5/12.9
BP reduction (mm Hg) (Active tt vs. Placebo)	20/9	13/10	19.5/8.1	12/4	10/5	15.0/6.1
Achieved BP (mm Hg) with active treatment	150/85	152/76	167/87	143/64	151/79	144/78
Mean follow-up (years)	4.3	5.8	2.1	4.5	2.0	1.8
Percent reduction in events						
Stroke	36	25[a]	47[a]	33	42[a]	30
CAD	20	19	13[b]	27	30	28
CHF	22	–	51[a]	55[a]	29	64[a]
All CVD	29[a]	17[a]	40[a]	32[a]	31[a]	34[a]

[a]Statiscally significant
[a]Myocardial infarction only
BL, baseline; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure, CVD, cardiovascular disease; EWPHE, European Working Party on Hypertension in the Elderly; HCTZ, hydrochlorothiazide; MRC, Medical Research Council; SBP, systolic blood pressure; STOP, Swedish Trial in Old Patients; tt, treatment

Hence, the suggestion of standing BP measurement and its evaluation and use in treatment goals in older age groups was given by National High BP Education Working Group.[23]

Antihypertensives should be started in low doses and later titrated and added cautiously in older patients (as compared with young patients) in view of postural hypotension, syncope, and falls and frailty.

Some older patients on antihypertensives may have an increased nocturnal dipping of BP, which may lead to cerebral hypoperfusion so BP is routinely measured in waking hours. These patients have more risks of CV events.

Cognitive Impairment

Many studies have suggested an association between elevated BP in mid-age groups and the impaired cognition risk.

Duration of hypertension, levels of BP, cognitive profile, and testing may contribute in the discrepancy in the relationship between hypertension and decline of cognition.

Few studies have shown that markers of aging of arteries may recognize patients at higher risk of cognitive decline, whereas BP alone does not appear in having a significant predictive value.[24-26]

Conclusion

Elderly patients are the most rapidly increasing section in the society and age is a major risk factor for the development of hypertension. These population are associated with multiple comorbidities, frailty, cognitive decline, and loss of autonomic functions.

For diagnosis, clinical examination, physical examination, lab investigations, as well as complete geriatric assessment should be done properly.

While treating the patients, lifestyle modifications should be advised initially. Later, drug therapy should be started after consideration of factors like age, sex, comorbidities, frailty, and cognitive status. Adverse effects of the drug should be kept in mind while starting the drugs and the patient should be continuously monitored.

So finally, it should be noted that hypertension in older age groups has to be managed from a life-course perspective with proper investigations and timely treatment of high BP as compared with younger age groups.[27]

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CHAPTER

19 Apparent Treatment Resistant Hypertension—What a Physician Needs to Ponder

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Abstract

Treatment resistant hypertension (TRH) and apparent treatment-resistant hypertension (aTRH) are two different identities. Compared to overall hypertensives, people with TRH have more poor outcomes, and hence BP control is much more important in such population. Low adherence to the medication intake is the major modifiable patient-related barrier in achieving controlled blood pressure. aTRH is used when issues of dosing, medication adherence, and white coat hypertension have not yet been ruled out, and have measurements as systolic BP ≥140 mm Hg and/or ≥90 mm Hg diastolic on ≥3 BP medications. The prevalence of controlled hypertension in India is 35% and, in the world, it ranges between 6% and 17%. MMAS-8 (Morisky Medication Adherence Scale) with 93% sensitivity and 53% specificity is used in validating medication non-adherence in very low-income patients who were being treated for hypertension in routine care clinic setting. The patients with aTRH were significantly associated with older age groups (>55 years), obesity (BMI >27.5 kg/m^2), diabetes mellitus, prolonged hypertension (>10 years), female sex, black race, and comorbidity like ischemic heart disease, depression as risk factors as compared to patients with non-resistant hypertension. The prognosis of the patients suffering from aTRH compared with controlled hypertension should be impaired in aTRH as such patients typically have longstanding history of sub-standardly controlled BP and usually have other associated comorbidities and cardiovascular risk factors like diabetes, obstructive sleep apnea, left ventricular hypertrophy, and/or chronic kidney disease. Among aTRH patients, decrease adherence to antihypertensives is a significant problem and, spreading awareness for better medications adherence and proper measurement of BP can easily tackle it. This article discusses about the various causes of aTRH, role of medication adherence in aTRH, and factors affecting it, risk factors of aTRH and workup of aTRH in detail.

Introduction

Treatment resistant hypertension (TRH) and apparent treatment-resistant hypertension (aTRH) are two different identities. Term aTRH is used when issues of dosing, medication adherence and white coat hypertension have not yet been ruled out. The prevalence of TRH and aTRH internationally is found to be 11.8% and from 6% to 17%, respectively. More poor outcomes are noted in TRH patients compared to the overall hypertensive population, and hence BP control is much more important in such population. Low adherence to the medication intake is the major modifiable patient-related barrier in achieving controlled blood pressure. This article mainly focuses on various aspects of evaluation of a case of aTRH.

Definition

Hypertension by definition is an office systolic blood pressure (SBP) more than equal to 140 mm Hg and/or diastolic blood pressure (DBP) more than 90 mm Hg.

Treatment resistant hypertension (TRH) by definition is blood pressure reading more than 140/90 mm Hg in spite of simultaneous use of three antihypertensive

medications of various classes. Ideally one drug should be diuretic and all the three antihypertensives must be taken in their optimal doses.[1] This number of medications is arbitrarily and not scientific. It is to note that patients having controlled blood pressure (i.e., <140/90 mm Hg) with ≥4 antihypertensive drugs should also be categorized as having TRH.

Apparent treatment-resistant hypertension (aTRH) is used when issues of dosing, medication adherence, and white coat hypertension have not yet been ruled out. In different studies, uncontrolled aTRH has been described as systolic BP ≥140 mm Hg and/or ≥90 mm Hg diastolic on ≥3 BP medications. Controlled aTRH by definition is BP <140 mm Hg systolic and <90 mm Hg diastolic on ≥4 antihypertensives drugs unless specified otherwise.[1]

Optimum dose of a medication is the quantity of the drug that will produce the desired effect without any unfavorable side effects. It is not necessarily a maximum dose.

The purpose of defining TRH and aTRH is to find out patients having reversible causes of hypertension and who will be benefitted with special diagnostic and therapeutic considerations.

Prevalence of TRH and aTRH

The prevalence of true TRH is unknown. Nearly 10% of the patients with diagnosed hypertension have true TRH. Above the BP value of 120/70 mm Hg, cardiovascular diseases (CVDs) mortality doubles usually with every 10 and 5 mm Hg increase in SBP and DBP respectively.

Prevalence of aTRH: International Scenario

The prevalence of aTRH varies from 6% to 17% **(Table 1)**.

aTRH: Indian Scenario

The prevalence of controlled hypertension in India is 35%.[2] Since at present there is unavailability of good and robust data from India, thus the exact prevalence of resistant hypertension is difficult to quote. In a study by Mandal et al. in Kolkata, among 300 hypertensive subjects, 23.33% were identified as aTRH.[9]

Causes for aTRH and TRH

The causes of resistant hypertension are divided into apparent cause and true cause **(Table 2)**.

Role of Medication Adherence in Hypertension

Adherence to medication is a crucial part of patient care and indispensable for reaching goals. Medication adherence is defined as "The extent to which the medication taking behavior of a patient corresponds with agreed recommendations from the health-care provider."[15] The different factors that affect patients' adherence to the drugs are demographic features, disease severity, complexity of drug regime (number and frequency of the drug prescribed), drug classes (tolerability and side effects profile of the drug), patients' forgetfulness, and lack of understanding on the nature of disease.[16]

TABLE 1 The prevalence of aTRH in various international studies

Study (reference)	*Study location*	*Study period*	*Prevalence of aTRH % (N=sample size)*
Cushman et al.[2]	North America	1994–2002	9.4% (N=33,357)
INVEST[3]	Canada, South Africa, United States, Spain, Mexico, New Zealand, Israel, Italy, Australia, Germany, France	1997–2003	12.9% (N=22,576)
McAdam-Max et al.[4]	United States	2002–2005	12.4% (N=29,474)
Persell[5]	United States	2003–2008	9.2% (N=15,968)
Sim et al.[6]	United States	2006–2007	9.4% (N=470,386)
Sarganas et al.[7]	German	2008–2011	6.8%. (N=7,115)
Choi et al.[8]	Korea	2015	11.9% (N=2,439)

TABLE 2 Listing the causes of TRH and aTRH

Apparent cause (Pseudoresistance or aTRH)	***True cause (True TRH)***
Pseudoadherence to antihypertensive drug therapy	*High risk patients—which includes following:* • Female sex • Elderly • Black race • Comorbidities like obesity,[1,10] diabetes mellitus, chronic kidney disease, left ventricular hypertrophy, and high baseline blood pressure
Improper technique to record BP	*Lifestyle which include:* • Increase dietary salt intake (>10 gm/day)[11,12] • Increase alcohol consumption[13,14] • Lack of exercise
White coat hypertension	*Drug related cause which include:* • Following medications can cause difficulty in controlling BP— • Non-steroidal anti-inflammatory agents—Aspirin • Selective COX-2 inhibitors • Sympathomimetic agents—decongestants, diet pills, cocaine • Stimulants—amphetamine, modafinil, methylphenidate, methamphetamine • Alcohol[13,14] • Erythropoietin • Cyclosporin • Natural licorice • Oral contraceptives • Herbal compounds—ma-huang or ephedra
	Secondary causes include: • Renal parenchymal disease • Primary aldosteronism • Obstructive sleep apnea • Renal artery stenosis • Drug induced or heavy alcohol use • Thyroid disorders
	• *Genetic causes*—CYP3A5 allele (CYP3A5*1)[1]

Adherence to treatment can be measured using different methods:

- Pill counting
- Drug concentration in the body fluids and response to therapy.
- Measures which involves Electronic Medication Packaging (EMP's) devices, clinician assessments and self-report.

World Health Organization (WHO) reports that secondary to substandard availability and accessibility of medications and health-care services, adherence to drugs in patients who are chronically ill averages nearly 50% in developing countries.[17] The asymptomatic nature of the disease augments the issue of non-adherence to medications in hypertension.[18]

In cohort study, which retrospectively studied the variance in medication adherence among hypertensive patients, it was noticed that the factors like duration of hypertension (shorter duration corresponds with better adherence) and use of newer agents (like calcium channel blockers and ACE inhibitors) had the strongest positive effect on medication adherence.[19]

Choosing a Suitable Medication Adherence Measure

An ideal medication adherence measure should have the following characteristics—low cost, practical, user friendly, highly reliable, easy to carry out and flexible. Eight-item MMAS-8 (Morisky Medication Adherence Scale) is the one easy and validated tool.[20] In 2008 using Medication Adherence Questionnaires (MAQ), Morisky et al. developed this 8-item MMAS (MMAS-8) tool which has 93% sensitivity and 53% specificity in validating

TABLE 3 Studies which studied medication adherence using MMAS (4 points/6 points/8 points)

Studies (reference)	*Results as percentage of non-adherence to medication*	*Factors responsible for non-adherence*
Irvin et al.[21]	The distribution of MMAS scores of 0 (best adherence) and 1, 2, 3, or 4 (worst adherence), was 68.8%, 24.1%, 5.0%, and 2.0%, respectively	After adjustments for age/gender/geographic region of residence, blacks were found to have low medication adherence. Also women compared to men, have low drug adherence
Pandey et al.[22]	Adherence score less than 6 was seen in 26% of patients. The actual prevalence of non-adherence using therapeutic drug monitoring was 51%	This study suggested that there is limited accuracy of the MMAS-8 tool in detecting drug adherence in patients of aTRH
Hema et al.[23]	Adherence was seen as— • High—15.3% • Low adherence—(62%, n=248) (majority of study population) • Medium adherence—22.7% (n=91)	Higher adherence was found in— • 50 years & above age group (46.6%) • Among females (51.6%) • Among nuclear families (47.1%) • Among literates (44.2%)
Nagarkar et al.[24]	Using MMAS-8, 23.4% were high adherent and 76.5% showed low adherence to the medication	Medication adherence was found— • Significantly associated with age, family type, and experience of symptoms • Not associated with gender, education, frequency, and number of medications
Behnood-Rod et al.[25]	49.6% showed MMAS-8 score less than 6	Following has been noted— • Negative linear association between systolic BP as well as diastolic BP • Factors recognized to have statistically significant association with the MMAS-8 score were—overweight/obesity/previous history of admission to emergency services due to hypertensive crisis/getting medication directly from drugstore without revised prescription

TABLE 4 Non-adherence to medication in aTRH

Study	*Location*	*Method of non-adherent assess*	*Baseline blood pressure*	*Non-adherent*
Yakovlevitch and Black[26]	New Haven, CT, USA	MD interview	176/103	9/91 (9.9%)
De Souza et al.[27]	São Paulo, Brazil	Pill count	163/103	16/44 (36%)
Cereal et al.[28]	Prague Czech R	Serum level	171/97	55/84 (65.5%)
Jung et al.[29]	Frankfurt, Germany	Urine level	Not stated	40/76 (53%)
Blinker et al.[30]	Dallas, TX, USA	Urine level	169/103	23/40 (57.5%)

medication non-adherence in very low-income patients who were being treated for hypertension in routine care clinic setting.[20] Soon similar success was obtained in validating MMAS with high reliability in patients with other chronic illnesses **(Table 3)**.[11]

Role of Medication Adherence in aTRH

There is risk of poor outcomes in patients with aTRH. Drug adherence and intensification ameliorate BP control in the patients who receive pharmacological treatment; however, less is studied about the outcomes of these processes in aTRH. Substandard adherence or failing to take ≥75% of prescribed drug, influence ~10–60% of aTRH **(Table 4)**.[1]

Factors Affecting Medication Adherence in aTRH

There are very few studies which studied about factors affecting medications adherence in aTRH. **Table 5** comprises few studies which have studied these factors.

TABLE 5 Studies related to the factors affecting medications adherence

Study (reference)	*Year of study*	*Results as prevalence of non-adherence (%)*	*Results as factors responsible for poor adherence of the medications*
Bhandari et al.[33]	2015	≥80	The following patients were more likely to be adherent to treatment: • Patients hypertensive for ≥5 years (2.98 times) • Whose hypertension was detected during checkups for conditions related to hypertension (2.35 times) • Patients living with ≤4 family members (2.01 times) • Family income of ≥3,000 rupees (2.56 times) • Who were getting free drugs (4.16 times) • Patients perceiving current blood pressure to be under control (2.23 times) • Those satisfied with current treatment (3.77)
Venkatachalam J[34]	2015	24.1	Adherence was found to be higher in following groups: • Age groups 30–39 years (27%) and above 60 years (27.1%) as compared with other age groups • Among female (25.5%) respondents than male respondents (22.6%) • Married (24.8%) respondents than unmarried respondents (21.1%)
Patel and Taylor[35]	2002	32	No statistically significant differences in medication adherence based on: • Age • Gender • Education • Total household income • Living arrangements • Total number of years with hypertension • Number of medications
Karakurt et al.[36]	2012	57.9	Significant association between old age and non-adherence
Ramli et al.[37]	2012	46.6	Female were one and a half times more adherent than male
Gupta et al.[38]	2016		• Age has an inverse association with non-adherence to antihypertensive treatment • Every 10-year increase in age was associated with more than 30% reduction in the odds of non-adherence in the UK and the Czech populations • Females were found to be more non-adherent compared to males
Yang et al.[39]	2016	43.5	Better medication adherence seen in: • Older participants • Patients having more knowledge of hypertension

Alsabbhag et al. extracted data of 40 cohorts in 30 studies reporting socioeconomic status (SES) variable and did a structured review and meta-analysis study to discover the relationship between SES with adherence to antihypertensives.

They noticed that higher SES was associated with a lower risk of non-adherence in 31 cohorts (77.5%), with no difference in 1 cohort, and with an increased risk of non-adherence in 8 cohorts.[31] A study by Siegel et al. entitled "Antihypertensive medication adherence in the department of veterans affairs," which comprised of 95% of all patients included in this review noticed that patients with an ICD-9 diagnosis of depression were found to be less likely adherent to medication in multivariate analysis.[32]

Risk Factors for aTRH

The patients with aTRH were significantly associated with older age groups (>55 years), obesity (BMI >27.5 kg/m^2), diabetes mellitus, prolonged hypertension (>10 years), female sex, black race, and comorbidity like ischemic heart disease, depression as risk factors as compared to patients with non-resistant hypertension.

Workup to Differentiate aTRH from TRH

Peudo or aTRH

In clinical practice it is the most common form of resistance.[1] It inferred absence of true resistance to drugs and is due to either wrong technique of measuring

BP, substandard adherence to treatment or white coat hypertension.

Poor Measurement Technique

Faulty measurement techniques can result in false high readings of BP and thus can result in aTRH. The two most common mistakes in clinical scenario are—

- Measuring the BP immediately and not allowing the patient to sit calmly
- Use of inappropriate size cuff

This results in falsely high BP readings of the patients who otherwise are having normal or controlled BP.

Substandard Adherence

One of the major reasons of inadequate BP control is poor adherence to antihypertensives. It is seen that substandard adherence is usual at primary care level and it is less frequent among patients who are being treated by specialists. Inadequate BP control and treatment resistance are two different identities. Before labeling failed antihypertensive regimen, it is mandatory and wise to ensure that the regimen was taken correctly as advised by the treating physician.

White Coat Effect

White coat hypertension is persistently higher values of clinic BP while home recordings are significantly lower. Studies specify that significant white coat effect is as usual in aTRH patients as in more general hypertensive population. Patients of resistant hypertension on the basis of white coat effect show less severe target organ damage and have less cardiovascular risk compared with patients who have persistently higher ambulatory BP values.

Fragmented Health Services

India like other developing countries is facing an important problem of lacking access to chronic care. Patients shift to different physicians at will and the majority of primary and secondary care physicians have no robust system to track patient's data. This effects in inappropriate care, substandard lifestyle advice, and revising pharmacological therapy with substandard BP control.

Workup for TRH/aTRH

Workup of TRH and aTRH is summarized in **Table 6**.

Guiding Principles or Clinical Pearls to Evaluate Resistant Hypertension

What a clinician should know to evaluate a case of resistant hypertension is summarized below:[1]

- 1. Confirm TRH—
  - Clinic BP >130/80 mm Hg
  - Patient taking ≥3 antihypertensive agents (including a long acting calcium channel blocker,

TABLE 6 Resistant hypertension (TRH and ATRH) workup[40]

Find out and correct pseudohypertension (aTRH)	• Properly measure BP • Check white coat effect with help of authentic home or 24-hour ambulatory BP measurements • Evaluate treatment adherence and boost it with—education and awareness Prescribing cost effective drug regimen Prescribing drugs with least and tolerable adverse effects Prefer once daily fixed-dose combination products
Life style changes	• Whether patient is using any pharmacological/herbal substances that may cause increase in BP—if yes, remove it • Find out the amount of daily alcohol intake and advise to cut down it to zero or recommended daily intake • Find out daily dietary salt intake and recommend sodium restriction to <100 mmol (2.4 gm) per day • Evaluate the degree of obesity, abdominal obesity, and physical activity. Also advise weight reduction and regular aerobic exercise (at least 30 min/day, most days of the week)
Find out contributing factors to true resistant hypertension	• Evaluate renal function (estimate glomerular filtration rate) and modify treatment accordingly • Find out causes of secondary hypertension
Treatment should be customized as per the patient characteristics with optimal doses of suitable medications. Refer to the hypertension specialist if everything fails.	

a blocker of renin-angiotensin system, and a diuretic)
  - Medications are at maximal or maximally tolerated doses
- Assess for pseudo or aTRH—
  - Confirm adherence to antihypertensive treatment
  - Monitor 24-hour ambulatory BP to eliminate white coat effect
  - Use home BP monitoring in case of non-availability of 24-hour ambulatory BP monitoring
- Assess for secondary hypertension—look for the following—
  - Primary aldosteronism
  - Renal parenchymal disease
  - Renal artery stenosis
  - Pheochromocytoma/paraganglioma
  - Cushing syndrome
  - Obstructive sleep apnea
  - Coarctation of aorta
  - Other endocrine causes like—hypothyroidism, hyperthyroidism, hypercalcemia, and primary hyperparathyroidism, congenital adrenal hyperplasia, acromegaly
- Assess for target organ damage—
  - Ocular: fundoscopic exam
  - Cardiac: left ventricular hypertrophy, coronary artery disease
  - Renal: proteinuria, decreased glomerular filtration rate
  - Peripheral arterial disease: ankle/brachial index

Prognosis

The prognosis of the patients suffering from aTRH compared with controlled hypertension has not been particularly studied in detail. Uncertainly but likely, prognosis should be impaired in aTRH as such patients typically have longstanding history of sub-standardly controlled BP and usually have other associated comorbidities and cardiovascular risk factors like diabetes, obstructive sleep apnea, left ventricular hypertrophy, and/or chronic kidney disease. It is also unknown so far that post-successful treatment of aTRH in such patients, how much this cardiovascular risk will reduce. However, the advantage of successful treatment is likely considerable as suggested by hypertension outcome studies in general and by the early Veterans Administration cooperative studies, which illustrated a 96% reduction in cardiovascular events over 18 months with help of triple antihypertensive regimens compared with placebo in patients with severe hypertension (diastolic BP 115–129 mm Hg).[41]

Conclusion

Spreading awareness for better medications adherence and proper measurement of BP can easily tackle the aTRH, which is otherwise a significant issue. Among aTRH patients, decrease adherence to antihypertensives is a significant problem. Thus, it is emphasized that health-care professionals should pay attention to this fact while developing a treatment program for aTRH patients in order to enhance adherence to antihypertensive medications and improve health outcomes.

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CHAPTER

20 Resistant Hypertension

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Abstract

Resistant hypertension refers to elevated blood pressure above the target level in spite of concurrent use of three antihypertensive agents from three different classes (including a diuretic) in the maximum tolerated/recommended doses. It is important to exclude pseudo-resistant hypertension before making a diagnosis of resistant hypertension. Adverse cardiovascular event rate is almost 50% higher in cases of resistant hypertension than in general hypertensive patients. Chlorthalidone/indapamide is the agent of first choice while selecting a diuretic. It is important to uptitrate the doses of three existing antihypertensive agents to the maximum permissible/tolerable levels before adding the fourth agent. The fourth preferred agent of choice is spironolactone provided the serum potassium is $\leq$4.5 mmol/L. Next comes the role of beta blockers, alpha blockers, centrally acting agents, direct vasodilators, and direct renin inhibitors. Device-based therapies like renal denervation and carotid baroreceptor stimulation have a very limited role restricted to highly specialized centers.

Introduction

Hypertension is one of the most common ailments seen by a primary care physician and failure to detect and treat it timely leads to many complications like stroke, myocardial infarction, and chronic kidney disease. It is unfortunate that in spite of having well established diagnostic and therapeutic protocols, more than half of patients are not controlled to target levels. Resistant hypertension refers to elevated blood pressure above the target goal of 140/90 mm Hg in spite of using three antihypertensive agents from three different classes, including a diuretic, in the maximum permissible/tolerable doses.[1] Target goal of blood pressure is 130/80 mm Hg for patients of chronic kidney disease and established cardiovascular disease. Here, it is worth mentioning that a proper combination means a combination of three antihypertensive drugs having synergistic action—angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) plus a calcium channel blocker (CCB) and a thiazide like diuretic.

Prevalence

Exact prevalence of resistant hypertension is not known but 20–30% of patients become resistant to treatment with the passage of time.[2] In largest hypertension trial (ALLHAT), only 67% patients attained a systolic blood pressure of less than 140 mm Hg and 92% attained a diastolic blood pressure of less than 90 mm Hg. Refractory hypertension is not synonymous to resistant hypertension as refractory hypertension is much more severe form of disease where the blood pressure cannot be controlled even with five or more drugs including spironolactone and have to be referred to specialized centers for more invasive/devised based therapies.

Pseudo-resistant Hypertension

As the name indicates it is not truly resistant, but looks like resistant and one must rule it out before making a diagnosis of resistant hypertension. Important causes of pseudo-resistance are as follows:

- Improper blood pressure measurement technique or inappropriate sized blood pressure cuff.
- Poor compliance to prescribed medicines due to cost, side effects, or inadequate counseling. A renal denervation trial revealed that only 20% of patients were adherent to the prescribed medicines.[3]
- Inadequate/suboptimal doses or improper combination of drugs. A general practitioner's prescription review of uncontrolled hypertensive patients revealed that only 18% of these patients were prescribed three antihypertensive agents including a diuretic.[4]
- Non-adherence to diet and lifestyle modification like reduction of salt intake, cessation of cigarette smoking, and moderation of alcohol intake.
- White coat hypertension—here the blood pressure is high in doctor's chamber but otherwise it is normal. Best way to diagnose white coat hypertension is either ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). White coat hypertension should be suspected in patients having orthostatic hypotension and in those having very high blood pressure readings in the absence of target organ damage.

Medications Interfering with Hypertension Treatment

A variety of drugs can raise the blood pressure or interfere with the working of antihypertensive drugs making them less effective.[5] Commonly used such drugs are:

- NSAIDs
- Oral contraceptives
- Glucocorticoids
- Sympathomimetics including nasal decongestants
- Antidepressants
- Cocaine
- Erythropoietin
- Amphetamine

Secondary Hypertension

About 5% to 10% of total hypertensive patients have secondary hypertension and it is more prevalent in resistant hypertension.[5] Common causes of secondary hypertension are obstructive sleep apnea (OSA), renal artery stenosis (RAS), chronic kidney disease (CKD), primary aldosteronism. Less common causes are pheochromocytoma, Cushing's syndrome, hyperthyroidism, hypothyroidism, coarctation of aorta, and drugs.

Obstructive Sleep Apnea (OSA)

Clinical features of OSA are obesity, snoring, and day time sleepiness. Sleep apnea is more severe and more common in men than women.[6] Sleep apnea gives rise to hypoxia which stimulates sympathetic nervous system and is responsible for resistant hypertension.

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA. Once OSA is treated with CPAP, the blood pressure starts coming down and lesser and lesser medicines are required to control blood pressure.

Primary Aldosteronism

As the name indicates, primarily there is excessive production of aldosterone from the adrenal cortex. Control of hyperaldosteronism can control the blood pressure to a reasonable level. It is of two types:

- Bilateral adrenal hyperplasia or idiopathic hyperaldosteronism (IHA)
- Unilateral aldosterone producing adenoma (APA)

Bilateral hyperplasia (IHA) is much more common than unilateral adenoma (APA). 10% to 20% patients of resistant hypertension are found to have primary aldosteronism.[7]

Clinical indicators of primary aldosteronism include:

- Hypertension with hypokalemia
- Adrenal mass on ultrasound in patients with hypertension
- Resistant hypertension especially in young individuals

Usually there is high plasma aldosterone concentration (PAC) and low plasma renin activity (PRA), and therefore PAC/PRA ratio is elevated. Aldosterone antagonists like spironolactone or eplerenone can effectively control blood pressure in such cases. Surgical treatment is restricted to patients who do not respond to medical management and have unilateral adrenal mass.

Renovascular Hypertension[8]

Overall prevalence of significant renovascular disease is 6–8%. Here the hypertension is due to an obstructive lesion in the renal artery.

- Atherosclerotic RAS—this is the main cause of RAS found in 80–90% of cases. It is typically seen after the age of 55 years and is usually associated with atherosclerotic lesions elsewhere like coronary or cerebral vessels.
- Fibromuscular dysplasia—this is second most important cause of RAS, responsible for 10–20% cases of RAS. It is more common in young females.

Clinical indicators of RAS:

- Onset of high blood pressure after 55 years of age
- More than 25% increase in serum creatinine after starting ACE inhibitors or ARBs
- Unexplained atrophic kidneys or difference of 1.5 cm or more in the size of two kidneys
- Abdominal bruit

Diagnosis is confirmed by renal Doppler studies and CT/MR angiography.

Aim of treatment is to control blood pressure mainly with the help of antihypertensives like ACE inhibitors or ARB, diuretics, especially chlorthalidone or indapamide and CCBs, keeping a close watch on serum creatinine and serum potassium.

Stenotic lesions unresponsive to medical treatment are treated with revascularization. However, ASTRAL study[9] could not produce evidence that interventional therapy with angioplasty is a better choice.

Chronic Kidney Disease (CKD)

CKD has a very strong association with resistant hypertension. It is both a cause and complication of resistant hypertension.[10] Resistant hypertension in cases of CKD is due to salt retention, increased action of renin angiotensin aldosterone system, and increased activity of sympathetic nervous system. ACE inhibitors and ARBs are the drugs of first choice. Initially, there is mild increase in serum creatinine/serum potassium levels after starting these agents and the same needs to be monitored closely. Diuretics along with fluid and salt restriction are also very effective. However, thiazides lose their potency once the GFR is below 40 mL and should be substituted with loop diuretics.

Other Causes of Secondary Hypertension

See **Table 1**.

TABLE 1 Other causes of secondary hypertension

Disorder	*Clinical features*
Cushing's syndrome	Moon shaped facies, obesity, hirsutism, and hyperglycemia along with hypertension
Coarctation of aorta	• Higher blood pressure in arms and lower blood pressure in legs • Weak femoral pulses
Hypothyroidism	• Weight gain, fatigue, anorexia, dry skin • Amenorrhea • Increased TSH • Decreased free T4
Hyperparathyroidism	• Fatigue, constipation, joint pains • Nephrolithiasis, heartburn, polydipsia
Pheochromocytoma	• Paroxysmal hypertension • Spikes of headache, sweating, tremors, and palpitations

Work Up for a Patient of Resistant Hypertension

Once the diagnosis of resistant hypertension is made, it is very important to record a detailed history and clinical examination to exclude pseudo-resistant hypertension.

- Confirm that the patient is taking all prescribed medicines
- Review the prescription for proper drug combination and doses
- Confirm adherence to lifestyle measures
- Exclude white coat effect by ABPM or HBPM
- Look for consumption of excessive salt or alcohol or smoking
- Look for consumption of offending drugs like NSAIDs, oral contraceptives, or corticosteroids
- Look for secondary causes of hypertension

Management

Non-pharmacological Intervention

Lifestyle modifications can significantly decrease the blood pressure.

- Dietary sodium—it has been found that restriction of sodium to 2.4 gm/day or salt to 6 gm/day reduces both systolic and diastolic blood pressure by reducing extracellular volume.[11]
- Restrict the use of alcohol and smoking.

- Weight loss if overweight.
- Consume high fiber and low fat diet.
- Increase physical activity.

Antihypertensive Drugs

It is presumed that when the patient is diagnosed as having resistant hypertension, he is already taking a synergistic combination of three antihypertensive drugs, that is, a combination of ACE inhibitors or ARB plus a CCB plus a thiazide like diuretic.

First of all, one should optimize the doses of the three antihypertensive agents as a large majority of patients are taking suboptimal doses. It is worth mentioning that chlorthalidone is twice as potent as hydrochlorothiazide and so, those patients who are taking hydrochlorothiazide should be changed to chlorthalidone or indapamide.

Spironolactone

Spironolactone is the fourth agent of choice in resistant hypertension provided serum potassium is ≤4.5 mmol/L. Its dose is usually 12.5–50 mg/day. It has got a long half-life and maximal effect is seen after 3–4 weeks. Therefore, dose titration needs to be done every 4–6 weeks. It has an additional property of regressing left ventricular hypertrophy. The main side effect of spironolactone is breast tenderness and hypertrophy which is both dose and duration dependent, and is reversible once the drug is withdrawn. The second important side effect is hyperkalemia, especially in combination with ACE inhibitor or ARB. It is important to monitor serum potassium before starting and 2 weeks after drug initiation. Another side effect is hyponatremia, especially in elderly population after long-term use.

Beta Blockers

A beta blocker like metoprolol, nebivolol, or carvedilol is the next choice in resistant hypertension. These agents are of special use in cases of coronary artery disease, heart failure, and tachyarrhythmias.

Alpha Blockers

An alpha blocker can be used especially in the presence of benign enlargement of prostrate.

Centrally Acting Agents

Centrally acting agents like clonidine and alpha methyldopa can also be used in the management of resistant hypertension if the patient is refractory to other classes of drugs. Rebound hypertension can occur if the drug is suddenly stopped.

Direct Vasodilators

A vasodilator like hydralazine is the next agent to be used. Main side effect of hydralazine is fluid retention and tachycardia, and therefore concomitant therapy with a diuretic and beta blocker is usually required.

Direct Renin Inhibitors

Aliskiren is particularly useful in patients of resistant hypertension associated with features of metabolic syndrome.

Newer Drugs for the Management of Resistant Hypertension[12]

Endothelin receptor antagonists like darusentan gave promising results initially but could not show similar results in subsequent studies. Nitric oxide donors are other promising agents for the management of resistant hypertension. Nitrates with phosphodiesterase-5 inhibitors showed good results in a small study of six patients suffering from resistant hypertension. However, these agents can drastically lower the blood pressure, and hence are to be used with great caution.

Night Time Administration of Antihypertensives

Early morning fall of blood pressure (nocturnal dipping) is a normal physiological process and this is impaired in all hypertensive patients and more so in cases of resistant hypertension. Night time administration of at least one antihypertensive medication can restore the impaired night time dipping and reduces cardiovascular risk.[3] American Diabetes Association in 2013 recommended in its guidelines to administer at least one antihypertensive medication at bedtime in cases of resistant hypertension.[13]

Procedures and Devices for Resistant Hypertension

Renal Denervation (RDN)[14]

As the name indicates, this procedure involves bilateral destruction of renal nerves travelling along the renal arteries using radio frequency ablation. The underlying principle is to decrease the renal sympathetic tone and thereby reduce the renal vascular resistance.

The initial Simplicity HTN-1 and HTN-2 RDN trials showed quite good results and the blood pressure was reduced by 30/15 mm Hg and the results were maintained for more than 2 years. However, the subsequent trial (Simplicity HTN-3) did not show any significant reduction in blood pressure after 6–12 months of renal denervation.

Carotid Baroreceptor Activation

It has been observed that carotid baroreceptor activation by implanting an electrical device (Baroreceptor Activation Therapy—BAT) in the carotid sinus can significantly reduce both systolic and diastolic blood pressure. Moreover, this procedure gives an additional benefit of reducing left ventricular hypertrophy and arterial stiffness. However, these studies have involved only a limited number of patients. This is an expensive and invasive procedure and more randomized controlled trials with larger number of individuals are required to establish the safety and beneficial effects of this procedure.

Conclusion

Resistant hypertension is an established entity and it is important to diagnose it because of its close association with the complications of hypertension. One should exclude pseudo-resistant hypertension especially white coat hypertension and uptitrate the doses of all the three existing antihypertensive agents to the maximum recommended/tolerable levels before labeling resistant hypertension. Compliance to treatment need to be re-emphasized along with lifestyle changes before adding further antihypertensive agents. Role of procedures like renal denervation and carotid baroreceptor stimulation is still in the experimental stage and large randomized controlled studies are required to establish their usefulness.

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CHAPTER

21

Role of ARB in Hypertension

Sangram S Biradar

Abstract

Hypertension being one of the important diseases and risk factors of CVD and stroke in India. In management of hypertension all Indian guidelines recommend (ARBs) as an initial angiotensin receptor blockers or add-on drugs therapy. Hence, ARBs have demonstrated evidence-based benefits in management of hypertension, heart failure, and diabetic renal disease. ARBs are very well tolerated as monotherapy as well as in combination with other antihypertensive medications that improve adherence to therapy and have become a mainstay in the treatment of stages 1 and 2 hypertension.

Introduction

Hypertension is one of the risk factors of (CVD) and leading to disability and death in spite progresses happened in management in past three decades. In India up to 33% of urban and 25% of the rural population are afflicted with the disease. Attainment of (BP) goals in the population at large is a major challenge and area of focus of health systems worldwide.

Angiotensin II receptor blockers (ARBs) are advocated for people with stage I–II hypertension and type 1 or 2 diabetes. Since 1995, the role of ARBs has been in clinical use. ARBs are supposed to be better antihypertensive agents with good tolerance. ARBs have additive BP-lowering effects when they are combined with thiazide diuretics and dihydropyridine calcium channel blockers (CCBs), ARBs have proven mortality and morbidity effects in heart failure and chronic renal disease, particularly when associated with T2DM, concerns were raised surrounding the association of ARBs with development of solid cancers and coronary artery disease.

Pharmacology of Angiotensin Receptor Blockers

The renin–angiotensin–aldosterone system has been a major target pathway for development of antihypertensive medications. The major four groups of medications, like ARBs aldosterone antagonists, and direct rennin inhibitors, and ACE inhibitors, act on the same pathway. The interest in this pathway is due to the action of angiotensin II on the vascular system, renal sodium and water handling, and cellular proliferation. Inhibition of ACE only partially inhibits formation of angiotensin II. Angiotensin II activates two types of angiotensin II receptors (ATR): ATR1 and ATR2. ATR1 are abundant in the vessels, brain, heart, kidney, adrenal gland, and nerves, while ATR2 are prominently expressed in the fetus but decrease in number during the postnatal period, where they are only available in small numbers in the adult kidney, adrenal gland, heart, brain, uterus, and ovary. Activation of ATR1 increases inositol triphosphate and various arachidonic acid metabolites, and decreases cyclic adenosine monophosphate.[1,2]

TABLE 1 Pharmacological characteristics of angiotensin receptor blockers[10]

ARB	*Half-tife (h)*	*T_{max} (h)*	*Bioavailability (%)*	*Route of elimination: renal % (R) biliary/ faecal % (B)*	*Food interaction*	*Drug interaction*	*CYP metabolism*
Losartan	2	1–1.5	33	35 R; 60 B	Yes	Rifampin fluconazole	2C9, 3A4
Candesartan cilexetil	9	2–5	42	33 R; 67 B	No	None	2C9 (negligible)
Eprosartan	5–9	1–3	63	7 R; 90 B	Yes	None	No
Irbesartan	11–15	1.3–3	60–80	20 R; 80 B	No		2C9, 3A4 (negligible)
Telmisartan	24	0.5–1	43	<1 R; >97 B	No	Digoxin	No
Valsartan	6	2–4	23 (capsule) 50 (capsule)	13 R; 83 B	Yes	None	2C9 (weak)
Olmesartan medoxomil	12–14	1.7–2.5	26	35–50 R; 50–65 B	No	None	No
Azilsartan medoxomil	12	1.5–3	60	42 R; 55 B	No	None	2C9, 2B6 (negligible), 2C8 (negigible)

The mechanism of generalized vasoconstriction of vascular smooth muscle from contraction, which intern increases aldosterone thereby increase in reabsorption of sodium in the proximal tubal and cell growth in arteries and heart occurs. Therefore, angiotensin II which facilitates release of catecholamine from adrenal medulla and nerve endings thereby increasing hyperactivity from sympathetic nervous system occurs. Angiotensin II is believed to have an important mechanistic role in promoting CV diseases that is unrelated to its effect on BP. Several animal studies have shown that it causes cardiac hypertrophy in the absence of elevated BP.[3]

Individuals with a high renin–sodium profile have a greater risk of myocardial infarction than those with a normal or low profile. The function of ATR2 (Alderman) remains unclear, but it inhibits cell growth by stimulation and differentiation of cell and apoptosis leads to vasodilation,[4] However, ATR2 studies in animal show cardiac function improvements by stimulation and thereby preventing remodeling of cardiac post-myocardial infarction **(Table 1)**.[5]

Angiotensin Receptor Blocker Available

Presently ARBs available in the market for hypertension and cardiac indications, that is, losartan, valsartan, candesartan, eprosartan, irbesartan telmisartan, olmesartan, and azilsartan. All these above are accepted for hypertension treatment.

Losartan and irbesartan are approved in diabetic nephropathy, losartan in stroke prophylaxis, candesartan and valsartan for heart failure and also reduce CV mortality in left ventricular failure patients or left ventricular dysfunction followed by myocardial infarction. ARBs also have demonstrated reducing proteinuria by preserving kidney function in diabetic patients and also decreasing endothelial dysfunction thereby increasing fibrinolysis and have demonstrated their effectiveness in preventing atheromas.

The eight ARBs approved for use in the USA and Europe are nonpeptide compounds having biphenyl, tetrazole, benzimidazole or non biphenyl non tetrazole groups. Candesartan, olmesartan, valsartan, losartan, and irbesartan have a common tetrazolobiphenyl structure; telmisartan, and candesartan have a benzimidazole in common group; and eprosartan has a nontetrazole and nonbiphenyl, chemical structure. Whereas the irbesartan as an exception, and all have free carboxylic acid group. ARBs have more affinity for ATR1 than for ATR2 and can block the activities of angiotensin II on ATR1 regardless of whether it was created from ACE or other enzymes such as cardiac chymase **(Table 2)**.[5]

TABLE 2 Doses for hypertension and other indications of the angiotensin receptor blockers[5]

ARBs	*Starting dose (mg/day)*	*Maximum dose (mg/day)*	*Dosing interval*	*Other approved indications, aprat from hypertension*
Losartan	50	100	Once daily or twice daily	Diabetic nephropathy when serum creatinine is increased and proteinuria is present in patients with hypertension and type 2 diabetes; strok reduction in patients with hypertension and left ventricular hypertrophy (non-black only)
Candesartan cilexetil	16	32	Once daily or twice daily	Treatment of heart failure (NYHA classes II-IV)
Eprosartan	600	800	Once daily or twice daily	None
Irbesartan	150	300	Once daily	Diabetic nephropathy when serum creatinine is increased and proteinuria is present in patients with hypertension and type 2 diabetes
Telmisartan	40	80	Once daily	Cardiovascular risk reduction in patients unable to take ACE inhibitors
Valsartan	80 or 160	320	Once daily	Treatment of heart failure (NYHA classes II-IV); reduction of cardiovascular mortality in clincally stable patients with left ventricular failure or dysfunction following myocardial infarction
Olmesartan medoxomil	20	40	Once daily	None
Azilsartan medoxomil	40 or 80	80	Once daily	None

TABLE 3 Blood pressure reductions in randomized controlled trials of angiotensin receptor antagonists[5]

Study and year	*Duration (weeks)*	*Titration type*	*Drug*	*Dosage (mg)*	*Sample size (n)*	*Mean baseline BP (mm Hg)*	*Mean BP reduction (mm Hg)*
Telmisartan (TEL) vesus other ARBs							
Mallion et al.	6	None	Telmisartan Telmisartan Losartan	40 80 50	57 54 57	162/101 164/102 164/100	14/19 16/10 10/16
Lee et al.	4	Optimal	Telmisartan Losartan	40–80 50–100	86 90	154/101 155/102	17/9 14/9
Derosa et al.	54	None	Telmisartan Eprosartan	40 600	40 39	143/92 144/91	8/8 7/4
Zhu et al.	8	Optimal	Telmisartan Losartan	40–80 50–100	164 166	149/99 165/100	13/11 9/9
Calvo et al.	12	None	Telmisartan Valsartan	80 160	34 36	152/89 157/92	11/8 19/12
White et al.	8	Forced	Telmisartan Valsartan	40/80 80/160	244 246	154/99 153/99	12/8 11/7

ARBs and their Pharmacological Characteristics

The mechanism of action of ARBs is by blocking the angiotensin II via the AT1 receptor irrespective of the biochemical pathway lead by angiotensin II formation.

ARBs cause a several-fold rise in circulating angiotensin II levels, AT2 receptors are activated by ARBs. Because AT1 receptors are blocked by ARBs, the increase level of angiotensin II activates AT2 receptors. Hence, AT2 receptor is thought to activation the opposite effect of AT1 receptor, which are protective for cardiovascular system and for protection of target organs damage.[5,6]

Pharmacokinetic Considerations

Lithium is increased by affect of all ARBs in renal reabsorption; hence, ARBs with concomitant use with lithium should be avoided.

Peak action of ARBs on BP occurs at 3–6 hours after intake. Losartan metabolism occurs in liver via CYP system to its metabolite EXP3174, which has 10–40 times potent than IV losartan; hence, its dose is given half in severe hepatic impairment.

Although food delays its absorption and reduces its maximum plasma concentration (Cmax), this is not clinically significant. As such, any CYP2C9 enzyme inhibitors or inducers may reduce the effectiveness of losartan, and this must be considered during drug selection.

The ARBs (olmesartan medoxomil, candesartan cilexetil, and azilsartan medoxomil) require GIT and liver for activation as all three are prodrugs (olmesartan, candesartan, and azilsartan, respectively). The drug irbesartan has highest bioavailability among the ARBs. Telmisartan has longest action available in the market with half-life of 24 hours and has mechanism action rapidly about 0.5–1.0 hour **(Table 3)**.[5]

BP Reductions Trials in ARBs

In patients with T2DM with proteinuria and/or renal insufficiency, ARB-based treatment is recommended because these agents delay the progression of nephropathy.

ARBs in Diabetic and Kidney Disease

The intraglomerular hypertension is reduced in patients with diabetic nephropathy by ARBs. By reducing the gradient in glomerulus and thereby fibrosis of the nephron is averted (IRMA 2) that over 1 year trial.

The endpoints of reduction in NIDDM with angiotensin II antagonist losartan (RENAAL) trial showed losartan reduced incidence of doubling of serum creatinine (risk reduction 25%, p=0.006), 35% proteinuria reduction occur in end-stage renal disease (risk reduction 28%, p=0.002). Except for lowering the rate of first hospitalizations for heart failure (risk reduction 32%, p=0.005), the composite endpoint was similar after 3.4 years of therapy.[1,7,8]

CKD and ARBs

The important aim was preservation of renal function. In 2007, a scientific statement by AHA developed on treating hypertension and CKD population as a high (CAD) risk group as recommended blood pressure less than 130/80 mm Hg as goal. (ACEIs) or (ARBs) antihypertensive drugs were preferred agents CKD.[9]

Post-MI Survival

After acute MI, approximately 50% of patients show signs and symptoms of heart failure and approximately 10% have asymptomatic LV systolic dysfunction. Post-MI patients with heart failure, LV dysfunction, or anterior Q-wave MI have poor prognosis. Although large clinical trials show that ACE-inhibitors can reduce mortality and cardiovascular events, the prognosis of these high-risk patients is not satisfactory.[10]

Vascular Remodeling

Most vascular actions of angiotensin II are mediated through the AT1 receptors located on vascular smooth muscle and endothelial cells. The hallmark of vascular injury by hypertensive patients and vascular hypertrophy indeed may involve AT1 activation of receptor. And novel mechanism of AT2 receptor is by nitric oxide generation which promoted by AT2 receptors, which help in and induce apoptosis.[3]

Conclusion

All ARBs are highly proven effective class of drugs in treatment of hypertension and its associated comorbid condition from two decades. Presently there are eight ARBs approved for treatment of hypertension. There longer half-lives and high potency made BP reductions into enhanced duration of action, combining ARBs with other antihypertensive drugs like beta-blocker nebivolol made better BP control in some studies.

While there are added benefits by combining ARBs with ACEi (e.g., reduction in proteinuria), whereas some studies show combining these demonstrated increases in adverse renal events. Therefore, no clinical benefits seen by combining ARBs with ACE inhibitors (or direct rennin inhibitors) in treatment of hypertension.

The excellent safety and tolerability profile of the ARB class have improved the adherence to antihypertensive therapy and enhanced our ability to manage hypertension in those patients with sensitivities to other antihypertensive drug classes, including ACE inhibitors

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CHAPTER

22 Novel Calcium Channel Blockers: What's New

Nikhil Gupta

Abstract

Novel calcium channel blockers have shown a promising role in management of hypertension due to their antisympathetic actions and their renoprotective, cardioprotective and neuroprotective effects. There are six subtypes of calcium channels L, N, P, Q, R, and T-type. They are differentiated on basis of their electrophysiological properties. N type calcium channels are found at nerve endings. T-type Ca channels are found in pacemaker cells, atrial cells, purkinje fibres, juxtamedullary efferent, and afferent arterioles. The novel calcium channel blockers predominantly act on N and T type calcium channels along with L type calcium channels and decreases norepinephrine release which leads to vasodilatation, decrease in heart rate, and increase in renal blood flow.

Introduction

Hypertension accounts for major stroke and cardiovascular deaths all over the world. Globally an estimated 26% of world population has hypertension and prevalence is expected to increase to 29% by 2025. Hypertension is widely prevalent in India with significant variations in urban and rural population and regional variations. Prevalence is 20–40% in urban and 12–17% in rural adult population in India. But it is also the most modifiable factor with effective lifestyle changes and pharmacotherapy. A 2-mm Hg decrease in blood pressure can prevent 1,51,000 stroke and 1,53,000 coronary heart disease deaths in India.

Calcium channel blockers (CCBs) are one of the first-line drugs used in hypertension. Novel CCBs have further shown a promising role in the management due to their antisympathetic actions. Further their renoprotective, cardioprotective, and neuroprotective effects have also been demonstrated with lesser side effects.

Classification of Calcium Channels

There are six subtypes of calcium channels L-, N-, P-, Q-, R-, and T-type. They are differentiated on basis of their electrophysiological properties. The T-type Ca^{2+} channels are low voltage activated Ca^{2+} channels that activate and deactivate slowly and other five types of Ca^{2+} channels are high voltage-activated Ca^{2+} channels, which depolarize approximately at –40 mV. These channels consist of four subunits, $\alpha 1$, $\alpha 2\text{-}\delta$, β, and γ. An $\alpha 1$ subunit is the most dominant component of the calcium channels. Each $\alpha 1$ subunits are of 10 different types and each of them has specific distribution in body and ion conductance of its channels as mentioned **(Table 1)**.

Calcium Channel Blockers: Classification and Mechanism of Action

CCB are classified into three categories:

- Benzothiazepines (e.g., diltiazem)

TABLE 1 Distribution and ion conductance of calcium channels

Current	*α1 subunit*	*Channel*	*Distribution*
P	α1A	CaV2.1	Neurons
Q	α1A	CaV2.1	Neurons
N	α1B	CaV2.2	Neurons
R	α1E	CaV2.3	Neurons
L	α1S	CaV 1.1	Skeletal muscle
	α1C	CaV1.2	Heart, endocrine, neurons
	α1D	CaV1.3	Endocrine, neurons
	α1F	CaV1.4	Retina
T	α1G	CaV3.1	Neurons, heart
	α1H	CaV 3.2	Neurons, heart
	α1I	CaV3.3	Neurons

- Phenylalkylamines (e.g., verapamil)
- Dihydropyridines.

Dihydropyridine are classified into four generations:

- First generation—Nifedipine, Nicardipine
- Second generation—
  - Slow release formula—Nifedipine SR (slow release), Felodipine ER (extended release)
  - Newer chemical structures—Benidipine, Manidipine, Nilvadipine, and Nitrendipine.
- Third generation—to avoid reflex tachycardia:
  - Long acting—Amlodepine
  - Lipophilic—Lercanidipine, Lacidipine, and Azelnidipine
- Fourth generation—block multiple calcium channels:
  - Cilnidipine and Efonidipine

CCBs bind to α1 subunit and prevent release of internal calcium stores into cytosol of cell thus inhibiting cell excitability. Traditionally CCB acted on L-type calcium channels which are predominantly expressed in heart and vessels so they regulated cardiac contractility, sinus node function and vascular tone. Novel CCBs act on N- and T-type calcium channels also. N-type calcium channels are found at nerve endings so they regulate the release of neurotransmitters norepinephrine. Hypertension is closely related to increase sympathetic nerve activity so decrease in norepinephrine release helps in decreasing blood pressure and their other effects. T-type Ca channels are found in pacemaker cells, atrial cells, Purkinje fibers, juxtamedullary efferent and afferent arterioles and regulates afferent and efferent arteriole and adrenal secretion. **Table 2** shows different CCB and types of calcium channels blocked.

TABLE 2 CCB and Ca channel blocked

Drugs	*L-type*	*T-type*	*N-type*
Nifedipine	+	–	–
Amlodipine	+		
Cilnidipine	+	–	+
Efonidipine	+	+	
Azelnidipine	+	+	
Benidipine	+	+	+

Novel Calcium Channel Blockers

Cilnidipine

Cilnidipine has got both L- and N-type channel blocking property. It prevents excitation and contraction coupling in vascular smooth muscle cell leading to arterial vasodilatation with reduction in peripheral resistance, same mechanism in cardiac muscle leads to negative ionotrophic effect, results in slowing of sinus rate and inhibits the release of sympathetic neurotransmitter norepinephrine. Recommended dose is 5–20 mg once daily.

Morning hypertension involves increased sympathetic activity and the renin-angiotensin system (RAS). In ACHIEVE-ONE trial, 2,319 hypertensive patients were divided into four quartiles depending upon baseline SBP and were treated with cilnidipine for 12 weeks. Cilnidipine reduced both morning SBP and PR more markedly in patients with higher baseline morning SBP and PR. Cilnidipine independent BP- and PR-lowering effects were due to neuronal N-type Ca channel blocking.[1] In achieve one subanalysis hypertensive patients were classified into four groups according to nocturnal SBP reduction rate (%), extreme dippers, a nocturnal SBP reduction rate of 20%, dippers, a nocturnal SBP reduction rate of 10% to <20%, nondippers, a nocturnal SBP reduction rate of 0% to <10% and risers, a nocturnal SBP reduction rate of <0%. Cilnidipine reduced nighttime BP more than daytime BP in risers, nighttime and daytime BPs equally in nondippers, and daytime BP more than nighttime

BP in dippers.[2] It does not cause reflex tachycardia as it attenuates norepinephrine release.

Cilnidipine dilates afferent and efferent arterioles by inhibiting N-type Ca channels and causing no increase in intraglomerular pressure. It causes reduction in urinary protein excretion and suppression of any serum creatinine increase.[3] A study comparing cilnidipine and amlodipine effect on renal function and proteinuria showed significant decrease in proteinuria in cilnidipine group at 12 months of treatment.[4] It causes less pedal edema as it causes venodilation so that the pressure in the afferent capillaries peripheral to the resistance arteries decreases.

Cilnidipine can provide synergistic effect with angiotensin II receptor blockers as it suppresses RAS through sympathetic N-type Ca^{2+} channel blockade. Cilnidipine is beneficial for the suppression of pathological cardiac remodeling, at least partly, via a superior improving effect on ambulatory BP profile compared with control CCBs in hypertensive CKD patients.[5]

Cilnidipine improves LV diastolic function in hypertensive heart disease by suppressing cardiac sympathetic over-activity. It exerts vasodilatory action without stimulating sympathetic nervous activity, thus improving insulin sensitivity. Antioxidant activity of cilnidipine and amlodipine was compared by measuring ionomycin-stimulated superoxide production in cultured human mesangial cells. Cilnidipine showed a significantly higher antioxidant activity than amlodipine.

Azelnidipine

It is a CCB with a half-life of about 8 hours. Dosage is 8–16 mg orally once daily. It blocks L- and T-type calcium channels Azelnidipine primarily undergoes first-pass hepatic metabolism and has no active metabolite product. It is highly lipid soluble so it is retained in the vascular wall after clearance from the blood and continues to elicit a hypotensive effect. So it causes a gradual and prolonged fall in blood pressure in hypertensive patients and no reflex tachycardia. It has a strong anti-arteriosclerotic action in vessels and antioxidative activity due to its high affinity for vascular tissue. Azelnidipine reduces heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity and also prevents insulin resistance.

CALVLOC trial studied effect of azelnidipine on diastolic function left ventricular filling pressure in patients with preserved ejection fraction and diastolic dysfunction. Results showed it is associated with improvements in LV diastolic function, a reduction in LV filling pressure, and a decrease in the brain natriuretic peptide level.[6]

Benidipine

Benidipine blocks all the three L-, N- and T-type calcium channels. It has a strong and long effect due to its high affinity for the DHP binding site. There is slow binding and slow dissociation from the DHP binding site. This is known as "membrane approach" (approach to the cell membrane followed by long retention in the DHP binding site). This state contributes to the long-lasting antihypertensive effects of benidipine. Its cardio- and vasoprotective effects are due to vascular selectivity and enhanced nitric oxide (NO) production. It is absorbed rapidly and reaches maximum drug concentration within 2 hours.[7] Dosing is 2–8 mg once daily.

Benidipine renoprotective effects are due to

- Dilation of the efferent arterioles due to inhibition of T-type Ca^{2+} channels
- Marked increase in renal plasma flow rate
- Natriuretic effect by acting on both the upper segment of tubules and the distal tubules
- Increased NO formation in the renal parenchyma
- Suppression of increased expression of transforming growth factor (TGF)-β and α-smooth muscle actin in the glomeruli.

It has an anti-oxidant effect. In a study using cultured endothelial cells, benidipine suppressed endothelial damage induced by lysophosphatidylcholine [one of the lipids constituting oxidized low density lipoprotein (LDL)] more potently than nifedipine and amlodipine.[8] Benidipine suppresses the progression of atherosclerosis by stimulating the formation of NO by its direct action on vascular endothelial cells.

Benidipine increases coronary blood flow as it increases NO production during ischemia. Vascular selectivity of various CCBs was evaluated using isolated coronary arteries and the right ventricular papillary muscles of dogs; the coronary artery selectivity of benidipine was 14.4 times higher than that of nifedipine[9] and 19 times higher than that of amlodipine. These effects protect the myocardium, contributing to better prognosis for angina pectoris. It also stimulates the differentiation of osteoblasts, suppresses the proliferation of vascular smooth muscles, suppresses

the proliferation of mesangial cells, and protects the myocardium.

Efonidipine

Efonidipine blocks both, L- and T-type Ca^{2+} channels. It prolongs the late phase 4 depolarization of the sinoatrial node action potential through blockade of both L- and T-type Ca^{2+} channels, leading to its potent negative chronotropic effect. It has long lasting vasodilator actions and less reflex tachycardia.[10] It increases adiponectin levels without a corresponding change in BMI. Increasing adiponectin levels are predicted to improve both insulin sensitivity and endothelial function by multiple mechanisms.[11]

Conclusion

Thus, novel CCBs due to their action on N- and T-type calcium channels along with L-type calcium channels decrease norepinephrine release and lead to vasodilatation, decrease in heart rate, and increase in renal blood flow. They cause prolonged antihypertensive action, less reflex tachycardia, less pedal edema, better control of proteinuria, increase insulin sensitivity and, more antioxidation activities.

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CHAPTER

23 Beta-adrenergic Receptor Blockers in Hypertension

Amit Kumar Das

Abstract

Hypertension remains one of the most important preventable causes of morbidity and mortality because of cardiovascular disease. Beta adrenergic receptor blockers are one of the most used and easily available antihypertensive agents. By blocking the beta receptors, they reduce the cardiac output and cause bradycardia. Selective beta 2 receptor agonism can lead to peripheral vasodilatation and reduce peripheral vascular resistance. All of these and decreased rennin all lead to effective lowering of blood pressure without decreasing cardiac output. Apart from that some drugs in this category lead to prolongation of phase 2 (repolarization) of action potential and give additional antiarrhythmic advantage. As antihypertensive agents, beta adrenoreceptors are particularly suitable in hypertensive patients with coexistent Ischemic Heart Disease. They are also valuable antihypertensive agents when used in combination with other agents like CCB, ARB, and diuretics. Certain contraindications like Bronchial Asthma, COPD, High Degree AV block, etc. need to be taken care of before prescribing these agents. Despite its share of controversies, beta blockers still remain useful antihypertensive agents.

Introduction

Despite its high prevalence, associated morbidity, and increased mortality, hypertension still remains inadequately treated in the majority of patients. From epidemiological perspective, several data have clarified the importance of blood pressure as a risk factor for CVD.[1] In the largest and the most detailed analysis, information from one million adults with no known vascular disease at baseline, included in 61 prospective observational studies of the relationship between blood pressure and mortality, was observed.[1]

Primary goal of treatment of hypertension is to prevent cardiovascular disease and death based on results of recent trials the choice of antihypertensive can be adjusted according to the presence or absence of associated conditions.

Beta (β)-adrenergic receptor blockers are among the most widely used agents in clinical medicine. Since 1976 after availability of propranolol for treatment of hypertension, quite a few β-blockers have been introduced.[2]

In this article I will deal with the role of β-blockers in the management of hypertension.

Types and Mode of Action

These drugs act as competitive inhibitors of the binding of epinephrine and norepinephrine to β-adrenergic receptor sites. Two subtypes of β-adrenergic receptors exist: the β_1 subtype (predominates in the heart) and the β_2 subtype (predominates in the peripheral vasculature and bronchial smooth muscle). Most β-adrenergic receptor blockers exist as pairs of optical isomers. Almost all clinical activities are due to the levorotatory (negative) stereoisomer.

By reducing systemic vascular resistance β-blockers decrease blood pressure while maintaining cardiac output

TABLE 1 β-blockers pharmacology

Property	*Description*	*Drugs*
Selectivity	Greater β_1 affinity at common therapeutic ranges (selectivity is dose dependent: at high doses even selective drugs interact with β_2-receptors	Acebutolol, atenolol, bisoprolol, betaxolol, esmolol, metaprolol
Intrinsic symptomatic activity (ISA)	Partial β-adrenergic agonist activity in the absence of catecholamines (milder rest bradycardia)	Acebutolol, oxprenolol, pindolol
β_1-Receptor inhibition	α-β-blocked; vasodilation is due to β-blockade	Carvedilol, labetalol, nebivolol
Additional antiarrhythmic properties	Prolongation of phase 2 (repolarization) of action potential (class III)	Sotalol

and cardiac afterload and preload reduced due peripheral vasodilation.[3] Compensatory peripheral vasoconstriction due to reduced cardiac output abets increased peripheral resistance **(Table 1)**.[4]

β-blockers in the Treatment of Hypertension

Effects of various β-blockers on outcomes in hypertensive patients have already evaluated in many trials. When β-blockers were compared with diuretics it has observed that there was no statistically significant differences between the two treatments and three-fourths of patients achieved their DBP goals receiving either drug class.[5] Recent clinical data suggest that although brachial (arm) blood pressure effectively reduced by traditional β-blockers but compared with other antihypertensive classes they may have less effect on reducing central aortic pressure.[6-8]

There were several trials which confirm the potency of labetalol to rapidly lowers of blood pressure.[9,10] Carvedilol in a placebo-controlled, double-blind trial in 338 patients with essential hypertension shows statistical significant reduction in mean 24-hour systolic blood pressure (SBP) and diastolic blood pressure (DBP) assessed by ambulatory blood pressure monitoring compared with placebo ($p \leq 0.001$ for all).[11] In an open-label, 6-week trial significantly lowered mean systolic blood pressure and diastolic blood pressure from baseline (–24 and –13 mm Hg, respectively, $p < 0.001$ for both) by nebivolol (5–10 mg/day) in 6,356 patients with mild hypertension (defined as DBP of 90–115 mm Hg) and mean baseline SBP of 162 mm Hg.[12] In 2,838 patients with type 2 diabetes mellitus for ≥3 months and hypertension nebivolol (2.5–10 mg/day) was also assessed as monotherapy or as add-on therapy and lowered SBP and DBP from baseline by 21 and 11 mm Hg, respectively.[13] Nebivolol has already documented to exhibit safe and well tolerated profile and higher achievement of blood pressure targets or goal reductions than that of ACE inhibitors (odds ratio 1.92, $p = 0.001$) and similar to that of other β-blockers, CCBs, and losartan.[14-16]

Combination Therapy with β-blockers

Single drug therapy remains the preferred way to begin treatment of hypertension although in many patients this is unable to bring blood pressure to goal levels. It is increasingly being seen that the elusive goal of a "Normal BP" is achieved only if multidrug therapy is employed.

β-blockers and calcium channel blockers combination offers a potential therapeutic benefits for uncontrolled hypertensive patients. These two interacted by complementary hemodynamic mechanisms with the calcium channel antagonists reducing α adrenergic reflex vasoconstriction induced by β-blockers and the β-blockers acting through a reduction in cardiac output. Combination products do not employ non-dihydropyridine calcium channel blockers due to concern for excessive effects on sinus and AV nodal junction.[17] The commonly employed combinations contain the CCB amlodipine and metoprolol for which the response rate is good and which preserves the normal diurnal BP rhythm.[18] Adverse effects like β-blockers related cold extremities are less common.

β-blockers blunt RAA axis activation produced by diuretics while the latter curb any Na^+ retention provided by β-blockers. β-blockers and diuretics reduce BP additively not synergistically.[19] Dose dependent adverse effects occur less frequently with low dose combinations and less so with β selective antagonists.

Why β-blockers Recommended in Hypertension with Ischemic Heart Disease

A combination of effects accounts for the efficacy of β-blockers in ischemic heart disease (IHD). β-blockers are competitive antagonists of β-adrenergic receptors. β-receptors inhibition slows the heart and atrioventricular conduction and lowers blood pressure and contractility, thus decreasing myocardial oxygen demand. The slower heart rate also enhances diastolic perfusion time.

β-blockers are also effective antihypertensive agents and antiarrhythmics. They reduce the risk of death and major cardiovascular events after myocardial infarction (MI). They also relieve symptoms at rest, increase exercise tolerance and prolong survival in many groups of patients. For this reasons they are a first-line choice in IHD.

A few small randomized studies have tested β-blockers in patients with stable angina, normal blood pressure and no history of MI. The Total Ischemic Burden European Trial (TIBET) reported nonsignificant reduction of the risk of death and MI with the combination of atenolol and nifedipine.[20] The results did not differ from those with either drug in monotherapy. The Angina Prognosis Study In Stockholm (APSIS) found no difference between metaprolol and verapamil in terms of death, major cardiovascular events, or quality of life.[20] The Atenolol Silent Ischemia Study (ASIST) versus placebo showed that atenolol decreased cardiovascular events and the frequency and duration of ischemic episodes and increased event free survival.[20] The Total Ischemic Burden Bisoprolol Study (TIBBS) showed bisoprolol to be more effective than nifedipine in reducing the frequency and duration of ischemic episodes.[20] The International Multicentre Angina Exercise (IMAGE) study showed that both nifedipine and metoprolol increased time to ischemia during exercise.[20] The combination of the two drugs was more effective than either as monotherapy.

Controversy

Few recently published data have argued that use of β-blockers is not beneficial for treating hypertensive patients as a first-line treatment mainly because there is no significant reduction in mortality or coronary heart disease as well as due to their modest effect on stroke as compared to placebo or other antihypertensive agents.[21]

As compare to traditional β-blockers (atenolol, metoprolol, and propranolol), vasodilatory β-blockers (carvedilol, nebivolol) lower blood pressure to a similar degree as other antihypertensive drugs and are associated with neutral or favorable metabolic effects. In most of the metanalysis and even guidelines consider mainly these traditional β-blockers in which data are not favoring the use of β-blockers in uncomplicated hypertension as a first-line agent.

High dose of β-blockers may worsen diabetic control, by increasing insulin resistance. β-blockers, by blunting the catecholamine response, mask hypoglycemic symptoms so that hypoglycemia manifests only when severe.[22] Poorly controlled diabetes mellitus, particularly if treated with insulin: β-blocked can interfere with receptor sensitivity to insulin, causing hypo- or hyperglycemia; in addition, its sympathetic effect may conceal symptoms of endogenous hypoglycemia, preventing correction, and thus endangering the patient. With pooled data of 94,492 patients with hypertension, the traditional β-blockers atenolol and propranolol compared with placebo ($n = 16,372$, $p = 0.33$), reported a 44% increased new-onset diabetes risk.[22] β-blocker–based therapies (atenolol, metoprolol, and any β-blocker and diuretic together) increase the new-onset diabetes risk by 21% as compared with CCBs ($p < 0.0001$) and 23% as compared with ACE inhibitors or ARBs ($p = 0.007$).[6] In contrast, GEMINI[23] (Glycemic Effect in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) trial conducted on 1,235 patients confirms that with same BP control the discontinuation rate because of poor glycemic control was only 0.6% with carvedilol ($p = 0.04$) and no adverse effect on glycosylated hemoglobin values as compare to traditional β-blockers like metaprolol. In another study with nebivolol arm there is statistical significant reduction in glycated hemoglobin (HbA1c%) and fasting blood glucose ($p < 0.001$).[13]

β-blockers exacerbate asthma and should not be used in patients with asthma. Severe chronic obstructive pulmonary disease (COPD) due to broncho stenosis and increasing hypoxia and hypercapnia: selective β_1-blockers can be used at very low doses if there is a strong indication of β-blocked, but they not tolerate; β-blockers may worsen symptoms even in mild COPD and have to be withdrawn.

β-blockers should be administrated with caution in first degree atrioventricular block. Well recognized

side effects include asthenia, fatigue, insomnia, and nightmares. Some erectile dysfunction is relatively common (in up to 25% of patients), but persistent impotence is rare (1%). Lipid effects are mild and not a reason for treatment withdrawal. Though most β-blockers increase triglyceride and decrease HDL-cholesterol levels, they certainly reduce the incidence of sudden death, overall mortality and recurrent MI. In summary, the vast majority of patients are eligible for β-blockers therapy, provided the drug is carefully chosen and titrated.

Conclusion

More than 45 years in various other clinical situations along with the treatment of hypertension β-adrenergic receptor blockers have been used extensively. From 1973 to till date numerous clinical trials and meta-analysis were performed to evaluate the functional role of β-blockers in the management of hypertension and it has established their efficacy in the reduction of cardiovascular morbidity and mortality associated with hypertension. In modern clinical practice, clinicians require combination of two or multiple drugs to control hypertension and require more aggressive goal especially with comorbidities. To achieve target goal in hypertension patients with comorbidities like high coronary artery disease risk or even with diabetes β-blockers are a beneficial, guideline-recommended treatment option. Thus, in conclusion, the vast majority of patients are eligible for β-blockers therapy, provided the drug is carefully chosen and titrated.

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CHAPTER

24 Centrally-acting Agents in Hypertension

Girish Verma, Ashee Verma, Abdul Wahid Qureshi

Abstract

Centrally-acting antihypertensive is usually used as add on therapy in a patient who requires multiple drugs to control the hypertension.

Various available drugs (Clonidine, α-Methyldopa, Guanfacine, Guanabenz, Moxonidine, and Rilmenidine) though belong to same group, act with subtle different mechanism and thus one drug has advantage over other for its use in specific condition.

Clonidine being the non selective (acting on α-2 Adrenoceptors and imidazoline-1 receptors) has more adverse effect and sometimes intolerant for the patients (causing sedation, postural hypotension). Methyldopa can be used safely in pregnancy as it maintains the uterine blood flow. Guanfacine and guanabenz can be used and better tolerated in cases where patient is intolerant to clonidine.

The moxonidine and rilmenidine due to their mechanism of action (selective for imidazoline receptor) cause less adverse effects thus better tolerated. However, both drugs are cautiously given in advanced renal failure and moxonidine is avoided in advanced heart failure.

Introduction

Patient suffering from hypertension may require multiple drugs, if they are labelled suffering from resistant hypertension. These patients frequently respond to centrally acting antihypertensives.[1]

Drugs that block sympathetic activity within the brain called centrally acting sympatholytic drugs.

Various presently available centrally acting antihypertensive (centrally acting sympatholytic) drugs are **(Table 1)**:

- Clonidine
- α-Methyldopa
- Guanfacine
- Guanabenz
- Moxonidine
- Rilmenidine

Mechanism of Action

The centrally-acting antihypertensive (clonidine, α-methyldopa, guanfacine, guanabenz, moxonidine, and rilmenidine) have different antihypertensive actions,[2,3] which result in sodium excretion and decrease in cardiac output, heart rate, total peripheral resistance, and renin release **(Flowchart 1)**.

These centrally acting antihypertensive agents cross the blood brain barrier and stimulate imidazolin-1 (I_1) receptor and/or central postsynaptic α_2 adrenoceptor in the brain stem's sympathetic nervous control centers, the rostral ventrolateral medulla (RVLM) and the nucleus tractus solitarii.

Clonidine non selectively stimulates both α_2 adrenocepters and I_1 imidazolin receptors as compared to methyldopa, guanabenz, and guanfacine, which

TABLE 1 Centrally-acting antihypertensive agents[5,6]

Drug	*Preparation*	*Pharmacodynamics*	*Daily dose*	*Adverse effect*	*Contraindication*
Clonidine	• 0.1 mg • 0.2 mg • 0.3 mg	• Onsete 0.5–1 hour • Peak 3–5 hours • Plasma half-life, 12–16 hours • Metabolism—Lliver	• Initial—0.1 mg • Range 0.2–1.2 mg • Max 1.2 mg • Usually BID	• Sedation drowsiness, dry mouth • Withdral syndrom, • Rebound hypertnesion (Uncommon with dose <1.2 mg daily)	• Sick sinus syndrome • 2nd and 3rd degree AV block
Transdermal	• Containing 2.5 mg • Containing 5 mg • Containing 7.5 mg	Duration of BP lowering 1 week	1, 2, 3, once weekly	• Headache, bradycardia, orthostatic hyportension • Impotence (Uncommon 4%), hepatitis	
Methyldopa	• 125 mg • 250 mg • 500 mg	• Onse —2–3 hours • Peak—5 hours • Plasma half-life 12 hours • Metabolism —Renal	• Average: 250–300 mg • BID • Max 3000 mg	• Sedation, Drowsiness, Dry mouth • Positive Coomb's test and anemia, Lupus like syndrom withdraw syndrome • Rebound hypertension	Active hepatic disease
Guanabenz	• 4 mg • 8 mg	• Onse—1 hour • Peak—4 hour • Plasma half-life—6 hours • Metabolism 76% • Excretion: Renal 80%	• Average 16 mg • Range 8–46 mg • Max 48 mg	• Sedation, Drowsiness, Dry mouth widhrawal syndrome • Rebound hypertension • Impotence	Pregnancy
Guanfacine	• 1 mg • 2 mg	• Onset—1 hour • Peak—4 hour • Plasma half-life—12 hours • Excretion: Renal	• 1 mg at bed time • Max 3 mg	Same as clonidine	Allergy to Guanfacine
Moxonidine	• 0.2 mg • 0.3 mg	• Peak—0.5–3 hours • Plasma half-life—2–3 hours • Excretion: Renal 57–75%	• Average 0.2 mg • once daily • Max 0.6 mg		• Several renal impairment • GFR <30 mL/min • Advanced heart failure
Rilmenidine	1 mg	• Peak—1.7 hour • Plasma half-life—8.5 hours • Excretion: Renal 52–93%	1–2 mg/day		Advanced stage of CKD (relatively contraindicated) 1 mg alternate day if, GFR < 15mL/min

selectively stimulates α_2 adrenoceptor more than the Imidzaolin (I_1) receptors.

Moxonidine and Rilmenidine selectively stimulate Imidazolin (I_1) receptors.

α-Methyldopa blood pressure lowering mechanism requires specific mentioning here, it is converted into active metabolite. α-Methyl norepinephrine, which dislodges nor-epinephrine from Alpha adrenergic receptors,[4] while other molecules belonging to this group are effective as their intact molecules.[5]

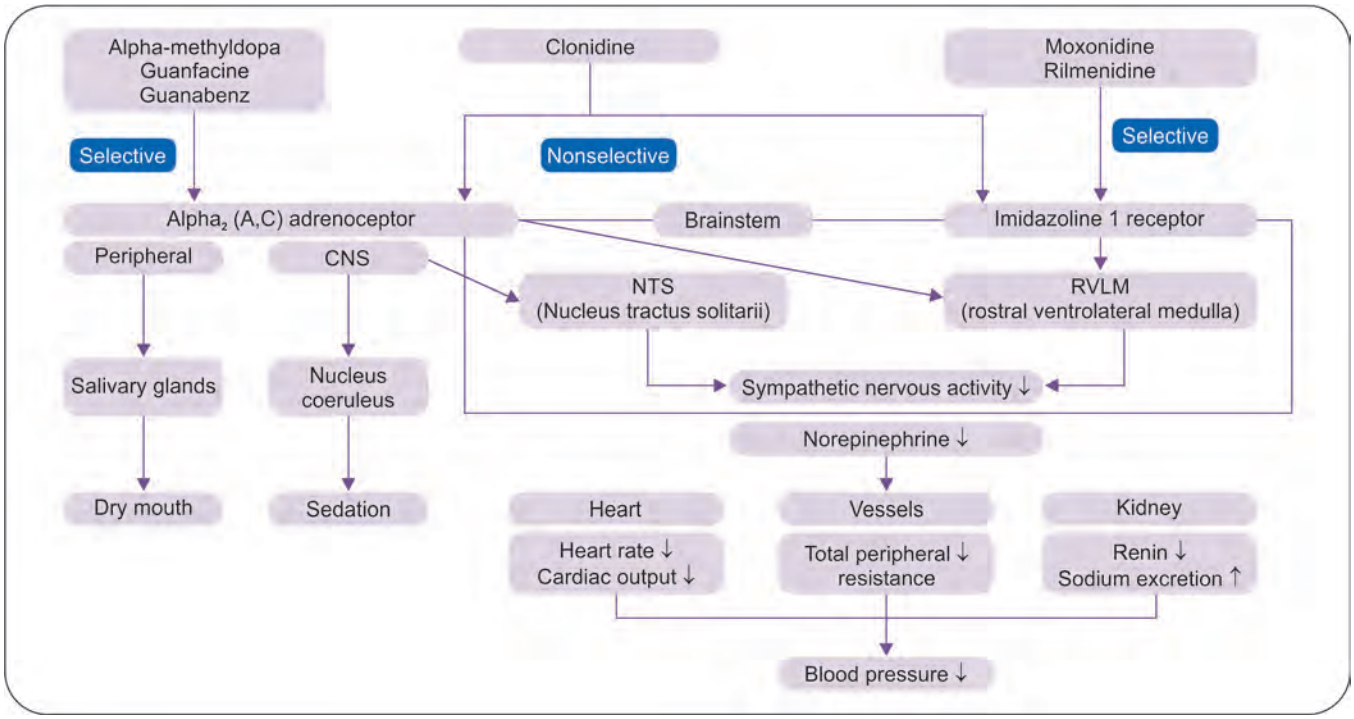
Individual Characteristics of Centrally-acting Agent in Hypertension

Clonidine: This drug has 30–60 minutes onset of action so it can be used in hypertensive emergencies; however, requires frequent dosing due to its shorter duration of action.[6,7]

The clinical indications of clonidine:

- Primary hypertension—as fourth or fifth line drug
- Menopause associated vasomotor syndrome

Flowchart 1: Mechanism of action, centrally acting antihypertensive agents



- Hypertension with restless leg syndrome

Clonidine is also available as Transdermal patch and is of particular utility for management of:

- The labile hypertension which require multiple medication,
- The hospitalized patient unable to take oral medication, and
- The patient with prominent early morning blood pressure surge.

Transdermal clonidine patch is best absorbed from the chest or upper arm[8] and it causes more dose dependent salt and water retention as compare to oral clonidine.[9]

Transdermal patch delivers drug daily for 7 days, but it starts its action at least 1 day later after its application; hence oral clonidine is given for 1–2 days after application of clonidine transdermal patch. Even when transdermal patch is removed drug present in the skin continue its antihypertenive effect.[10]

Clonidine has its suppressing effect on sinus as well as atrioventricular nodal function sometimes causing significant bradycardia. Hence, this drug should be best avoided in patients with sinus node dysfunction and those suffering from CKD who are at risk of developing significant bradycardia.[11]

When clonidine is suddenly stopped it causes rebound hypertension,[12] which may be quite significant if patient is also receiving beta-blocker but not in the presence α/β adrenergic antagonist like labetalol or carvedilol.[6] This rebound hypertension has not been observed with moxonidine and rilmenidine.[13,14]

Methyldopa: Indications of using this drug are—

- In patient who are intolerant to clonidine[15]
- Pregnancy induced hypertension[16,17]
- In hypertensive emergencies—used intravenously dose 20–40 mg/kg/day 6 hourly

However, intravenous use of methyldopa is infrequent due to availability of other effective drugs.

As it is excreted through kidneys, reduced doses are desirable in renal failure; however, methyldopa is dialyzable.

Methyldopa, besides its common side effect somnolence and depression, causes hypersensitivity reactions leading to hepatitis and coombs positive hemolytic anemia. It occurs only 10–20% patients receiving

methyldopa.[18] If patient has coombs test positive but no hemolytic anemia, it is not wise to stop methyldopa.

Flu like symptoms, lupus like syndromes and enhanced prolactin release (pseudo lactation) have also been observed.[5,6]

Guanabenz: This drug acts similarly as that of clonidine, but its duration of action is prolonged. It is less frequently associated with rebound hypertension, salt, and water retention and/or significant postural hypotension.[19] Guanabenz is broadly biotransformed and does not accumulate in the patient with significant reduction in renal function.[20] Guanabenz reduces total cholesterol level 10–20%.[21] Sedation with this drug is dose-dependent decreases over the period of time.

This drug has been found to reduce left ventricular hypertrophy in hypertensive patients and also reducing morning hypertension when given at night time.[5,6]

Guanfacine: This drug has longer duration of action (24 hours) hence given once daily.[22] Guanfacine has its antihypertensive effect longer than guanabenz. It is preferably given in the evening so as to suppress early morning surge of catecholamines and blood pressure. Its blood pressure effect is enhanced when given with diuretic. This drug can be used instead of clonidine when excessive sedation is the problem.[23]

Moxonidine: This drug when used alone or in combination with other antihypertensive agents, it significantly reduces the blood pressure.[13] It does not decrease heart rate like clonidine. This drug is mainly excreted through kidneys. Its dose adjustment according to the glomerular filtration rate (GFR) is mandatory.[24]

This drug should not be used when GFR falls 30 Ml/min or less and also in advanced heart failure.[25]

Rilmenidine: This drug is used in the treatment of mild to moderate hypertension. Rilmenidine can be use alone (1–2 mg/day) or in combination with other antihypertensive and has been well tolerated and effective in studies.[26] This drug does not affect heart rate while reducing blood pressure as it increases parasympathetic tone.[27]

Treatment withdrawal rebound hypertension does not appear to occur with rilmenidine. It is much less frequently associated with sedation and dry mouth. The low rate of orthostatic hypotension with rilmenidine may be related to an enhancement in baroreflex sensitivity.[28] Rilmenidine is relatively contraindicated in advance stage chronic kidney disease.

Usefulness of Centrally-acting Antihypertensive in Other Clinical Conditions

Clonidine has been used:

- In migraine prophylaxis.
- Post-traumatic stress syndrome.
- To reduce postmenopausal flushes.
- In moderate alcohol and opioid withdrawal syndrome.
- To secondarily reduce aqueous humor production in open angle glaucoma.
- In short gut syndrome and/or high output proximal ileojejunostomies for effectively reducing fecal output.[29]
- In diagnosis of pheochromocytoma: After administration of 0.1 mg clonidine per hour for 3 hours, plasma, nor-epinephrine levels decreases in patient with essential hypertension but remained unaffected in patient with pheochromocytoma.[30]
- In new onset of atrial fibrillation can control the ventricular rate.

Similarly guanfacine can be used in:

- Attention deficit order
- The fragile X-syndrome

Drug Interactions[5]

Certain catecholamine assay can be disturbed by methyldopa and its metabolites. This also interferes with levodopa, bromocriptine, and monoamino oxidase inhibitors. Therapeutic effect of methyldopa is reduced with coingestion of iron.

Guanabenz may increase the absorption of hydrochlorothiazide when given concomitantly.

The antihypertensive effect of clonidine and guanfacine is reduced by tricyclic antidepressents (imipramine, amitriptyline, etc.) because they are antagonist to central α_2 receptors.

The moxonidine and rilmenidine should not be given with monoamino oxidase inhibitors.

Conclusion

In the present context centrally acting antihypertensive agents can be used as add on therapy in the treatment of hypertension, especially resistant hypertension. However, in sympathetically mediated hypertension they can be used with preference.

Though due to dose dependent side effects, the use of clonidine and methyldopa is now less; however, methyldopa is an agent that can be used safely in pregnancy induced hypertension. Guanfacine and Guanabenz can be used and better tolerated in cases where patient is intolerant to clonidine.

The moxonidine and rilmenidine due to their mechanism of action (selectively for imidazoline receptors), causeless sedation, dryness of mouth, and postural hypotension, thus better tolerated.

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CHAPTER

25

Hypertension in Young Adults

Abhishek Kumar, Anupam Prakash

Abstract

Hypertension in the young is commonly essential hypertension and is on the rise because of rapid urbanization, increasing stress, addictions (tobacco and alcohol), and changing lifestyles. However, secondary hypertension also needs to be ruled out as it is remediable and appropriate management can obviate the need for lifelong treatment. It is imperative that a judicious approach is adopted while evaluating the young hypertensive and pharmacological as well as non-pharmacological measures are adopted while managing these patients. Anxiety levels are high in young patients, and renin-angiotensin system (RAS) activity also is heightened. Drug usage should therefore be chosen to inhibit the RAS, have long-term control, and minimize side-effects.

Introduction

Cardiovascular disorders are the leading cause of morbidity and mortality worldwide. Nearly 30% of global deaths are attributable to cardiovascular disease (CVD). Systemic hypertension is the leading root cause of premature mortality and morbidity among the patients of CVD.[1] Prevalence of hypertension is rapidly increasing in the community and it is estimated that the world will have about 1.5 billion adult hypertensives by end of this decade.

In India, the situation is alarming as its prevalence is about 33% in urban part and about 27% in rural area. The overall prevalence of hypertension is about 29% suggesting urban rural convergence due to rapidly changing lifestyle.[2] The current BP control rates of less than 10% in the rural and less than 20% in the urban areas is itself a big challenge. India has wide variations in race, ethnicity, socioeconomic status, and cultural practices. The lifestyle is rapidly changing becoming more sedentary due to rapid urbanization. Thus, the incidence of chronic illness like diabetes, hypertension, and CVD are increasing.

Weight gain, obesity, and physical inactivity are important risk factors for development of hypertension in young adults. These patients are more likely to respond to lifestyle changes and weight management but they are less likely to believe that they have disease. In Indians, hypertension develops relatively early in life. In individuals aged between 15 and 49 years, the prevalence is about 18% with variations between rural/urban and amongst different regions of country.[3] Moreover, only about 44% of young hypertensives are aware of their diagnosis and only 14% are receiving treatment.

Definition and Classification

Definition of "Young adults" for hypertension is not defined, but age between 20 and 49 years may be taken as in Framingham Offspring Study.

There is a continuous relationship between the level of blood pressure and the risk of complications starting at BP of 115/75 mm Hg. As Asian, Indians are more prone to CVDs, the risk for cardiovascular events is higher and

TABLE 1 Classification of blood pressure for adults age 18 and older

Category	*Systolic (mm Hg)*		*Diastolic (mm Hg)*
Optimal	<120	and	<80
Normal	<130	and	<85
High-normal	130–139	or	85–89
Hypertension			
Stage 1	140–159	or	90–99
Stage 2	160–179	or	100–109
Stage 3	≥180	or	>110
Isolated systolic hypertension			
Grade 1	140–159	and	<90
Grade 2	>160	and	<90

commence at relatively lower levels of BP. The recent ACC/AHA guidelines changed the definition of hypertension at 130/80, but European guidelines and recently published Indian guidelines for hypertension IV continue with the previous definition of 140/90 mm Hg.[4] The same definition of hypertension applies in young adults. Classification is for adults more than 18 years of age, who are not on antihypertensive medication and have no acute illness. It is based on the average of two or more office blood pressure readings taken at least on two occasions **(Table 1)**.

In addition to classifying stages of hypertension on the basis of average blood pressure levels, clinicians should specify presence or absence of target organ disease and additional risk factors.

The screening for hypertension in all adults is recommended.[5] All adults (18 years or older) should have their office BP measured at every point of contact with health professionals or allied health staff. This will include all points and levels of care—the village/multipurpose health worker, trained non-physician staff at sub-centers, primary health center, community health center, and referral hospital (District hospital, Medical College). This screening will enable people with high normal BP to be identified, so that they can be prevented from developing hypertension by use of appropriate lifestyle modifications.

Risk Factors of Hypertension in Young Adults

Incidence of hypertension is higher among young men than women, increasing threefold from second to fifth decade in men and eightfold in women.[6] Under age 40, men were twice as likely as women to develop hypertension, but after age 40, 8-year incidence rates were similar in men (14.2%) and women (12.9%). The proposed ominous octet of "S," a constellation of risk factors starting with the letter "S," leading to development of non-communicable diseases are sex, salt, sugar, sleep, smoking, stress, sunlight, and sedentary behavior. These become more prominent in today's tech savvy young adults. Consumption of saturated fat and prolonged sitting may be added to complete the list.[7] Risk factors like physical inactivity, weight gain, obesity, metabolic syndrome, and obstructive sleep apnea are more common in these patients. Smoking, alcohol, illicit drug intake, and psychosocial stress are becoming more common in this age group. High sodium intake, low potassium and calcium in diet are the other factors responsible.

Psychosocial stress is a major contributor to development of hypertension in young. This group has enormous work, travel related, and domestic pressure leading to busy and erratic schedule.[8] This must be considered in planning treatment strategies.

Causes of Hypertension in Young Adults

Most of the hypertension in young adults are essential hypertension having no identifiable cause. Secondary cause of hypertension should be ruled out if blood pressure is very high at first presentation, episodic rise in blood pressure, non-responding hypertension, or poorly responding hypertension despite good adherence and resistant hypertension. Some endocrine disorders causing hypertension have their obvious signs and symptoms at presentation. Special enquiry of illicit drug use, oral contraceptive pills, and other medications must be made in this group of patients. The important etiologies of hypertension are enumerated in **Table 2**.

Approach to the Patient

The key elements of evaluation of a patient of hypertension are accurate measurement of blood pressure, focused medical history and physical examination, and laboratory investigations. These are aimed to determine presence of end-organ disease, possible causes of hypertension, cardiovascular risk factors, and to get baseline values for starting and judging biochemical effects of therapy.

TABLE 2 Causes of hypertension in adults

Essential hypertension (80–95%)	
Secondary hypertension (5–20%)	
Renal	Parenchymal disease, polycystic kidney disease, renal tumor, obstructive uropathy
Renovascular	Fibromuscular dysplasia, atherosclerotic
Adrenal	Primary aldosteronism, Cushing's syndrome, pheochromocytoma
Neurogenic	Psychogenic, raised intracranial tension (acute)
Miscellaneous	Obstructive sleep apnea, thyroid disorders, acromegaly, preeclempsia/eclampsia
Medications	Estrogens, adrenal steroids, appetite suppressants, cyclosporine, tricyclic antidepressants, decongestants, NSAIDs, cocaine, Herbal medicines

Baseline investigations are urine dipstick, blood urea and electrolytes +/- eGFR, 12 lead ECG, fundoscopy, blood glucose, and serum lipid profile.

A judicious search for secondary causes warrants in this age group. A secondary etiology may be suggested by symptoms like flushing and sweating in pheochromocytoma, by clinical findings; a renal bruit in renal artery stenosis, or laboratory abnormalities, for example, hypokalemia suggestive of aldosteronism. In the absence of clinical signs to suggest possible secondary hypertension, indications for further evaluation are if blood pressure having early onset, rapid onset, or resistant hypertension. In young women, renal artery stenosis caused by fibromuscular dysplasia is one of the most common secondary etiologies. It can be detected by abdominal magnetic resonance imaging or computed tomography. For aldosteronism, the recommended initial diagnostic test is an aldosterone/renin ratio.[9] Obstructive sleep apnea can be a secondary cause of or contribute to hypertension. The standard diagnostic test is polysomnography, but clinical assessment tools (e.g., Epworth Sleepiness Scale, Sleep Apnea Clinical Score) with nighttime pulse oximetry may be used to get initial clue particularly in places of limited availability.

Counseling of patients for lifestyle changes and modification and/or treatment of contributory risk factors should start once the blood pressure crosses 130/80 mm Hg. In absence of comorbid conditions in patients with stage 1 hypertension at first visit lifestyle modifications should be started and blood pressure reading should be repeated within 2–3 weeks. Drug treatment may need to be started after 1 month. For stage II hypertension shorter repeat interval is desirable. And in stage III hypertension BP should be repeated after few hours to start pharmacological management. The target blood pressure should be 130/80 mm Hg.[4]

Young patients with secondary causes may have first presentation with hypertensive crisis. A wise clinical examination is needed to rule out hypertensive emergency and target organ damage.

BOX 1 Measures to reduce sedentary behavior

- Daily physical activity like covering short distance by foot, taking staircase instead of lift and use of cycle for nearby activities
- Avoid prolonged sitting in the office, practice the norm of leaving the chair hourly and walk for 5 minutes
- Reduce the screen time to <30 min/day, less use of mobile, and electronic gadgets

Management of Hypertension in Young Patients

Non-Pharmacological Therapy

The young hypertensives are better responders to non-pharmacological measures. Regular physical activity, weight loss, avoidance of tobacco, excessive alcohol, and stress management are important component of such therapy. Daily brisk walking for 30 minutes and outdoor games have proven to reduce blood pressure. Just adding few habits in daily routine may amount for few miles of activity as listed in **Box 1**.

The patient who is having raised blood pressure either in high normal or hypertension range is encouraged to adopt dietary approaches to stop hypertension (DASH)-type dietary plan which is rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat. The total salt intake is to be restricted to less than 6 gm/day **(Box 2)**. Young working persons are relatively more habituated to outside food. Avoidance of fast food, excessive tea, coffee, and aerated drinks are key components of dietary advice. Adequate sleep, yoga, and meditation have proven to be beneficial in stress management.[10] Young adults should be advised to spend some quality time in these activities.

BOX 2 Measures to limit salt intake

- Avoid processed food, cheese, sandwiches, pizza, and salty snacks
- Avoid red meat, tinned food products, and aerated drinks
- Use olive oil and avoid salted butter
- Use vinegar and lemon juice instead of the salt where possible

Pharmacological Management

Unwillingness to take medicines and not believing the seriousness of raised blood pressure are more common in young adults. Besides these, inadequate counseling of patients and physician's inertia to start medicines are factors responsible for not getting desired blood pressure control. A patient centered approach should be followed while choosing drug for blood pressure management. As per current guidelines, the choice of medicines is similar in young adults and relatively older individuals but emphasis must be laid upon tolerability. Various classes of medicine may be associated with side effects like increased micturition, fatigue, sexual dysfunction, and peripheral edema. Many young working patients may find these inconvenient and troublesome. Side effects must not reduce the work capability of these young achievers. All these should be discussed prior to prescription and drug should be tailored accordingly. This will increase acceptability and adherence of medicines. Any of the first line medicines, viz. diuretics, calcium channel blockers, and renin angiotensin system (RAS) blockers, ACE inhibitors/ARBs may be used first. Young persons are having higher sympathetic tone and renin secretion, so ACEIs and ARBs are the preferred agents in young if not having any contraindication of its use. However, in young females who may be planning conception, due counseling to discontinue ACEIs and shift to alternative antihypertensive agent needs to be provided. A long half-life medicine with once daily dosing is preferred. Combination therapy in single pill is encouraged for better compliance.

Comprehensive Approach

Significant numbers of young patients having hypertension have other components of metabolic syndrome like diabetes/pre-diabetes, dyslipidemia, and obesity. Targeting other components of metabolic syndrome is an opportunity in these patients. Lifestyle changes like diet control and physical activity should be targeted to achieve good control of other components. Even modest weight loss may lead to reduction of blood pressure. The selected medicines should help control other metabolic risk factors or at least must be neutral. Thus, the beta blockers and diuretics should be avoided in patients with dyslipidemia and glucose intolerance.

Young and Technology

On an average a young patient is more technology savvy than their older counterparts. There are gadgets and mobile applications available in market, which monitor diet, physical activity, and act as reminder to support adherence to the treatment.[11] Online counseling, telehealth projects, and related services are easily accessible and offer help in management of hypertension. However, they have their own limitations. Many awareness programs and activity are conducted by various national and international societies of hypertension and social organizations are now focusing on primary prevention to educate the masses.

Conclusion

Hypertension in the young needs to be carefully considered and evaluated, as it is a significant cause of morbidity and mortality. Young individuals have a variable lifestyle, and are difficult to convince that they have the disease. Therefore treatment needs to be individualised. Lifestyle management, salt restriction, ACE-inhibitors/ARBs (unless contraindicated) need to be initiated and re-inforced for compliance on each visit.

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CHAPTER

26

Biosensors in Hypertension

HK Aggarwal, Deepak Jain, Taruna Pahuja

Abstract

Hypertension is recognized as one of the leading risk factors for human morbidity and mortality. It puts an individual at the risk of myocardial infarction, heart failure, cerebrovascular accident, and end stage renal disease. These diseases can thus be prevented and controlled early by screening and timely diagnosis of hypertension. Both the korotkoff sound and oscillometric method of blood pressure (BP) measurement require cuff. Also, BP changes can occur according to operator and prevailing conditions, for example. White coat hypertension. Hence new technologies which allow BP monitoring without the use of cuff are being developed. This chapter describes the fundamentals of current technology in cuffless blood pressure measurement using nanosensors or photoplethysmography (PPG) to monitor blood pressure frequently and accurately for outpatient care and general health monitoring.

Introduction

Hypertension (HTN) is an epidemic affecting around one billion people. Globally 29.2% of males and 24.8% of females have HTN.[1] It has been ranked on the top as a cause of disability-adjusted life years. However, awareness, treatment, and control rate for HTN are low. Approximately half of the total hypertensives are aware of having HTN and 50% of known hypertensives are not on any treatment. Moreover adequate control of BP is present only in 50% of patients taking treatment. Hypertensives patients are precarious to develop heart attack, stroke, coronary artery disease, chronic kidney disease, and congestive heart failure and thus are at increased risk of premature death. Early detection and timely initiation of treatment regime for adequate BP control is a major step toward reducing complications and deaths due to HTN. Conventional blood pressure measurement techniques change according to conditions and are operator dependent. Ambulatory monitoring was introduced to overcome the problems associated with current manual office blood pressure measurement. A 24-hour ambulatory monitoring can help identify "white-coat" HTN, masked HTN, nocturnal HTN, labile HTN as well as postural hypotension, thus providing improved estimates of true blood pressure to guide decisions about treatment. Ambulatory blood pressure monitoring (ABPM) is done with a portable version of conventional oscillometer, the cuff of which fits around upper arm and inflates periodically as programmed while the person continues regular daily activities. However, patient is required to keep the arm static while the cuff inflates, which interferes with sleep and other activities of person. Also, in rare cases, continuous BP monitoring via cuff has been reported to cause hematomas, bursitis, phlebitis, and acute neuralgia. Hence, a wearable cuffless BP technology that offers continuous and noninvasive measurements has gained more attention. Handheld and wearable apparatus, which are small, comfortable, and less expensive, are now being used to measure other physiological vitals as well like oxygen saturation, body temperature and respiratory rate.[2]

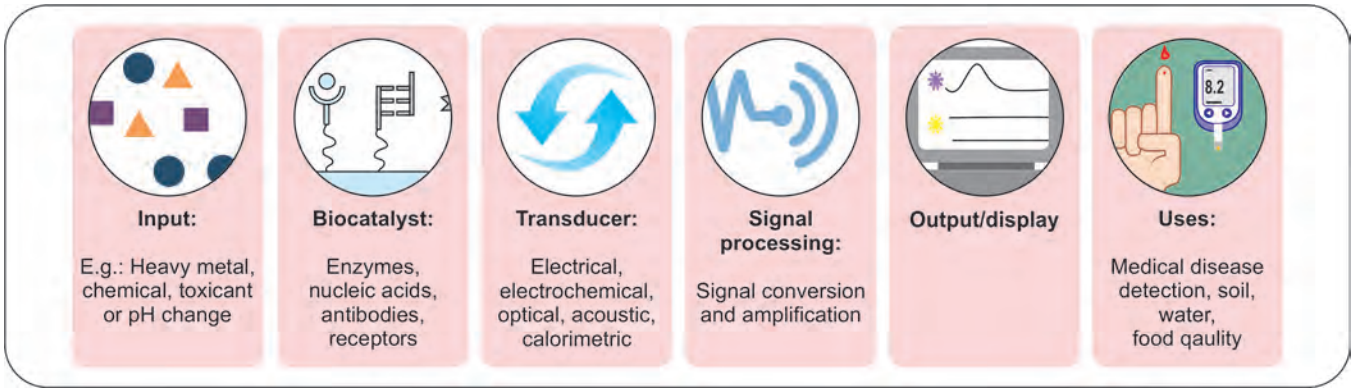

Fig. 1: Schematic description of biosensor

Biosensors

Biosensors are devices that convert a biological response into an electrical signal. These estimate the level of biological markers or any chemical reaction by producing the signals that are associated with the concentration of an analyte in that reaction. Biosensors consist of a biocatalyst that can detect a biological element/analyte and a transducer which converts the combination event of the biocatalyst and the analyte into discernible parameters **(Fig. 1)**.[3]

An ideal biosensor should be specific, sensitive, stable, and reproducible to detect a specific analyte in very small concentrations without being affected in and around the biosensing system with the ability to program identical output after replenishment of experiment. Linearity, which is defined as a considerable change in the signal with little change in concentration of an analyte, is considered an important component of the biosensor.

Types of Biosensors

Depending on the method of signal transduction, biosensors are classified into different groups. These are as follows:

- Optical/visual biosensors which detect changes in properties of light such as refraction index, fluorescence, or light scattering resulting from the interaction between an analyte and receptor. Photoplethysmography (PPG) sensor is an optical biosensor that measures the blood volumetric changes and can be used in wearable devices to monitor blood pressure.[4]
- Electrochemical biosensors consist of electrodes that translate the chemical signal into an electrical signal.
- Calorimetric biosensors measure the heat released or absorbed by the reaction.

Wearable biosensors (WBS) have gained attention recently with the use of technology for health monitoring, especially cardiovascular monitoring. These devices measure BP while person is performing routine daily activities, without creating any disturbance. By sensing elevated blood pressure, they can predict a missed dose of medication. Some of these devices are fitted with an alarm that is triggered by change in BP and serve as a reminder for patients to take medicine. WBS can be used in triage in waiting lobby of emergency rooms of hospital. In the era of COVID pandemic where telemedicine has become the "new normal," WBS fitted with alarm can allow increased surveillance by cardiovascular monitoring for patients at home and this data can be digitally shared with treating physician for the ease of teleconsultation and further reference.

Photoplethysmography

PPG is an optical biosensor used for measuring the amount of light that is absorbed or reflected by blood vessels in animate flesh, which depends on the amount of blood that is present in the optical path. It is a high-fusion signal that covers the activity of the heart's systolic and diastolic periods, the hemodynamics and network information of the peripheral microcirculation system. Thus, it is the external manifestation of various physiological processes in the cardiovascular system like heart rate, BP, cardiac output, and microcirculatory blood flow. PPG is a

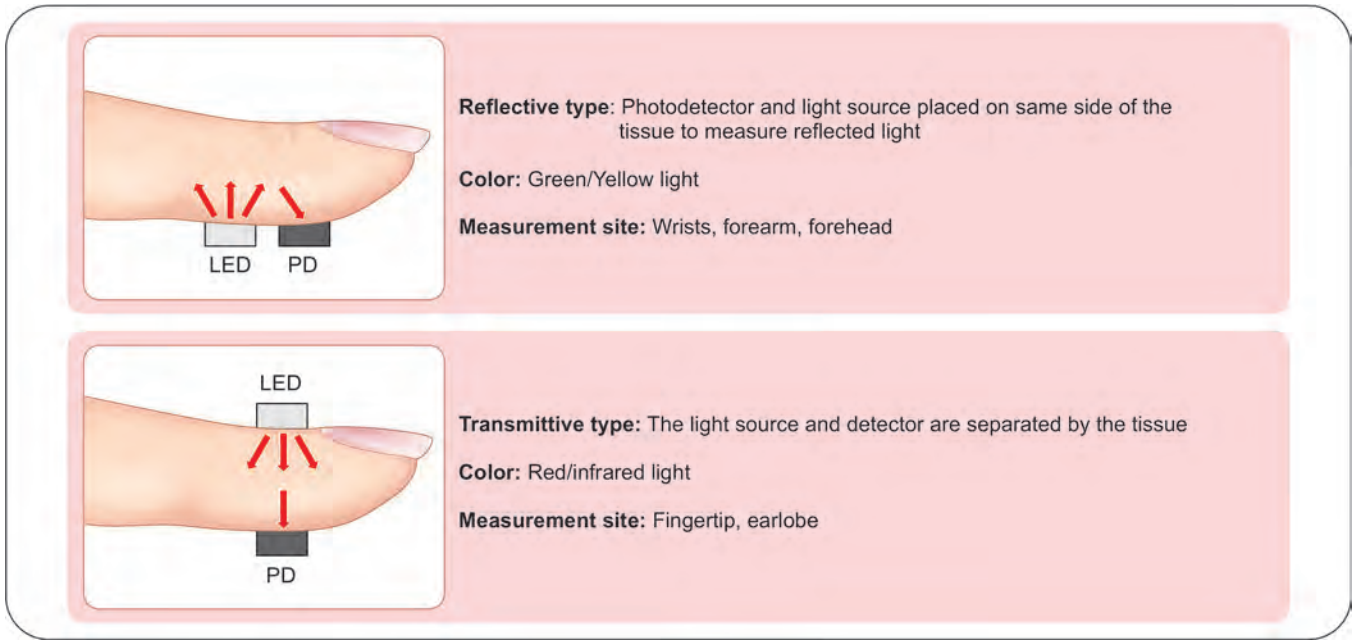

Fig. 2: Schematic representation of transmittive type and reflective type (PPG sensor and the light source)

convenient and inexpensive technique and its principles can be utilized for development of wearable cuffless BP monitoring devices.

PPG Signal Formation, Preprocessing, Feature Extraction

WBS is fitted with a LED (light emitting diode) transmitter, which either transmits or reflects red/infrared light to read PPG signal **(Fig. 2)**.

The raw PPG is corrupted, of poor quality and is difficult to access. This signal undergoes preprocessing via normalization and denoising/filtering with the help of median and notch filter. This uncorrupted PPG waveform contains the systolic phase and diastolic phase separated by dicrotic notch as shown in **Figure 3**.[5] It is used to extract useful features like peak to peak interval, systolic peak, stiffness index, crest time, and pulse area.

The systolic peak defined by the amplitude of PPG waveform is used to calculate heart rate. Systolic amplitude gives an indication of the pulsatile changes in blood volume. Stiffness index is a measure of arterial stiffness and depends on the height and age of person. It is obtained as the time interval between systolic peak and diastolic peak. Crest time is defined as duration of time from the base of PPG waveform to its peak. These parameters of PPG signal

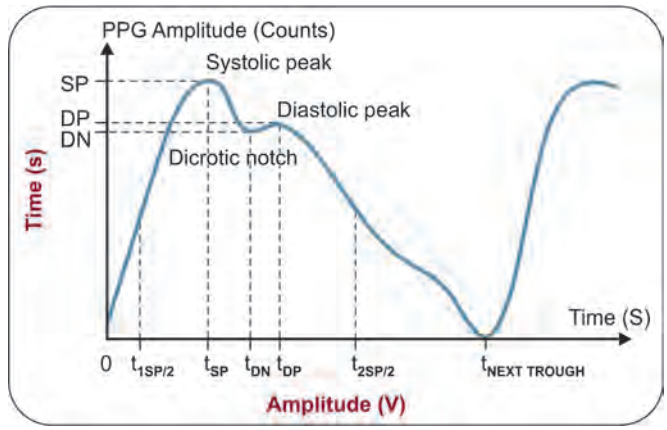

Fig. 3: PPG signal waveform consists of systolic phase, diastolic phase which are separated by dicrotic notch[5]

are used in various time-domain processing methods like peak detection, transition point calculation, etc.

PPG in Hypertension

Methods used for the continuous and cuffless measurement of BP via PPG are as follows:

- PTT based methods
- Non PTT based methods
- PTT based methods combined with non PTT based methods

PTT-based Methods

BP can be estimated by measuring pulse transit time (PTT), which is defined as the time taken by the pressure wave to travel from one point to another in the arterial tree within a particular cardiac cycle. The velocity of this pressure wave is termed as pulse wave velocity (PWV). PTT can be used to estimate PWV. The speed of transmission of pulse wave depends on the rigidity and resistance of the vessel wall. HTN causes an increase in thickness in the arterial media that leads to the rise in wall tension. Thus, PWV is influenced by BP. BP can therefore be estimated by measuring PTT and PWV.[6] PTT can be obtained by following methods.[6]

PPG Combined with Other Cardiovascular Signals

PTT can be calculated from PPG when it is combined with other cardiovascular signals, for example, electrocardiogram (ECG), ballistocardiogram (BCG), and phonocardiogram (PCG). PTT is measured as the temporal distance from one distinct point of the other signal to a specific point in the PPG waveform.

- *Electrocardiogram (ECG):* When PPG is combined with ECG, PTT is measured by calculating pulse arrival time (PAT). PAT can be measured as the distance between R wave of ECG and systolic peak of the PPG waveform. PAT = PTT + PET (Pre-ejection time). PET is the time elapsed between the electrical depolarization of the left ventricle (QRS on the ECG) and the beginning of mechanical ventricular ejection. PET is variable and gives different reading of BP. To avoid this variability, efforts are being done to establish PTT directly from multiple PPG signals instead of PPG-ECG combination **(Fig. 4)**.
- *Phonocardiogram (PCG):* It records the sounds produced by the movement of cardiac valves. When PPG is combined with PCG, PTT is measured by calculating vascular transit time (VTT). VTT can be measured as the distance between S1 (first heart sound produced by closure of atrioventricular valves) of a PCG and systolic peak of corresponding PPG.[4,6,7]
- *Ballistocardiography (BCG):* It records the movements of the body caused by contraction of the heart. When PPG signal is combined with BCG, PTT is measured by calculating time difference (TD). Mainly three waves (I,J,K) are defined in BCG. J wave peak corresponds approximately to the foot of the BP waveform at the outlet of the descending aorta. Time difference is measured as the time between J peak and systolic peak in PPG waveform **(Fig. 5)**.

Dual-Channel PPG

In this, PTT is measured at different peripheral sites, as the distance between the corresponding characteristic points of two PPG signals.

Single-Channel PPG

In this, PTT is measured as the distance between the forward and reflected wave of the second derivative of the PPG waveform.

Once PTT, PAT, and PWV parameters are estimated, mathematical models are used to derive BP. These models require two measurements from two sensors, for example, PPG and ECG signals. These sensors might have different sampling rates in real time, plus their operability depends on complicated arterial wave propagation models. Also, the extraction of feature points of each heartbeat correctly is a cumbersome method. It is very difficult to continuously monitor different physiological parameters in different point in time. This huge data can be well managed by artificial intelligence (AI). AI is a computer system that simulates human intelligence and performs tasks like speech recognition, decision-making, and visual perception. Machine learning (ML), a subset of AI, is a set of algorithms that analyzes data, learns from it and then applies what it has learned to make intelligent decisions. Machine learning requires various algorithms known as neural networks. Neural networks are built on the idea of human brain neural networks and consist of multiple layers, for example, input, output, and hidden layers to process, understand and produce result in a large data in continuous fashion, keeping in view the knowledge from previous result and modifying new results accordingly. Common pre-trained neural networks methods include GoogleNet, VGGNet, and AlexNet, which are trained based on ImageNet Large Scale Visual Recognition Challenge (ILSVRC).[8] PPG equipped with NN (Neural network) can deduce data from PPG signals which can be used to identify and classify HTN. This can provide real-time data and thus reduce morbidity and mortality. A mobile app named HeartSense was developed using a neural network to produce BP readings.[4]

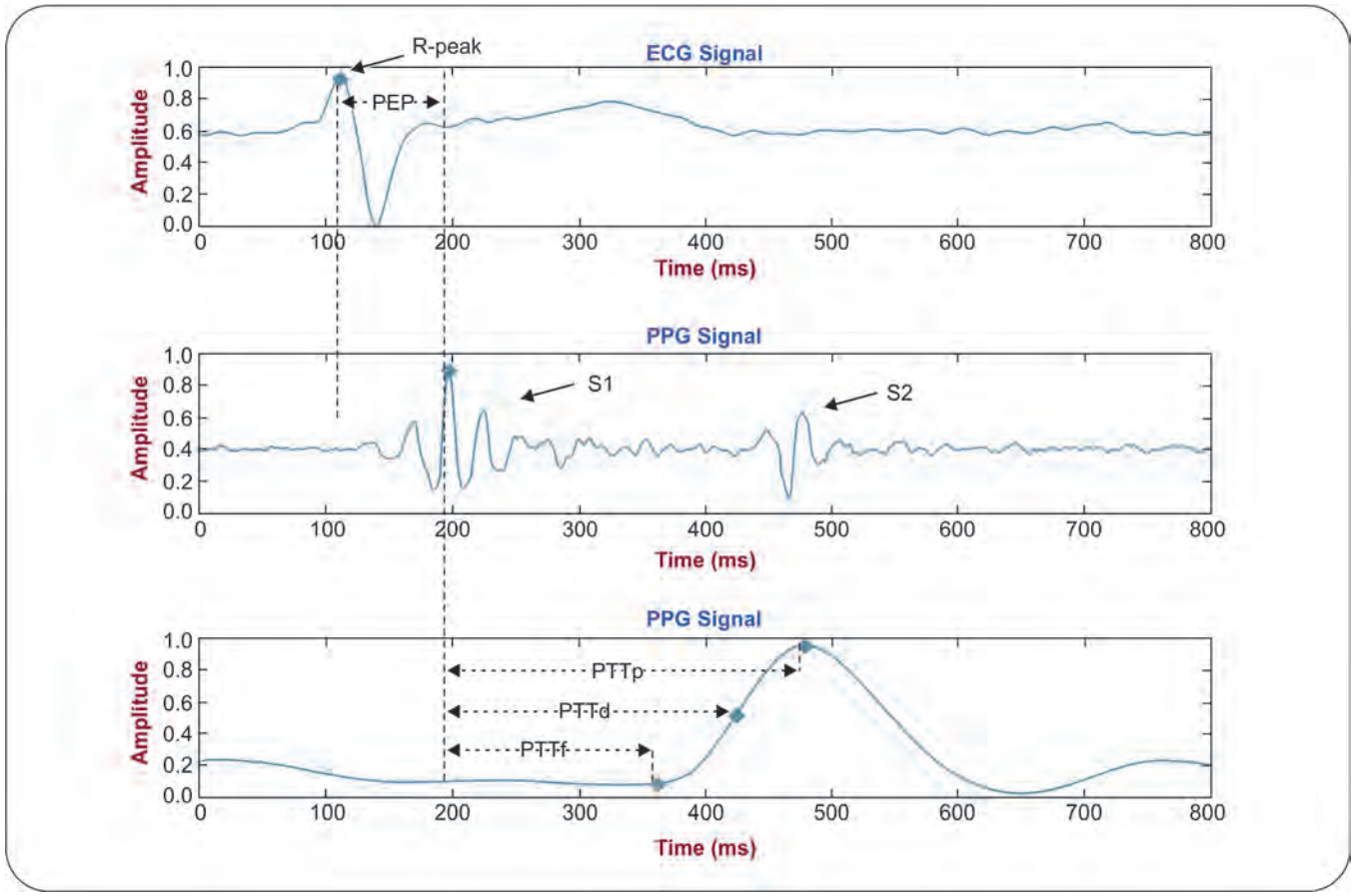

Fig. 4: ECG and PPG (first and third waveform, PAT = PEP + PTT); PCG and PPG (second and third waveform, VTT = S1 of PCG to systolic peak of PPG)

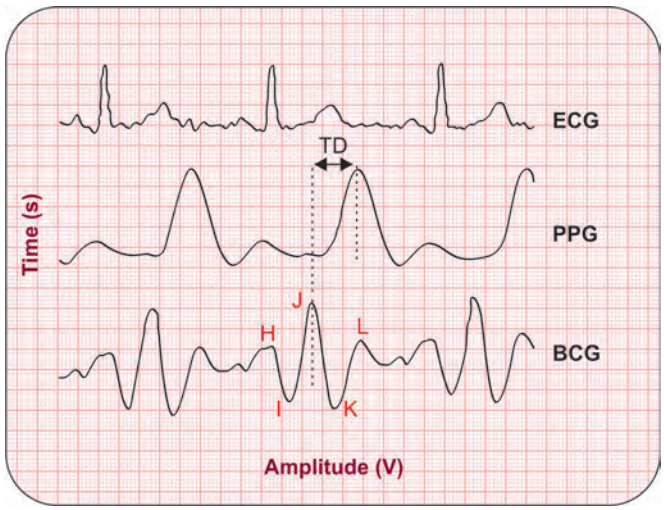

Fig. 5: PPG (Photoplethysmography) and BCG (Ballistocardiography). (TD = J peak in BCG to systolic peak in PPG)[4]

Non-PTT-based Method

In this method, morphological features of PPG such as pulse amplitude, signal steepness, peak to onset interval, signal amplitude, and many other time domain and frequency domain features have been used to estimate blood pressure.[6]

PTT-based Methods Combined with Non-PTT-based Methods

This method improves accuracy.

Implementation of PPG in Mobile and Wearable Health Devices

Out of hospital and continuous BP monitoring using handy and inexpensive instruments have become an

area of growing interest. Many companies have tried incorporating PPG in mobiles and wearable devices like wristband, armband, wristwatch, finger probe, eyeglass frame, chest belt.[9,10]

Wearable Rings

Wearable ring fitted with biosensor is an optimal device for measuring BP as the finger vasculature lies in proximity to the skin surface. It works on the concept of measuring arterial blood flow using PPG by optical biosensor that consist of LED, which illuminates the vessel of finger and photodetector that detects the amount of light transmitted/reflected.[11] This device can be worn by persons at all times for 24-hour BP measurement without the fear of finger necrosis, as the cuff is not used.

BP Monitoring Watch

Proximal timing (blood ejected from left ventricle into aorta) is obtained by an accelerometer, which measures the thoracic vibrations when user places the face of watch on his sternum for about 15 seconds. Distal timing (arrival of pulse wave at the radial artery on wrist) is obtained by PPG signal on the watch. The delay between these proximal and distal timing provides PTT, which is used to estimate BP. This device cannot be used for continuous measurement as one fiducial point is user dependent, but it can serve as a handy cuffless BP measurement technique where person can monitor BP as and when required by placing arm near chest wall.[12]

Eyeglasses

Especially designed eyeglasses are fitted with small-sized PPG sensors that sample pulse waveform at bridge of the nose (for angular artery pulsations), on side of the head (for temporal artery pulsations) and behind the ear (for occipital artery). The time delay between pulse time from one artery to the other provides PTT.[13] However, no clinical setting has validated this product to date.

Biosensor in Phone

By using the oscillometric mechanism, mobile phones can also be used as a tool for BP monitoring. The pressure of finger's vessel is increased when person presses his finger against the rear camera of phone. Pulsatile blood volume oscillations within the artery are measured via PPG and transducer, embedded in the phone. The amplitude of these oscillations is used to compute BP. Both android and iPhone have mobile applications based on this method to measure BP **(Fig. 6)**.

Smartphone devices can also measure BP using PPG signals by measuring PTT and VTT.[14] Phone cameras provide the proximal timing of PPG signal from person's finger. Another fiducial distal point is derived from heart sounds collected by microphone instilled in mobile phones. VTT is calculated between two points to estimate BP. Mobile applications like instant blood pressure (IBP) and wello, released by Auralife (Newport Beach, CA) and iPhone respectively, estimate BP using the above mentioned method of wave propagation.

Electrochemical Biosensors

Electrochemical sensors can be used for the quantification of various biological compounds that indirectly serve as markers of HTN. Cortisol, increased nitric oxide, galectin-3, ghrelin in saliva and inflammatory markers like C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukins, etc. are a few examples of such biological compounds.[15] Sodium-sensitive electrode is employed for the potentiometric detection of sodium from sweat samples based on the fact that high levels of sodium increase the stiffness of the endothelial cells leading to HTN. Kidneys control total sodium content through epithelial sodium channel (ENAC) and its deregulation is associated with HTN. Fabricated anti ENAC conjugates were detected by optical sensors. The fluorescence intensity enables discriminating between normotensives and hypertensives. Thus, represents a useful diagnostic tool for HTN.[16] Development of nanosensors for point of care diagnostics has led electrochemical sensors to display superior sensitivity, response time, precision time, and wider range for specific and reproducible detection of key markers that aid in diagnosing HTN. Although there are many hand-held or field biosensors available, most of these technologies have not been fully utilized for the detection of HTN and is used for research purpose only. The direction is yet to be explored as it holds immense promise for clinical applications but their specificity and cost efficiency are a major issue.

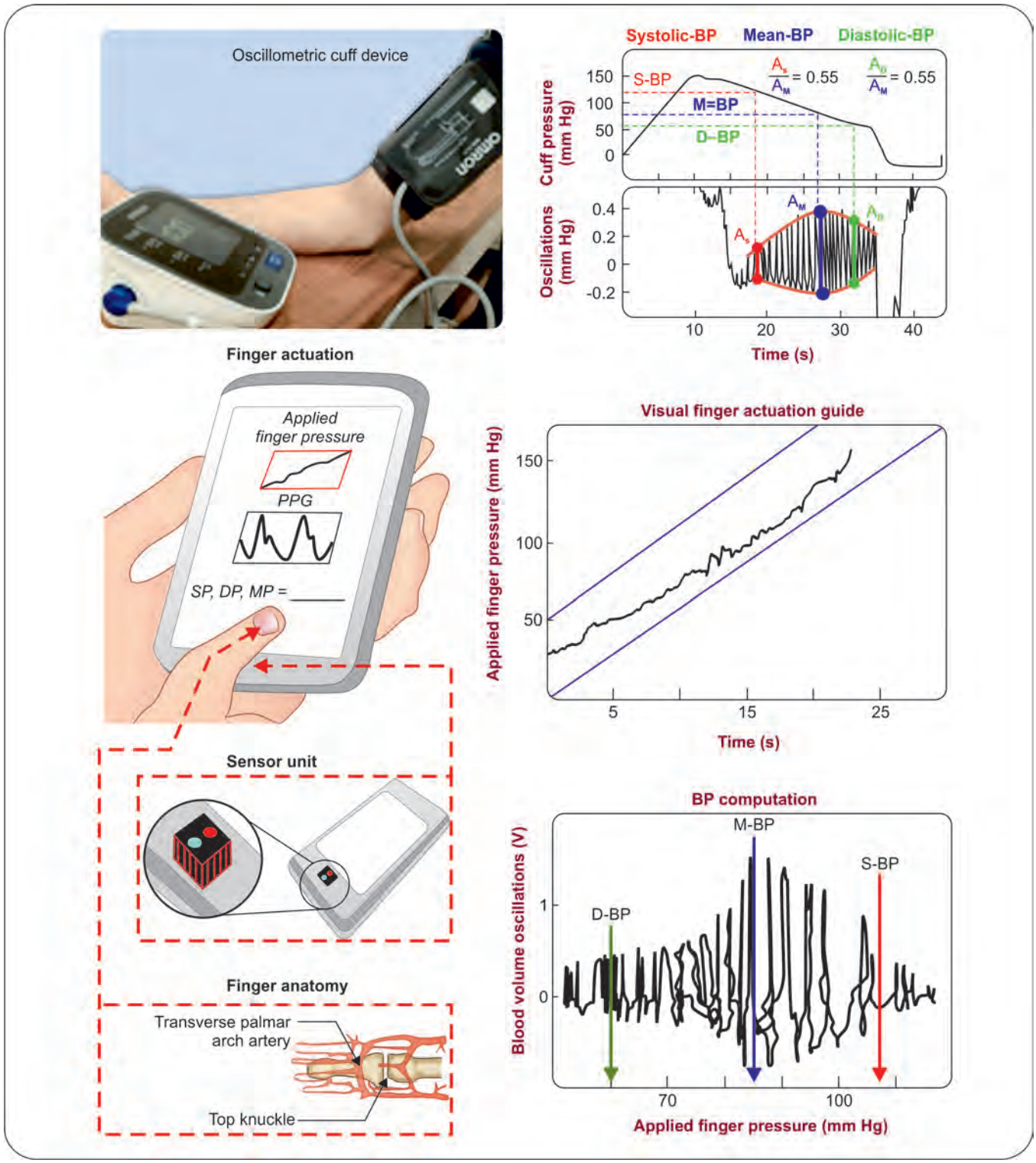

Fig. 6: Topmost figure shows conventional oscillometer. In second figure person places his finger on phone's camera, and phone embedded with photoplethysmography (PPG) and force transducers serves as the sensor to measure the blood volume oscillations and applied pressure[14]

Conclusion

The principle of PPG is widely used for measuring oxygen saturation. However, its use in clinical setting for BP is relatively new. Major phone companies like iPhone and Samsung have developed mobile applications that measure BP using PPG waveform that is obtained by pressing finger against phone camera. The widespread use of portable and wearable health devices allow timely BP measurement and monitoring, guides the health-care personnel of fluctuations patterns of person's BP, for example, nocturnal HTN and in some cases also reminds the person of missed dose by ringing an alarm. This prevents the complications related to HTN, prolongs customer's expected life span and also improves quality of life. In addition, these will bring down health costs in long run. However, high initial cost, less selectivity and a limited number of physiological parameter monitoring limit their use. A comprehensive understanding of PPG is required so that researchers can successfully develop advanced technologies for better care of hypertensive patients.

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Section 3

Section Editor: **Gurpreet S Wander**

Cardiology

CHAPTER

27 Coronary Intervention: What a Physician Should Know?

Nihar Mehta, Harish Surwade

Abstract

Coronary Intervention is a continuously evolving field. Over the last four decades, the innovations in this field have made coronary intervention a safer, more effective, and widely available procedure. A combination of physiological and anatomical evaluation is possible for detailed objective evaluation of the coronary tree. The refinement in the hardware and stent technology as well as the imaging modalities have lead to better outcomes in even complex coronary anatomies. As physicians, it is essential to know the basics of coronary anatomy and hardware along with the indications and options of revascularization, individualized to every patient.

Introduction

The use of coronary interventions has grown rapidly over the last few years. New improvements in techniques, hardware, operator experience, pharmacology, and safety as shown by clinical studies have expanded the use of coronary interventions. First Percutaneous Transcatheter Coronary Angioplasty (PTCA) was performed by Dr Andreas Gruntzig on 16 September 1977 in Zurich, Switzerland, with a balloon catheter. Since then use of PTCA has grown leaps and bounds. Balloon angioplasty was replaced by Bare Metal Stent implantation to reduce the incidence of recoil, restenosis, and complications like dissections. Drug eluting stents (DES) were the next innovation, which have replaced the bare metal stents (BMS) since 2003. The DES consisted of an antiproliferative drug, which was slowly released into the vessel to further reduce the rate of restenosis. Over the last two decades, several refinements have been made to DES such as reduction of stent strut size, use of newer anti-proliferative drugs, bioabsorbable stents, etc. This has led to improved outcomes of PTCA over the years. The indications have expanded to more complex coronary lesions, which were previously treated by surgery as a default.[1-4]

Epidemiology

The problem of coronary artery disease (CAD) or atherosclerotic lesions in coronary arteries has grown fourfold in India during last 40 years. Current epidemiological studies estimate its prevalence to be between 7% and 13% in urban and 2% and 7% in rural regions.[5-8]

According to epidemiological studies over 30 million cases of CAD are present in India. Of more than 10.5 million deaths reported in India annually, cardiovascular disease (CVD) led to 20.3% deaths in males and 16.9% deaths in females.[5] As per 2010–2013 data, the proportionate mortality from CVD increased to 23% of deaths. The mortality varies from less than 10% in rural locations in less developed states to more than 35% in more developed urban locations.[5] A study by Gajalakshmi et al. during 1995–1997 showed that CVD deaths are the highest (38.6%) in urban Chennai.[8] Similar data are published by Joshi et al. from Andhra Pradesh.[6]

Indications[9]

See **Table 1**.

Relative Contraindications

- Congestive cardiac failure
- Acute or chronic renal failure (unless dialysis is planned)
- Acute stroke
- Active gastrointestinal bleeding
- Electrolyte imbalances
- Bleeding diathesis
- History of allergic reaction to iodinated contrast agent
- History of allergy or bronchospasm to aspirin
- Bacteremia

Coronary Angiography and Percutaneous Coronary Intervention

Preprocedure

Preprocedural wearing of a lead apron, thyroid shield, lead goggles, and a lead cap protects against potential radiation hazard. A preprocedural evaluation should include a note of the last oral intake, a history of drug and a history of previous experience with sedative or contrast agents.[10]

The patient should be kept fasting for at least 3–4 hours before the start of the procedure. For diabetic patients, medications should be adjusted. Metformin should be stopped 48 hours before and after PCI to reduce the likelihood of lactic acidosis. Adequate hydration with IV fluids and N-Acetyl cysteine starting 12 hours before procedure in patients with mild renal dysfunction is advised for nephroprotection.

Strict aseptic precautions and cleaning and draping of the access sites should be done. The procedure is performed under local anesthesia in most cases with or without mild sedation.

Vascular Access

The procedure is usually preformed via the femoral or radial artery approach. Femoral artery access has a fairly straight course to the descending aorta, is larger and gives better catheter support during the procedure. However, complications like bleeding, pseudoaneurysms, retroperitoneal hematomas, or arteriovenous fistula are possible in 3–7% of cases. The radial artery is increasing in popularity as an access site due to early patient mobilization, reduced complications rates and fairly direct access into ascending aorta.[11,12] Smaller sheath and catheter sizes (4F, 5F) have replaced the larger catheters (8F), which lead to lower access site complications.

TABLE 1 Indications for coronary angiography

Coronary artery disease:
• *Asymptomatic*: – At high risk of coronary event based on noninvasive testing • *Symptomatic:* • Stable Angina with Canadian Cardiac Society Class II, III, or IV symptoms • Unstable angina or Non-ST Elevation Myocardial Infarction (Acute Coronary Syndrome) • ST Elevation Myocardial Infarction (STEMI): Reperfusion with a primary percutaneous coronary intervention (direct intervention without thrombolysis) or pharmaco-invasive approach (within 2–24 hours after thrombolysis) or Rescue PCI (in case of failed thrombolysis) • Complications of STEMI: Acute pulmonary edema, Cardiogenic shock, Mechanical complications (Ventricular septal defect or Mitral regurgitation)
Valvular heart disease:
• Prior to valve replacement surgery in patients suspected of having coronary artery disease
Cardiomyopathy:
• Newly diagnosed cardiomyopathy suspected to be due to coronary artery disease • Hypertrophic cardiomyopathy with angina
Congestive cardiac failure:
• New onset angina suspected to be due to coronary artery disease
Congenital heart disease:
• Suspected associated coronary artery anomalies
Cardiac transplantation:
• Preoperatively and post-transplant to detect coronary artery vasculopathy
Others:
• Survivors of sudden cardiac arrest • Sustained monomorphic ventricular tachycardia or non-sustained polymorphic tachycardia

Coronary Angiography/Arteriography

Once the vascular access has been secured by modified Seldinger technique, especially shaped coronary catheters are advanced up to the ascending aorta. They are engaged

into the left or right coronary artery (RCA) and hand injections are made using a radiopaque contrast material. The radiographic images (cine angiography) are recorded in several different orthogonal views. The anatomy of the epicardial coronary arteries and coronary bypass grafts can be outlined.

Normal Coronary Anatomy and Coronary Artery Disease

Although coronary anatomy can be variable between individuals, in general there are two coronary ostia—the left and right. The left main coronary artery divides into the left anterior descending (LAD) and the left circumflex artery (LCx). The LAD gives septal and diagonal branches whereas the LCx gives obtuse marginal branches **(Fig. 1A)**. In about 1–2% of individuals, a ramus intermedius branch directly arising from the left main coronary artery, between the LAD and the LCx.

The RCA divides distally into the posterior descending artery (PDA) and the posterior lateral artery/posterior left ventricular artery (PLV). This anatomy is called the right dominant circulation and is found in 85% of individuals **(Fig. 1B)**. In about 5% of individuals, the PDA arises from the LCx, which is defined as left dominant circulation. The remaining 10% have a codominant circulation.

Coronary artery stenoses are visualized by coronary angiography as luminal narrowing and the degree of narrowing is referred to as percentage stenosis. The percentage stenosis is determined visually by comparing the most severely diseased area to the distal normal artery segment. A coronary stenosis of 40–70% is considered intermediate and more than 70% is considered significant.

Coronary calcification can be visualized during angiography before injecting the radiocontrast material. Collateral blood vessels can also be seen between one vessel and the distal part of a severely stenosed vessel. Other abnormalities like dissections, thrombus, coronary ectasia, and myocardial bridges can also be visualized during coronary angiography.[9]

Patient Selection for Percutaneous Coronary Intervention (PCI)

Patients with significant CAD can be revascularized by percutaneous transluminal coronary angioplasty (PTCA/PCI) or coronary artery bypass graft (CABG) surgery. The choice between PCI and CABG vary depending on the type of presentation and characteristics of coronary anatomy.

- Chronic stable angina: The main aim of treatment is to improve symptoms or reduce mortality:
  - In asymptomatic or mildly symptomatic patients, revascularization can be deferred if procedural risks/bleeding risks are high. PCI is warranted only if symptoms worsen or there is evidence of severe ischemia on noninvasive testing in spite of optimal medical therapy.

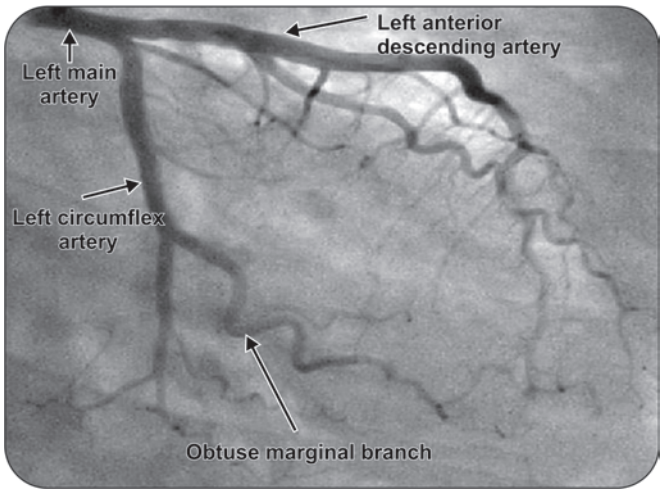


Fig. 1A: Left coronary artery anatomy
(*Source:* PJ Mehta's Practical Medicine, 20th edition)[13]

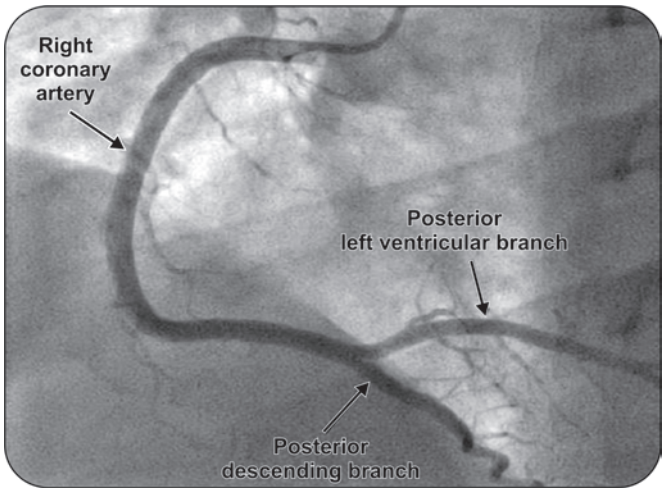


Fig. 1B: Right coronary artery anatomy in a right dominant circulation
(*Source:* PJ Mehta's Practical Medicine, 20th edition)[13]

  - Moderate to severely symptomatic patients should undergo ischemia-guided revascularization.
  - Left main CAD, triple vessel disease or diabetic patients have better outcomes with CABG surgery.
  - Less severe multi-vessel disease with or without diabetes have equal outcomes with PCI and CABG.
- Acute coronary syndromes: PCI is superior to optimal medical management due to high risk of mortality. PCI is preferred over CABG surgery except in case of severe multi-vessel disease or anatomical factors which are not amenable to successful treatment.
- ST elevation myocardial infarction (STEMI):
  - Primary PCI (Primary angioplasty in Myocardial Infarction—PAMI) is a preferred strategy (direct intervention without thrombolysis).
  - In the pharmaco-invasive approach, patients are thrombolyzed followed by PCI within 2–24 hours after thrombolysis.
  - In case of failed thrombolytic therapy (patients in whom there is ongoing angina 90 minutes after fibrinolysis and/or ECG persistently shows ST elevation), Rescue PCI should be performed.
- In patients presenting with cardiogenic shock or heart failure (HF), PCI is class I indication that increases survival.[14]
- Several coronary arterial anatomical factors influence success and safety of PCI such as location of the lesion (proximal or distal), tortuosity, calcification, length of lesion, size of vessel, thrombus, or chronic total occlusion (>3 months in duration). Patients with unfavorable anatomy are candidates for CABG surgery.
- Conversely, some patients are inoperable for CABG surgery due to comorbidities such as advanced age, frailty, chronic obstructive pulmonary disease (COPD), or poor LV function.

PTCA Procedure (Figs. 2 and 3)

Prior to the procedure, patients are given a loading dose of dual antiplatelet medications: aspirin (325 mg) and a P2Y12 inhibitor (clopidogrel 300–600 mg or prasugrel 60 mg or ticagrelor 180 mg) to prevent thrombotic complications.

The procedure is carried out under local anesthesia with or without mild sedation. Vascular access is obtained in the same way as outlined earlier using Seldingers technique. During the procedure, anticoagulation is achieved by using unfractionated heparin or bivalirudin (direct thrombin inhibitor). In the case of STEMI or large thrombus in the coronary arteries, intravenous glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, or eptifibatide) is used.

The most commonly used PCI equipment consists of four basic elements: a guiding catheter, a balloon catheter, a coronary guidewire, and a stent **(Fig. 4)**.

Via the introducer sheath at the vascular access site, a guiding catheter is used to selectively cannulate the culprit coronary artery. All subsequent coronary hardware is passed into the coronary artery through the guiding catheter. A flexible guidewire is passed into the coronary artery across the stenosis and is positioned in the distal coronary artery. The guidewire acts as a guiding "rail" for all subsequent hardware to be passed in and out of the coronary arterial tree.

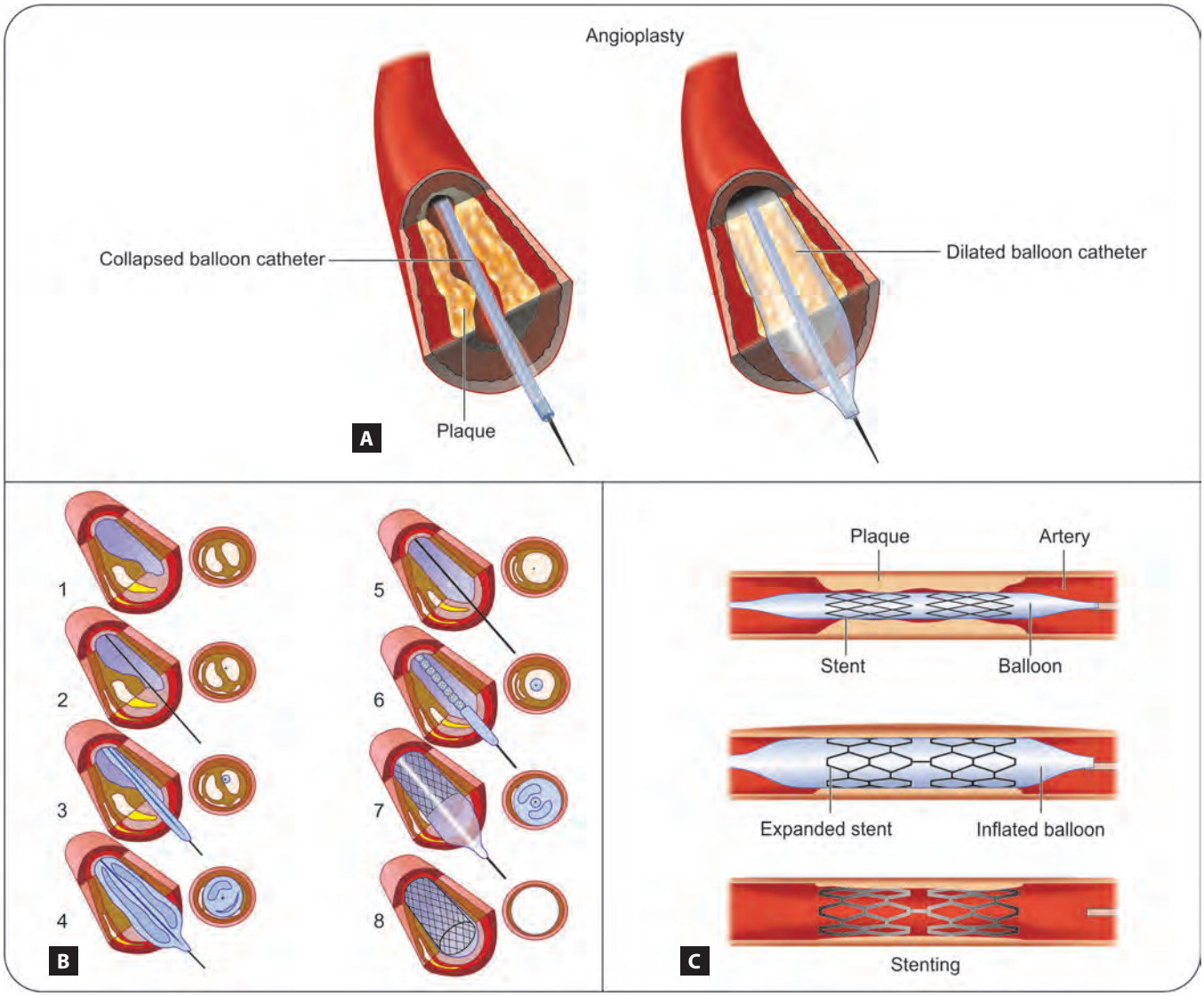
A balloon catheter is passed over the guidewire, positioned across the stenosis, and then dilated to stretch the coronary artery and displace the plaque to enlarge the coronary lumen thus improving blood flow. The balloon catheter is then removed over the guidewire, maintaining the position of the guidewire in the coronary artery.

A coronary stent is a stainless-steel mesh/scaffold which is available in a compressed state over a balloon catheter. It is passed over the guidewire, positioned across the stenosis and deployed by inflating the balloon. When the balloon is deflated, the stent stays in place in the coronary artery and the balloon catheter is removed. Normal blood flow is restored to the coronary artery. The guidewire, guiding catheter, and introducer sheath are subsequently removed. Hemostasis is achieved using manual pressure or vascular closure devices.[10,15]

The patient is then transferred to a recovery area and then to the patient's room. If no complications occur, the patient is discharged the next morning. The patient usually returns to work shortly (<7 days) thereafter.

Mechanism of Angioplasty and Stenting and Stent Composition

Mechanism of balloon angioplasty: The inflated balloon exerts pressure against the plaque and the arterial wall, causing fracturing and splitting. Concentric (round or circumferential) lesions fracture and split at the thinnest and weakest points. Eccentric lesions split at the junction of the plaque and the normal arterial wall. Dissection



Figs. 2A to C: Schematics of angioplasty and stenting

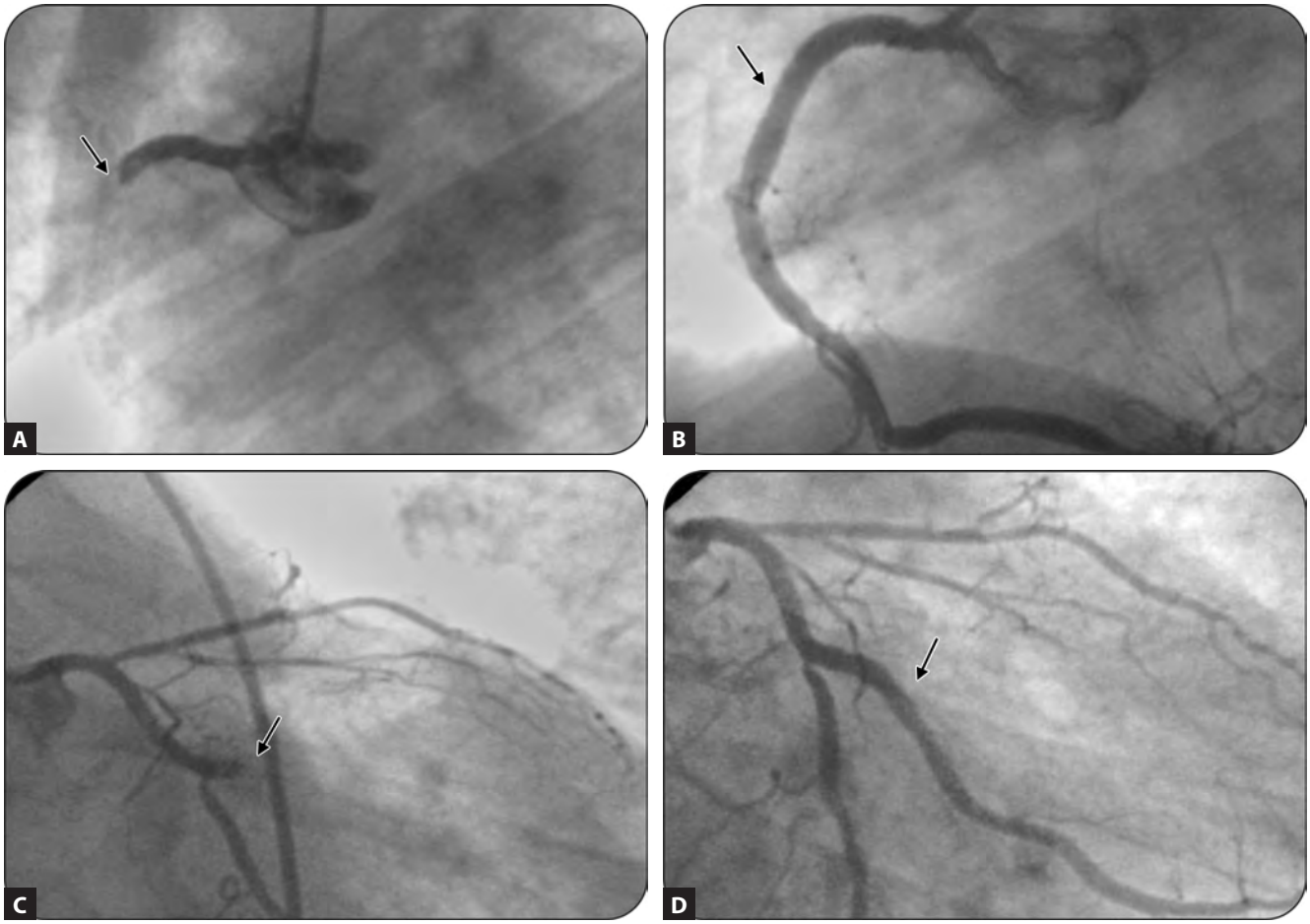
or separation of the plaque from the vessel wall releases the restraining effect caused by the lesion and results in a larger lumen.

Mechanisms of stenting: Placing a stent in the coronary artery leads to disruption and fracture of atheromatous plaque. The scaffold prevents elastic recoil of artery and leads to longitudinal compression of plaque material against the wall. The anti-proliferative drug inhibits the intimal proliferation and reduces the restenosis rates.

DES are made of a stainless-steel mesh/scaffold. They have a thin polymer coating, which holds an anti-proliferative drug, which is released into the atherosclerotic plaque slowly for 1–3 months. This reduces the rate of restenosis. The anti-proliferative drugs used are paclitaxel, sirolimus, everolimus, zotarolimus, or biolimus. Bioabsorbable vascular scaffold (BVS) stents were initially available, which gradually degraded over 2 years; however, the BVS stents were withdrawn due to late stent thrombosis.[9]

Additional Interventional Devices

Several other interventional devices are available such as thrombus aspiration catheters (to aspirate thrombus



Figs. 3A to D: (A and B) Primary angioplasty (PAMI) of right coronary artery (RCA) and (C and D) obtuse marginal (OM) branch of the left circumflex artery. Black arrows in A and C show thrombotically occluded RCA and OM arteries, respectively. Black arrows in B and D show final result after stenting the respective arteries

in case of a STEMI), distal embolic protection devices (to protect the distal vasculature from embolization in case of heavy thrombus burden in STEMI or degenerated saphenous vein graft intervention), rotational atherectomy or directional atherectomy or orbital atherectomy (devices used in heavily calcified lesions, which are resistant to balloon dilatation), among others.

IVUS, OCT, and FFR

In the case of intermediate stenoses (40–70%) additional modalities are to be used to determine if the stenosis is flow limiting. Intravascular Ultrasound and Optical Coherence Tomography provide an anatomical assessment of the coronary arteries, whereas fractional flow reserve (FFR) provides a physiological assessment of the coronary flow.[9]

Intravascular ultrasound (IVUS) is an ultrasound device mounted catheter that is advanced into lumen of diseased artery. It gives atherosclerotic plaque burden, reference vessel diameter and area, and morphology of stenosis **(Figs. 5A and B)**. IVUS can also be used after angioplasty to determine the adequacy of the stent placement.

Optical coherence tomography (OCT) is infrared-based imaging technique that has a higher resolution than IVUS, but has limited penetration (depth of visualization) **(Figs. 6A and B)**.

FFR is a ratio of pressure distal and proximal to the stenosis respectively when there is maximal vasodilation of the coronary microvasculature. It gives the physiologic significance of a borderline stenosis and can guide PCI

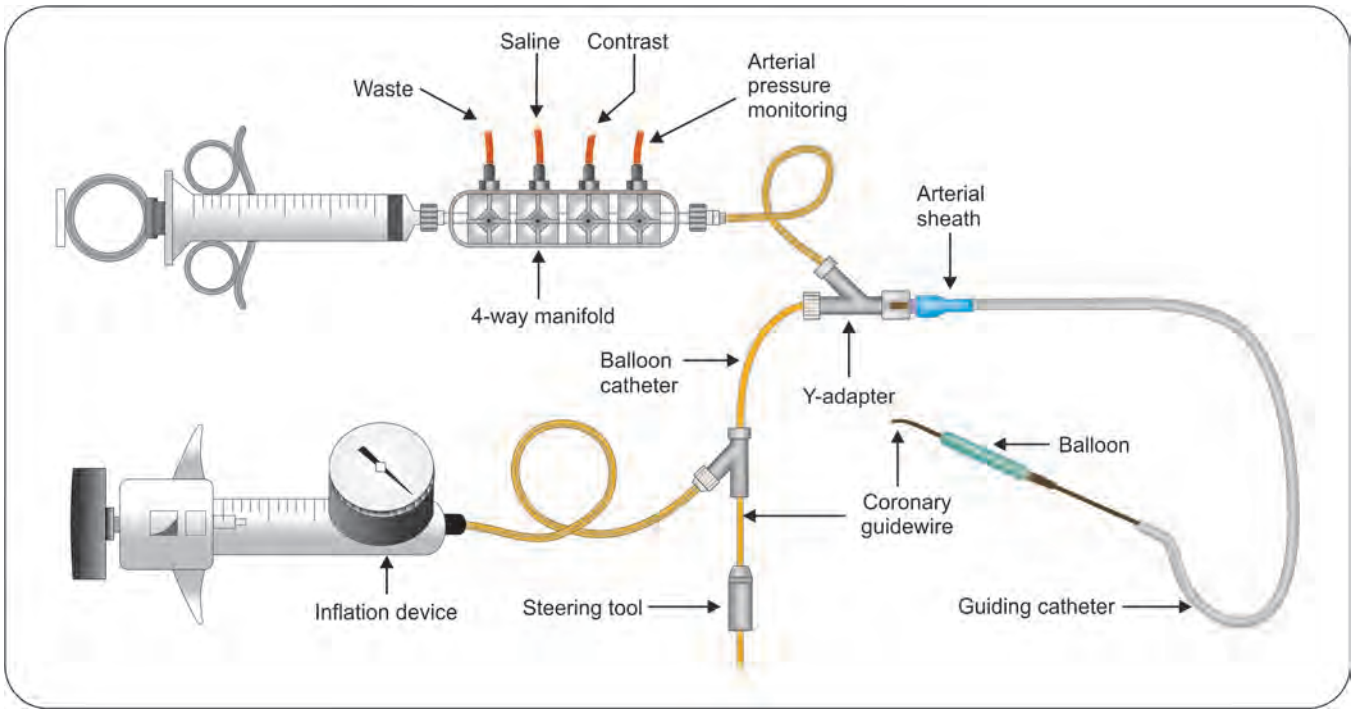
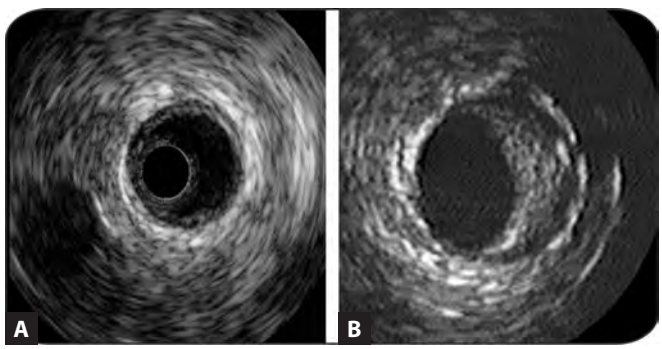
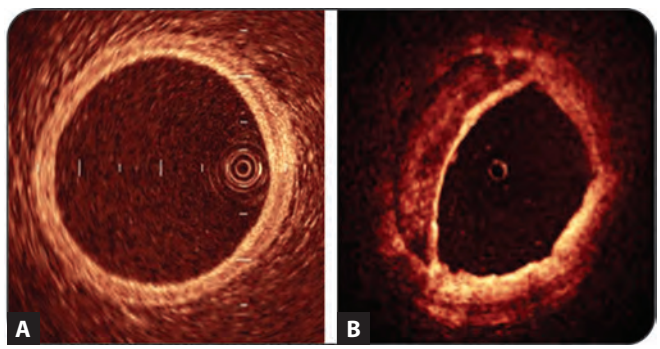


Fig. 4: PCI equipment



Figs. 5A and B: Intravascular ultrasound (IVUS) images: (A) Normal coronary artery with three layers: the intima, media, and the adventitia. The lumen is the dark central area within the intima. (B) Coronary artery with an atherosclerotic plaque encroaching into the lumen from 12 o'clock to 6 o'clock position

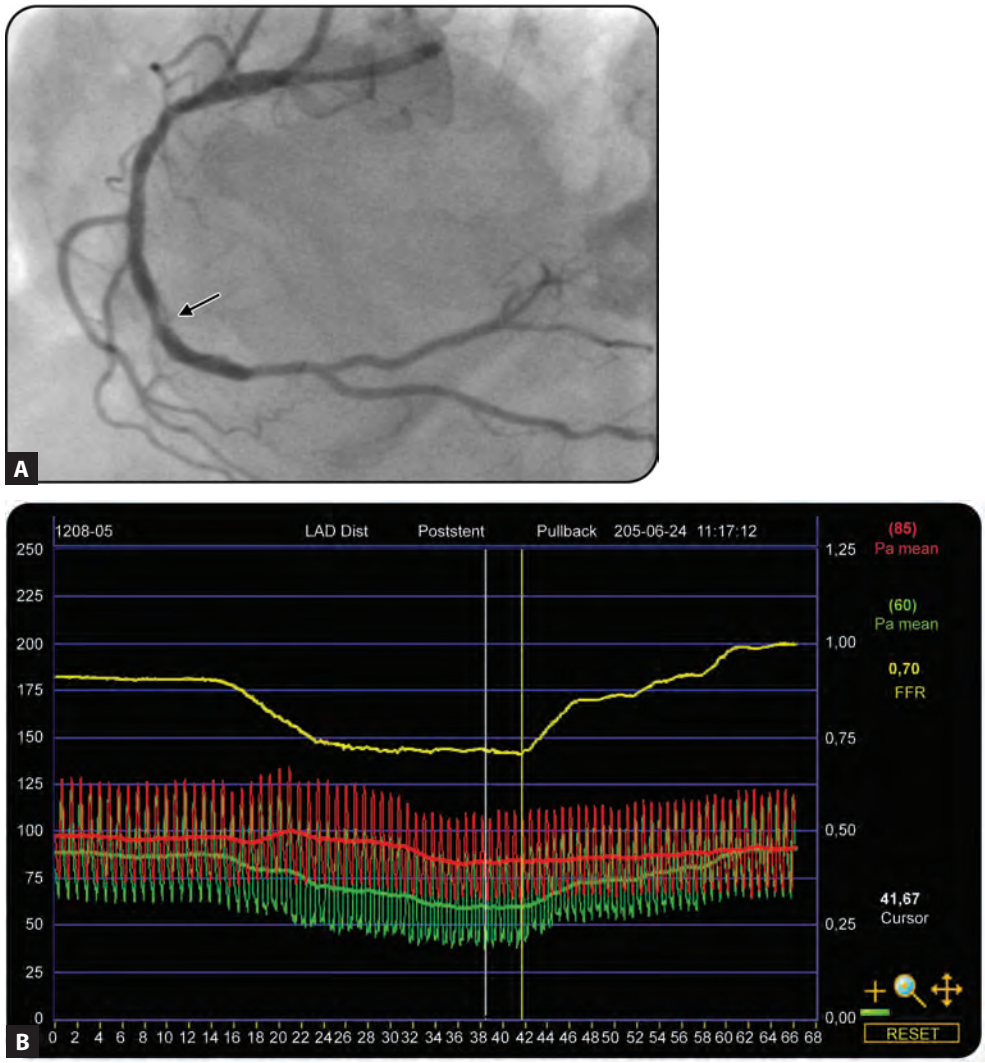


Figs. 6A and B: Optical coherence tomography images: (A) Normal coronary artery with three layers, the intima, media, and adventitia. The lumen is the inner black central area within the intima. (B) Coronary artery with a calcified atherosclerotic plaque from 7 o'clock to 1 o'clock position

decision. FFR less than 0.80 indicates a flow limiting stenosis that would benefit with revascularization **(Figs. 7A and B)**.[16]

Complications and Risks[17-19]

- *Vascular complications:* Bleeding, hematoma, pseudoaneurysm formation
- *Contrast induced nephropathy:* Rise in the serum creatinine by 0.5 mg/dL or by 25% above the baseline that occurs 48–72 hours after the procedure
- *Contrast allergy:* Severe anaphylactoid reaction, urticarial, nauseas, vomiting
- *Acute myocardial infarction:* Due to stent thrombosis, dissections, distal embolization or side branch closure



Figs. 7A and B: Fractional flow reserve (FFR): (A) Right coronary artery with an intermediate stenosis (black arrow). (B) Pressure tracing from the pressure wire across the lesion. FFR is ratio of the mean distal pressure (Pd)/mean pressure in aorta (Pa) at maximal hyperemia. In this case the Pd/Pa = 0.79, which shows that the lesion is flow limiting and should be revascularized

TABLE 2 High-risk PCI

Anatomic	*Clinical*
• Left main coronary artery disease • Triple vessel disease • Associated valvular disease (especially severe aortic stenosis) • Left ventricular dysfunction (EF <40%) • Severe peripheral vascular disease • Post CABG—Saphenous vein graft/Arterial graft interventions • Past PCI • Complex subsets: Chronic total occlusions/Calcified lesions/ Tortuous lesions	• Acute myocardial infarction • Cardiogenic shock/Hemodynamic instability • Atrial/Ventricular arrhythmias • Poorly controlled hypertension • Decompensated heart failure • Diabetes mellitus • Renal dysfunction • Pulmonary disease (COPD/Asthma/OSA) • Bleeding diathesis/Anemia/Thrombocytopenia/Deranged INR • Cerebrovascular disease • Contrast allergy • Elderly/Frail • Medications: Oral anticoagulants/Insulin/Diuretics • Emergent procedures

- *Cerebrovascular accident:* Acute or delayed stroke
- Stent thrombosis
- Restenosis due to neointimal hyperplasia
- *Tachy- or bradyarrhythmias:* Requiring pharmacotherapy, cardioversion or pacing
- *Death:* Relatively low risk

The risks associated with coronary angiographies are relatively low when performed electively. The risks are higher in certain subsets such as when done in an emergency or in hemodynamically unstable patients **(Table 2)**.

Considering the multiple factors in an individual patient, which dictate the decision of PCI versus CABG in multi-vessel CAD, it is ideal to have a heart team approach involving the interventional cardiologist, cardiac surgeon and physician while decision-making.

Conclusion

With the continuous innovations in the field of interventional cardiology, we have come a long way in the last four decades to make PTCA a safer and more effective procedure. The refinement in the hardware and stent technology has led to higher success rate in more complex anatomies with better long-term outcomes. As a physician, the decision to intervene is essential as well as offering the ideal mode of revascularization keeping in mind the risks, clinical and anatomical factors, individualized for every patient.

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CHAPTER

28 Current Status of Management of Rheumatic Heart Disease in India

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Abstract

Rheumatic heart disease continues to be a significant cause of cardiovascular morbidity and mortality in India and other low-middle income countries. In most endemic regions, the disease is often neglected and diagnosed late, with majority of the affected patients presenting for the first time with complications like heart failure, atrial fibrillation, and cardio-embolism. Echocardiography screening based on World Heart Federation echocardiographic criteria holds promise to identify patients earlier, when prophylaxis is more likely to be effective. This review focuses on the diagnostic and management approach to the patients with acute rheumatic fever and rheumatic heart disease based on the available literature and guidelines.

Introduction

Rheumatic heart disease (RHD) is a neglected disease which leads to significant cardiovascular morbidity and mortality in India and other low-middle income countries.[1] RHD occurs in response to rheumatic carditis either due to initial or recurrent episodes of acute rheumatic fever (ARF) and seen in 60% of patients with ARF.[2] ARF is a nonsuppurative sequelae of group A beta-hemolytic streptococcus (GAS) pharyngitis. ARF occurs in 0.3–3% of patients after a streptococcal sore throat.[3] Therefore, early detection and management of ARF is pivotal in the prevention of RHD.[4] Once it occurs, RHD causes significant morbidity and results in various long-term complications like stroke, peripheral embolism, heart failure, and premature death.[4] This review will highlight the diagnostic and management approach to the ARF/RHD patients based on the available literature and guidelines.

Epidemiology of RF/RHD

Despite a global decline in the incidence of RHD, it remains endemic in regions with overcrowded living conditions and inadequate health-care services. Worldwide, there is a gross disparity in the incidence rates in endemic versus non-endemic areas. The incidence rate varies from 3.4 per 100,000 population in the non-endemic countries to as high as 444 per 100,000 population in the endemic countries.[4] Unfortunately, India is the "RHD Capital" of the world, with nearly 40% of the global RHD burden.[4] However, in India, gross disparities exist in the socioeconomic statuses and the availability of health-care facilities across different states, within the states, and between the urban and the rural areas.[2] As a result, the burden of RHD in India is likely to differ widely within and across the states. Unfortunately, there are hardly any data from the worst affected states like Uttar Pradesh, Bihar, Jharkhand, West Bengal, and Odisha.[2]

Diagnosis and Management of Rheumatic Carditis

The ARF is most frequent in the age group of 5–15 years.[2] The diagnosis of ARF is based on Jones criteria, which were last revised in the year 2015 **(Table 1)**.[5] Carditis is the most severe manifestation of ARF because it may lead

TABLE 1 The 2015 revised Jones criteria for the diagnosis of acute rheumatic fever[5]

2015 Revised Jones criteria for the diagnosis of ARF		
For all patient population with evidence of preceding GAS infection		
Diagnosis of Initial ARF – 2 major or 1 major plus 2 minor manifestations Diagnosis of recurrent ARF – 2 major or 1 major plus 2 minor manifestations or 3 minor		
	Low-risk population: ARF incidence ≤2 per 100,000 school-aged children or all-age RHD prevalence of ≤1 per 1,000 population year	***Moderate to high-risk population: Children not clearly from a low-risk population***
Major criteria		
Carditis	Clinical and/or subclinical*	Clinical and/or subclinical*
Arthritis	Polyarthritis	Monoarthritis, polyarthritis, and/or polyarthralgia
	Chorea	Chorea
	Erythema marginatum	Erythema marginatum
	Subcutaneous nodules	Subcutaneous nodules
Minor criteria		
Carditis	Prolonged PR interval#	Prolonged PR interval#
Arthralgia	Polyarthralgia	Monoarthralgia
Fever	≥38.5°C	≥38°C
Markers of inflammation	Peak ESR ≥60 mm in 1 h and/or CRP ≥3.0 mg/dL	Peak ESR ≥30 mm in 1 h and/or CRP ≥3.0 mg/dL

*Subclinical carditis: Seen only on echocardiography without auscultatory findings.
#Accounting for age variability and only if carditis NOT counted as a major criteria.
ARF, acute rheumatic fever; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A beta hemolytic *Streptococcus*; RHD, rheumatic heart disease.

to chronic RHD with its attendant complications of heart failure, atrial fibrillation, thromboembolism, infective endocarditis, and death.[3] Clinical features depend on whether there is the involvement of the pericardium, myocardium, or heart valves. Myocarditis always occurs in presence of valvulitis, and isolated myocardial involvement in absence of valvular involvement, should raise doubts over the diagnosis of rheumatic carditis.[4] The mitral regurgitation is a dominant valvular lesion in 90% of ARF cases, causing an apical pansystolic murmur.[3] It may be accompanied by aortic regurgitation (AR). Isolated AR is seen in less than 5% of cases.[3] Stenotic lesions occur in the late stages of the disease. Among patients with previously diagnosed RHD, recurrence of acute rheumatic carditis is clinically suggested by a new murmur or a change in the character of the previously heard murmur. Nevertheless, echocardiography is strongly recommended in all patients with definite/suspected acute rheumatic carditis since it is more specific and sensitive than cardiac auscultation.[5] The aim of treatment in ARF is

- to suppress the inflammatory response and thus minimize the effects of inflammation on the heart and joints
- to provide symptomatic relief
- to eradicate the GAS harboring the pharynx
- to commence secondary prophylaxis.

The management of carditis during an episode of ARF aims at diagnosing and assessing the severity of cardiac involvement using echocardiography, and management of cardiac manifestations like congestive heart failure, and heart blocks.[5] Available literature does not suggest that anti-inflammatory treatment improves cardiac outcomes; however, glucocorticoids may prove beneficial in patients with acute cardiac failure secondary to severe carditis.[6] Prednisolone is preferred with an initial dose of 1–2 mg/kg/day, given for 2–3 weeks followed by gradual tapering and the total duration of therapy should be 8–12 weeks. Some recommend the introduction of salicylates as the dose of steroids is reduced to prevent rebound. In patients with clinical signs and symptoms of heart

TABLE 2 Secondary prophylaxis for rheumatic fever (drugs and duration of therapy)[7]

Antibiotic	*Route*	*Dose*
Benzathine benzylpenicillin	Single deep intramuscular injections every 3–4 weeks	If weight >30 kg then 1,200,000 IU If weight <30 kg then 600,000 IU
Penicillin V	Oral	250 mg twice daily
Sulfonamides (sulfadiazine, sulfisoxazole, sulfadoxine)	Oral	If weight >30 kg them 1 gm daily, if weight <30 kg then 500 mg daily
Erythromycin	Oral	250 mg twice daily
Duration of secondary prophylaxis for rheumatic fever		
In patients with no cardiac involvement	For 5 years after last attack or until 21 years of age (whichever is longer)	
In patients with preceding carditis and mild residual mitral regurgitation or valve lesion which resolved completely	For 10 years after last attack or until 21 years of age (whichever is longer)	
In patients with preceding carditis with moderate to severe valve damage	For 10 years after last attack or until 40 years of age (whichever is longer); Lifelong in high-risk patients	
In patients with relapses or high risk of infection	Lifelong	
After valve surgery	Lifelong	

failure, conventional treatment that includes diuretics and renin-angiotensin system blockers should be initiated. Valve surgery is rarely necessary in acute setting, and is usually reserved for patients with valve leaflet or chordae tendineae rupture where surgery can be lifesaving.[7]

The eradication of GAS from pharynx can be done by penicillin, which can be administered as a single intramuscular dose of benzathine penicillin or oral penicillin for 10 days.[7] Once the diagnosis of ARF/definite RHD is established, penicillin (preferably in form of 3 weekly intramuscular injections of benzathine penicillin) is recommended for secondary prevention **(Table 2)**. The benzathine penicillin can cause allergy and/or anaphylaxis in 3% and 0.3% of cases, respectively. There are few concerns with the use of intramuscular injections of penicillin, like difficulty in ensuring round-the-year availability in remote areas, fear associated with allergy/anaphylaxis, pain at the local site, and the long duration for which injections have to be administered on the 3–4 weekly basis. Azithromycin (once a week orally) and other oral drugs like erythromycin and sulfonamide are potential substitutes but are less effective.[8]

Diagnosis of Chronic RHD

Chronic RHD usually affects the patients in their most prime and productive years. In one of the most extensive contemporary Indian data on RHD patients, the HP-RHD (Himachal Pradesh rheumatic heart disease) registry, the mean age of patients was 40±14 years, and 70% of affected patients were females, and multivalvular disease was present in 67% of patients.[1] Early diagnosis of RHD, before the symptoms/manifestations become overt, along with early initiation of penicillin prophylaxis, can halt the disease progression and improve the outcomes. Criteria have been developed by "World Heart Federation (WHF) 2012" for echocardiographic diagnosis of RHD and to differentiate it from normal physiological variants **(Table 3)**.[9]

Management of Individual Valve Lesions

Mitral Stenosis

Medical Management

The medical management of mitral stenosis (MS) is directed at

- the prevention of recurrent rheumatic fever
- management of complications like atrial fibrillation, embolic complications, infective endocarditis, pulmonary artery hypertension (PAH) and right heart failure
- monitoring disease progression and allows intervention at an optimal time.

Asymptomatic patients with mild-moderate MS should be monitored annually. The management of severe

TABLE 3 Morphological features of rheumatic heart disease and the criteria for pathological regurgitation as defined by the World Heart Federation[9]

A. Morphological features of RHD	
Features in the MV: • AMVL thickening* ≥3 mm (age-specific) • Chordal thickening • Restricted leaflet motion • Excessive leaflet tip motion during systole	*Features in the AV:* • Irregular or focal thickening • Coaptation defect • Restricted leaflet motion • Prolapse
B. Criteria for pathological regurgitation	
Pathological mitral regurgitation (all four Doppler echocardiographic criteria must be met): • Seen in two views • In at least one view, jet length ≥2 cm* • Velocity ≥3 m/s for one complete envelope • Pan-systolic jet in at least one envelope	*Pathological aortic regurgitation:* (all four Doppler echocardiographic criteria must be met) • Seen in two views • In at least one view, jet length ≥1 cm* • Velocity ≥3 m/s in early diastole • Pan-diastolic jet in at least one envelope

*A regurgitant jet length should be measured from the vena contracta to the last pixel of regurgitant color (blue or red).
AMVL, anterior mitral valve leaflet; AV, aortic valve; MV, mitral valve; RHD, rheumatic heart disease.

disease includes the use of diuretics, beta-blockers, and/or digoxin for rate control. The anticoagulation with warfarin should be given to patients of MS having atrial fibrillation, LA/LAA (left atrium/left atrial appendage) clot, history of embolization, and if LA is grossly dilated (LA >55 mm).[10] The target INR (international normalized ratio) should be maintained between 2–3. The role of newer oral anticoagulants in the management of MS is controversial and needs further evaluation.[3,11] The factors responsible for acute worsening like anemia, pregnancy, infection, infective endocarditis, and ARF recurrence also need consideration while managing mitral stenosis.

Mitral Valvotomy

The older techniques of closed mitral valvotomy (CMV) and open mitral valvotomy (OMV) have now been replaced by percutaneous balloon mitral valvotomy (BMV), also known as percutaneous transvenous mitral commissurotomy (PTMC). BMV is strongly recommended in symptomatic and suitable patients with moderate to severe MS (i.e., valve area <1 cm^2/m^2 of BSA or <1.5 cm^2 in normal-sized adults with pliable noncalcified valves, no more than mild MR and with no evidence of LA/LAA thrombus).[12] Besides, BMV is a favorable option for asymptomatic patients with valve area less than 1 cm^2 or when MS results in the development of AF. BMV is done through the femoral vein approach, and after doing trans-septal puncture, the "Inoue balloon" is inflated across the orifice of mitral valve, which results in the fracture of nodular calcium, and separation of the mitral commissures, and as a result, increase in the orifice area of the mitral valve. BMV is, however, contraindicated in the presence of persistent left atrial or LAA thrombus, more than mild (moderate to severe) mitral regurgitation, and severe or bicommissural calcification. A meta-analysis comparing BMV with surgical commissurotomy suggested that, compared with surgical commissurotomy, BMV results in slightly smaller mitral valve area, a comparatively higher risk of developing MR, and an approximately threefold risk of reintervention.[13] However, with an increase in operator experience and familiarity, refined hardware, relative procedural ease, and perhaps being a cheaper option compared with surgical options, BMV remains the preferred treatment option for rheumatic MS.[3] The possible complications of BMV include cardiac perforation (1%), cerebral emboli (1%), development of MR (15% develop MR out of which 2% require surgery), and even death in 1–2% of patients.[3]

Mitral Valve Replacement

Valve replacement may be needed if the valve is severely calcific and non-pliable with echocardiography based Wilkins score greater than 8 (Wilkins score is based on leaflet mobility, leaflet calcification, leaflet thickening, and

subvalvular deformity), and also in the presence of more than grade 2 MR, and/or persistent LA/LAA clot.[12]

Mitral Regurgitation

The chronic mitral regurgitation (MR) has a long asymptomatic course, and usually symptoms appear after two decades of an ARF unless complicated by infective endocarditis or recurrent rheumatic fever.[12] The most common symptom of chronic MR is exertional fatigue due to low effectual cardiac output. However, acute MR causes a sudden increase in LA pressure and pulmonary venous hypertension, which requires treatment with afterload reducing agents and urgent surgical intervention. The mild to moderate degree of MR requires an annual follow-up with echocardiography to assess the progression of the disease, whereas the management of chronic severe MR is done based on the patient's symptom status. The drugs like beta-blockers and renin-angiotensin system blockers are recommended only once left ventricular dysfunction ensues, and their role in mild to moderate MR is controversial. The indications of surgical interventions in chronic severe mitral regurgitation are following:[12]

- Presence of symptoms with LVEF >30% [Class 1]
- Asymptomatic chronic severe MR with LVESD (left ventricular end-systolic diameter) ≥40 mm and or LVEF ≤60% [Class 2a]
- Asymptomatic chronic severe MR with either new-onset atrial fibrillation and/or pulmonary hypertension with pulmonary artery systolic pressure >50 mm Hg [Class 2a]

The decision to replace or repair the valve is of critical importance. Although repair is better than replacement, it maintains "annular-chordal-papillary muscle continuity" and prevents LV remodeling; however, it requires a steep learning curve. Furthermore, the repair is less successful in older patients with rigid, calcified and deformed valves due to RHD.[12] Furthermore, in countries with poor resources like India, where re-do surgeries are seldom performed, valve replacement is often the preferred option compared with valve repair, despite the possible consequences associated with prosthetic valves in the presence of inadequate INR monitoring and irregular warfarin supplies. The repair of primary degenerative MR is most often successful in

- Children's and adolescents with pliable valves
- Adults with MR secondary to MVP
- Cases of annular dilatation, chordal rupture, and leaflet perforation secondary to infective endocarditis.[12]

Aortic Stenosis

Unlike degenerative aortic stenosis (AS), isolated rheumatic AS occurs rarely.[3] The cardinal symptoms of AS are exertional angina, exertional dyspnea, syncope, and, ultimately, heart failure. Overall, the average survival without aortic valve replacement (AVR) is only 1–3 years after symptom onset.[12] Symptomatic AS is an indication for valve replacement. Patients undergoing concomitant surgery for other indication, and having associated moderate to severe AS should also undergo AVR. Patients with severe AS and left ventricular dysfunction and an EF (ejection fraction) of less than 50% can also be taken up for AVR. Patients with an abnormal response to stress testing should also undergo AVR. Aortic valve repair is not consistently possible with rheumatic AS, and replacement is needed. Over the last decade, transcatheter AVR (TAVR) has revolutionized the treatment of degenerative AS. However, the use of TAVR in RHD does not look promising, since AS in RHD seldom occurs as an isolated lesion and secondly because AS in RHD occurs at younger age compared with degenerative AS.[3]

Aortic Regurgitation

The isolated involvement of the aortic valve is rare and often accompanied by rheumatic mitral valve involvement.[3] There is a long latent period of the disease, and patients may only complain of uncomfortable awareness of heartbeat, especially on lying down. The exertional dyspnea and paroxysmal nocturnal dyspnea are only noticed when there is an onset of LV dysfunction or simultaneous mitral valve involvement. The mild to moderate degree of AR requires to follow-up by echocardiography, whereas severe AR requires treatment with renin-angiotensin system inhibitors to decrease the regurgitant fraction of AR and beta-blockers and diuretics in case of LV dysfunction.[12] The indications of AVR are following:

- Severe symptomatic AR [Class 1]
- Severe asymptomatic AR with LVEF <50% [Class 1]
- Severe asymptomatic AR with other cardiac surgery [Class 1]
- Severe asymptomatic AR with LVEF >50% with LVESD (LV end-systolic dimensions) >50 mm [Class 2a]

TABLE 4 Major highlights and implications from the HP-RHD (Himachal Pradesh Rheumatic Heart Disease) Registry[1] and the REMEDY registry[14]

	HP-RHD registry	*REMEDY registry*	*Implications*
Study population	2,005 patients (All Indian patients from the state of Himachal Pradesh)	3,343 patients (293 patients were Indians). This comparison includes patients from low-middle income countries (n=1,370)	Two of the largest contemporary data involving RHD patients
Age	Mean age = 40.3±14.3 years	Median age = 28 years	RHD involves young people mostly in their reproductive age groups
Female sex	72.3%	63%	High number of young women in childbearing age is a major concern
Schooling up to primary level only	40.4%	27.4%	A low level of education and socioeconomic status is often associated with RHD
Past history of ARF	25.1%	44.3%	Past history of ARF is elicitable in less than half of the patients. Therefore, the diagnosis relies more on detailed clinical and echocardiographic criteria and less on the past history of ARF
CHF PAH AF Stroke Peripheral embolism	15.7% 30.5% 24.4% 3.9% 4.1%	21% 34.2% 22% 3.8% 0.2%	High incidence of complications occurs before the patients seek medical care. This is mainly due to lack of awareness and early diagnosis
Multivalvular heart disease Moderate to severe valvular involvement	43.2% 69.3%	NA 63.9%	Majority of patients develop severe and multivalvular disease before they first seek tertiary level care
Use of secondary prophylaxis	28.5%	59.7%	Grossly inadequate use of secondary prophylaxis, probably the reason for high recurrence and prevalence of RF/RHD
Use of OAC in high risk patients	77.8%	69.5%	Inadequate use of OAC probably the reason for high rates of stroke and cardio-embolism
Use of valvuloplasty Use of valve surgery	16% 9.7%	4% 28%	Higher rates of surgical/percutaneous interventions are needed to decrease the morbidity and mortality

AF, atrial fibrillation; ARF, acute rheumatic fever; CHF, congestive heart failure; OAC, oral anticoagulant; PAH, pulmonary artery hypertension; RHD, rheumatic heart disease.

- Severe asymptomatic AR with LVEDD (LV end-diastolic dimensions) >65 mm [Class 2b]

If AVR is needed for stenosis or regurgitation, concurrent aortic root replacement is recommended if a maximum aortic dimension exceeds 45 mm.

Management of Tricuspid Valve Disease

The involvement of the tricuspid valve in RHD is most common due to PAH secondary to left-sided valve lesions (hypertensive tricuspid regurgitation). It has been increasingly recognized that the concept that "correcting

the left-sided lesion" will restore the tricuspid competence in hypertensive tricuspid regurgitation (TR) is not always true since, in the majority of patients, TR recurs in short/medium term follow-up and usually requires another intervention. Therefore, it is recommended to do tricuspid annulus repair using various annuloplasty techniques among patients undergoing left valve surgery[12] in the presence of:

- Severe TR
- Mild to moderate TR with annular dimensions >40 mm or 21 mm/m^2

Patients with normotensive TR (without PAH), organic tricuspid valve disease, and associated with tricuspid stenosis need to have their valves repaired or replacement (if repair not possible) preferably with a bioprosthetic valve. Patients with organic tricuspid stenosis and right heart failure should undergo tricuspid valvotomy at the time of their surgery. Isolated tricuspid stenosis should undergo balloon valvotomy if feasible.[3]

Current Situation in India

The available data suggests that the major reasons for high morbidity and mortality associated with RF/RHD include inadequate adherence to secondary prophylaxis, insufficient use and monitoring of oral anticoagulant therapy, and the limited access to surgical/percutaneous interventions.[1] Despite being home to 40% of the world's RHD burden, there are limited contemporary Indian data on

- RF/RHD mortality
- Complications of RHD (atrial fibrillation, cardio-embolism, heart failure, infective endocarditis, pregnancy morbidity)
- Treatment practices
- Long-term outcomes among RF/RHD patients.[1,2]

This is hugely disappointing since there is enough evidence that the existing preventive and therapeutic strategies can decrease the morbidity and mortality secondary to RHD. The focus of cardiovascular research has unfortunately shifted from RHD to coronary artery disease, despite India losing more than 100,000 patients to RHD every year.[4] The HP-RHD registry provides the most extensive published contemporary Indian data on the clinical characteristics, treatment practices, and outcomes in patients with RHD.[1] The other significant contemporary data comes from the REMEDY registry which included RHD patients from 25 hospitals across 12 African Countries, India, and Yemen.[14] Indian patients constituted 8.8% (293 patients) of the study population in REMEDY registry. The salient features of both the registries have been highlighted in the **Table 4**.[1,14]

Conclusion

Despite being one of the major causes of cardiovascular morbidity and mortality in low- and middle-income countries like India, RHD is often neglected cardiovascular disease, which causes significant morbidity and mortality. It primarily affects young patients in their most prime and reproductive ages. Although strategies for preventing RHD are proven, simple, cheap, and cost-effective, they are, unfortunately, adequately implemented. Furthermore, there is a gross inadequacy of data, especially from the worst affected regions. Percutaneous and surgical valve interventions are not available to the majority of the patients. There is a gross inadequacy in the availability and use of optimal preventive and therapeutic drugs and strategies. Patients are often not detected early and usually present to tertiary care centers when their disease is advanced and severe. The reasons for ARF and RHD remaining a burning problem in India are poor socioeconomic conditions, lack of hygiene and awareness, inadequate use of secondary prophylaxis, lack of vaccine, and absence of a national program to control RF/RHD in our country. These issues need to be addressed along with the encouragement of RF/RHD related research to make informed policies and programs to make India "RF/RHD free."

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CHAPTER

29 Role of Stress ECG in Preoperative Evaluation for Non-Cardiac Surgery

Neelima Singh, Sushma Trikha

Abstract

Acute coronary events lead to high risk period from few weeks to months before performing non-cardiac surgery. Exercise Stress test helps to estimate functional capacity and has prognostic implications. The aim of this review is to offer an approach in the preoperative evaluation of patients undergoing non-cardiac surgery and to stress the importance and indications of stress testing in patients with heart diseases.

Introduction

Perioperative cardiac mortality and morbidity are increased in adults and elderly population undergoing major surgery. Preoperative evaluation provides assessment of both short-term and long-term cardiac risks in addition to evaluation of current medical status. Acute coronary events lead to a high-risk period from few weeks to months before performing non-cardiac surgery.[1]

Multidisciplinary team should ideally be involved for assessing perioperative cardiac risks.[2] Cardiac stress testing is an important tool for diagnosis and management of patients with known or suspected heart disease. While stress testing can be performed in many ways, the most commonly used stress testing modalities are exercise electrocardiography (TMT non-imaging) and exercise or pharmacologic stress test combined with imaging [stress echocardiography or stress radionuclide myocardial perfusion imaging (MPI)].

The aim of this review is to offer an approach in the assessment of patients undergoing non cardiac surgery and stress the importance and indications of stress testing in preoperative patients with heart disease.

Cardiac Stress Tests (Stress ECG) for those who can Exercise

Stress Testing (TMT)

It is a simple and widely available tool. For those who can exercise. Noninvasive tests, Exercise stress test, Tread Mill Test (TMT) also called Stress ECG or Exercise ECG is a preferred component of stress testing in most patients.

Exercise capacity is a very important determinant of prognosis particularly in elderly. The ability to achieve 4 METs (metabolic equivalent of tasks) of activity without symptoms is thought to be a good prognostic indicator.

The onset of myocardial ischemic response at low exercise is associated with increased risk of perioperative and long-term cardiac events. In contrast, myocardial ischemia at high workload is associated with only a minor risk increase.

With normal baseline ECG, an exercise ECG test is able to produce a reliable and reproducible result almost comparable to Technetium 99m sestamibi perfusion—imaging.

Exercise ECG test is economical with reliable disease interpretation.[3] Stress testing is not a routine test for

preoperative patient. However, some clinicians prefer preoperative stress imaging in patients who are scheduled for major vascular surgery.

Exercise Stress Echocardiography

It is usually advised in patients scheduled for intermediate or high-risk surgical procedure. The choice of stress testing modality depends on many factors, including ability to perform adequate exercise.

Cardiac Stress Tests for those who cannot Exercise

- Stress echocardiography
- Myocardial perfusion studies

In patients with indications for stress testing who are unable to exercise, pharmacological stress testing with either DSE (Dobutamine Stress Echo) or MPI (Myocardial Perfusion Studies) may be appropriate. Intravenous dipyridamole and adenosine should be avoided in patients with heart block, bronchospasm, critical carotid occlusive disease.

Dobutamine should be avoided in patients with serious arrhythmias or severe hypertension. All stress agents should be avoided in unstable patients.[4] Imaging stress testing is generally not recommended before low-risk surgery.[5]

Stress Echocardiography

Stress echocardiography is 2D echocardiography with a physical, pharmacological, or electrical stress. Stress echocardiography is today the most cost-effective and risk-effective imaging technique for diagnosis of coronary artery disease.[6] Other advantages are low cost, wide availability, and lack of radiation exposure.[7]

Objectives of exercise stress echocardiography are diagnosis of CAD, assessment of residual myocardial ischemia after a revascularization and relationship with chest symptoms on exertion.[8]

Cardiac magnetic resonance perfusion stress testing may be appropriate for the testing patients with intermediate probability of coronary artery disease.[9]

Myocardial Perfusion Studies

Often called nuclear stress test is a noninvasive imaging technique that examines perfusion of heart muscles during exercise or at rest. There are two techniques for MPI, single-photon emission computerized tomography (SPECT), and positron emission tomography (PET).

Cardiac Nuclear Stress Test

Stress/Rest MPI uses PET or SPECT imaging of patient's heart before and after exercise to determine the effect of physical stress on blood flow through coronary arteries. MPI is the most appropriate test for diagnosing coronary artery disease early in patients at risk for MI. It also offers improved diagnostic accuracy over exercise. TMT, myocardial perfusion studies can be done in combination with exercise or with a pharmacologically induced stressor. Once the target heart rate is reached, the radionuclide is injected intravenously. The difference in the uptake of the radionuclide is then assessed either by SPECT or PET. Myocardial perfusion study can detect areas of ischemia or myocardial infarction.

Normal heart will have a normal uptake of radiotracer and a rapid wash-out time. Ischemic areas or reversible lesions will have a slow uptake of tracer, as well as a prolonged wash-out time. An infarcted region will not take up the tracer either at rest or during stress.[10]

Systematic Approach for Preoperative Evaluation

Issues Related to Cardiac Evaluation

- What are the underlying cardiac risk factors?
- Will such evaluation change the management plan of the patient?
- Will it postpone surgery?
- What will be the management in the postoperative period?

Determine the Cardiac Risk Factors

Valvular Heart Disease: Patient with severe aortic stenosis due to fixed cardiac output do not tolerate either spinal or general anesthesia because of associated vasodilatation. Patients having moderate to severe mitral stenosis do not tolerate surgery well. Patients with aortic and mitral regurgitation having preserved left ventricular function are less likely to have an adverse cardiac event.

Congestive Heart Failure: Preoperative congestive heart failure (CHF) increases the risk of pulmonary edema from

3% in New York Heart Association (NYHA) Class 1–25% in patients with NYHA Class IV CHF. Elective surgery should be deferred for at least a week after the signs of heart failure have settled.

Arrhythmias: Patients with arrhythmias may not tolerate surgery well. In supraventricular arrhythmias, rate needs to be controlled prior to surgery. Patients with ventricular arrhythmias should be evaluated by a cardiologist prior to surgery. Those with first-degree heart block and Mobitz type I heart block may tolerate surgery well, while patients with Mobitz type II and third degree heart block might require intraoperative pacing.

Major Clinical Predictor of Cardiac Risks: They include decompensated heart failure, acute coronary syndrome, arrhythmias, and severe valvular heart disease.

Intermediate Clinical Predictor of Cardiac Risks: Angina, heart failure, history of myocardial infarction, diabetes mellitus, and renal insufficiency.

Minor Clinical Predictor of Cardiac Risks: Advanced age, ECG changes, reduced functional capacity, history of cardiovascular accident, high blood pressure.

Revised Cardiac Risk Index (RCRI): For assessing preoperative cardiac risks—two models are often used. The RCRI is also called Lee index or the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) risk model. The RCRI is simple and has been widely used. The NSQIP calculator is more complex.

Evaluation of Surgical Patients and Different Categories of Surgery

Evaluation starts with history taking and clinical examination. An essential skill is the identification of high-risk patients, whose pre-existing condition need to be optimized prior to surgery.

Emergent Surgery—Where little or no time for clinical evaluation, e.g., life saving limb surgery.

Urgent Surgery—Limited time for clinical assessment prior to life saving or limb saving procedure (6–24) hours.

Time sensitive Surgery—A delay of 1–6 weeks is acceptable, e.g., oncologic surgeries.

Elective Surgery—Procedure were delay up to 1 year is acceptable.

Surgeries on the Basis of Risk

High Risk Surgeries: The American Society of Anesthesiologist (ASA) have stratified the surgical risk based on patient's functional state, comorbid diseases, and urgency of surgery.

High cardiac risks surgeries include emergency surgeries which are major in elderly, aortic and vascular surgeries, and peripheral arterial procedures.[11]

Intermediate Risk Surgeries: They include head and neck surgery, carotid endarterectomy, abdominal surgery, intrathoracic surgeries, prostate surgery, and orthopedic surgery.[11]

Low Risk Surgeries: They include endoscopic procedures, breast surgery, cataract surgeries, and superficial procedures.[11]

Functional Status

Energy expenditures for following activities such as eating, dressing, walking around the house, and dishwashing range from 1 to 4 METs, scrubbing floors, climbing a flight of stairs, running a short distance, walking on level ground at 6.4 km per hour represents 4–10 METs.

Strenuous sports such as singles tennis and football often exceed 10 METs. Every operation elicits a stress response triggered by tissue injury. Surgery also causes change in balance between prothrombotic and fibrinolytic factors leading to increased thrombogenicity.

The mortality rate overall of all surgeries is 0.3%. The mortality rate is less than 1% for major surgical procedures in patients younger than 65 years, but 5% for patients between 65 and 80 years. The incidence of myocardial infarction in postoperative general surgery patients over 50 years is 0.7%, and is 3.1% in those undergoing vascular surgery.

Death in the first 48 hours in the postoperative period is mainly due to cardiac causes, while death between 48 hours and 6 weeks is often due to pneumonia, sepsis, pulmonary embolism, renal failure.

Stress testing is not a routine test for pre operative patient. However, some experts routinely obtain preoperative stress imaging in patients who are scheduled for major vascular surgery.

Stepwise Approach

Step 1: Decide the Urgency of Surgery

In emergent situation, where little or no time for clinical assessment proceed directly to surgery. If surgery is not urgent proceed to Step 2.

Step 2: Assess for Unstable Cardiac Condition

If high cardiac risk predictors, e.g., acute coronary syndrome or MI, CCF, etc., present, cardiological evaluation is required. In unstable cardiac condition, patients can proceed for coronary artery intervention in addition to dual-antiplatelet therapy if the surgical procedure can be postponed, or may go directly for surgery if delay is impossible. If there is no unstable cardiac condition proceed to Step 3.

Step 3: In Cardiac Stable Patients Determine the Risk of Surgical

Procedure for (Major Adverse Cardiac Event (MACE) which includes MI or death).

For Low Risk Procedure: Proceed to surgery. In patients with ischemic heart disease low dose beta-blocker may be advised before surgery. In patients with heart failure ACE inhibitors should be given before surgeries.

For intermediate or high risk procedure assess functional capacity of the patient proceed to Step 4.

Step 4: Assess Functional Capacity of the Patient

If patient's functional capacity is good or more than 4 METs, in intermediate risk surgeries with one or more risk factors, it is appropriate to go for surgery. If the functional capacity is less than 4 METS proceed to Step 5.

Step 5: Consider the Risk of Surgical Procedure

Intermediate Risk Surgeries: Noninvasive stress testing may be considered in those with one or more risk factors. These patients can be taken for surgery. Baseline ECG is required to monitor changes during surgical procedure.

High Risk Surgeries: Assess RCRI.

Proceed to Step 6.

Step 6: Assess Revised Cardiac Risk Index (RCRI)

- Ischemic Heart Disease like previous MI or angina
- Heart failure
- Stroke or TIA
- Renal dysfunction serum creatinine 2 mg/dL or above
- Diabetes mellitus requiring insulin therapy.

If two risk factors and patient scheduled for high risk surgery consider non invasive testing. If three risk factors proceed to Step 7.

Step 7: Consider Noninvasive Testing

If no, mild, or moderate stress induced ischemia proceed with planned surgery. If extensive stress induced ischemia is present, an individualized perioperative management is indicated considering the potential benefit of the recommended surgical procedure compared with the predicted adverse outcome, and the effect of conservative management and/or coronary revascularization.

When to Perform Stress Tests in Preoperative Cases

Noninvasive (stress test) is indicated in those with major clinical predictors, or those with intermediate clinical predictors and poor functional capacity (4 METs) scheduled for high surgical risk procedures.

OR, in cases with minor clinical predictors and poor functional capacity undergoing high risk procedure.

Conclusion

Clinical risk factors should form the basis of risk assessment. Exercise stress test helps to estimate functional capacity and has prognostic implications. Thus, cardiac stress testing can be a valuable tool in determining whether a patient can safely proceed to surgery or a further consultation with cardiologist is needed before proceeding with intermediate or high risk surgery.

Acute coronary events, like new onset ischemia, infarction, or revascularization, lead to a high-risk period of 6 weeks, and an intermediate-risk period of 3 months before performing non-cardiac surgery.

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CHAPTER

30 Screening for Atrial Fibrillation for Stroke Prevention: Clinical Perspective

SB Gupta

Abstract

Atrial fibrillation, an important risk factor for stroke, is quiet prevalent in general population, especially in the elderly group. It remains silent, therefore remains undiagnosed and not treated adequately. Screening general population for silent atrial fibrillation is not feasible because of cost constraints and treating all silent atrial fibrillation patients may cause more harm than benefits. However, identifying atrial fibrillation in high-risk individuals and elderly population is a viable option. Various screening tools are available and proper utilization of such assets is the key to success.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia and affects 1–4% of the general population and is important risk factor for stroke.[1] Prevalence of AF is predicted to double over the next 30 years and is associated with a fivefold increased risk of ischemic stroke.[2] People with ischemic stroke, approximately one-third die within a year and approximately one-third of the survivors have some type of permanent disability.[3] Prevalence of AF keeps on rising as age advances and is about 3% in men and 2% in women of age 65–69 years and is about 10% of adults of age 85 years or above **(Fig. 1)**. Unfortunately, AF is diagnosed in 20% of the cases of ischemic stroke at the first presentation of stroke.[4]

Further, if AF detected early and treated with anticoagulants in eligible patients, the risk of stroke is reduced by around 65%. Unfortunately, AF in many people goes undetected and therefore untreated because either such patients are asymptomatic or have paroxysmal AF.[2]

Screening is logical one such approach to detect AF early and thereby initiating anticoagulant therapy early to reduce the incidence of ischemic stroke. However, the current recommendations of various international task forces are against mass screening, mainly because of the cost implications and the uncertainty of the benefits of the systematic screening vis-à-vis usual care.[2] US Preventive Services Task Force (USPSTF) in their latest recommendations have concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for AF with ECG.[4] In high-risk individuals, screening has been recommended as the strategy to detect AF early and start anticoagulant therapy at the earliest. European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) have recommended the screening for AF by opportunistic pulse palpation and/or electrocardiogram in all patients above the age of 65 years and who have symptoms suggestive of AF, respectively,[5,6] based on the landmark SAFE trial, showing 60% improvement in AF detection compared to routine care over a period of 12 months.[7]

Currently, AF remains undiagnosed in a vast population and, if detected, at least 75% of such individuals will be eligible for anticoagulation. In general population above the age of 65 years, systematic review of AF screening found the incidence of 1.4% of previously undiagnosed AF.[8]

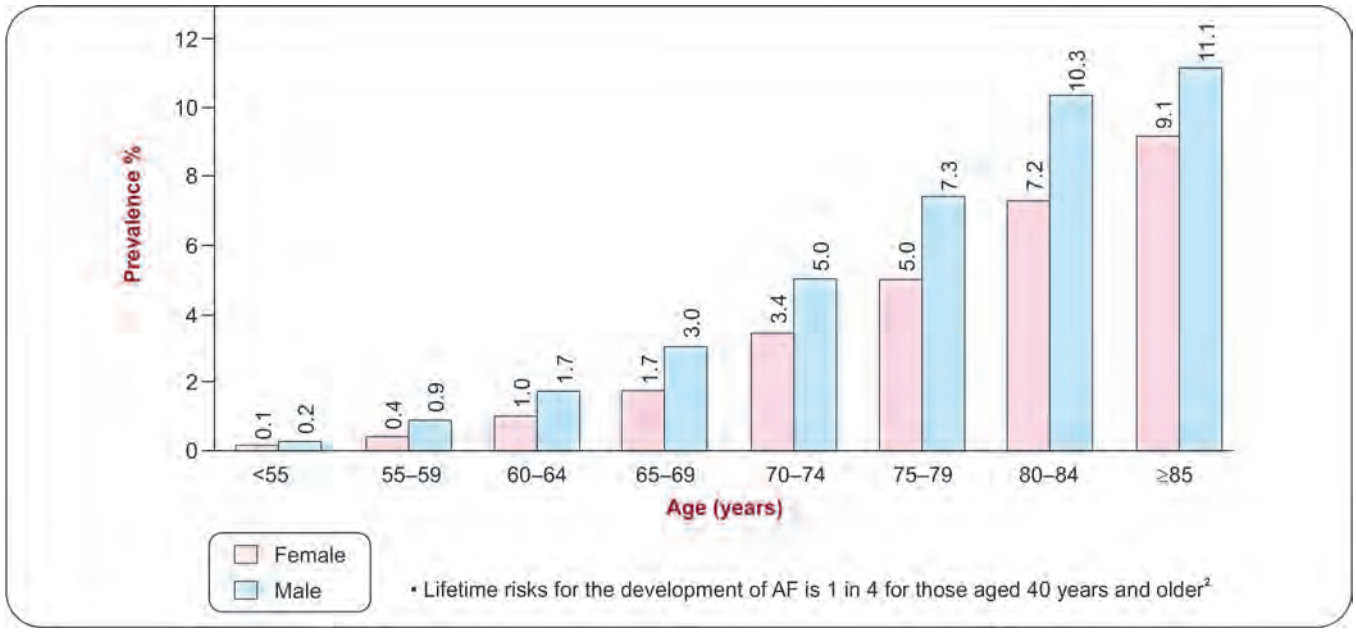

Fig. 1: Increasing incidence of AF as age advances

Repeat serial ECGs over 2 weeks improved the detection rates by fourfold.[9] Detection rate of asymptomatic AF may go up to 50% if patients having pacemakers or implantable cardiac devices where prolonged ECG monitoring happens **(Fig. 2)**. Detection of asymptomatic AF depends upon the definition of AF and duration of screening. 2,455 participants aged more than 65 years in the ASSERT study who have received either a dual-chamber pacemaker or internal cardioverter-defibrillator (ICD) with no prior history of AF showed asymptomatic AF in 18.8% when followed up for 2.5 years and in 11% of the patients had an episode of AF lasting for more than 24 hours in a 3-year follow-up **(Fig. 3)**.[10]

Patients with asymptomatic AF compared with no AF, showed 2.5-fold increased risk of stroke or systemic thromboembolism over a mean of 2.5 years follow-up.[10] There appears no doubt that asymptomatic AF carry increased stroke and mortality risk as compared to the persons having sinus rhythm. But whether the risk will be higher in the persons with silent AF, detected on screening in the general population, remains to be seen.

As compared to sustained AF, approximately 25% of the people have paroxysmal AF[11] and persons with persistent and permanent AF are at higher risk of thromboembolism and all-cause mortality as compared to the persons with paroxysmal AF.[12] In the ASSERT study, a significant increased risk of stroke and thromboembolism was noted in persons with asymptomatic AF of more than 24 hours duration as compared to those without AF and there was no increased risk with asymptomatic AF of less than 24 hours.[10]

Currently, if AF lasts for more than 30 seconds, the diagnosis of AF is established. And if treatment guidelines for treating AF will be followed, then people with low burden of AF will be put on anticoagulants[13] and under these circumstances, then the bleeding risk from anticoagulants will outweigh stroke risk reduction.

AF is not only linked to higher risk for ischemic stroke, but also for the cognitive decline. One such study from Korea, of 10,435 people diagnosed with AF, showed that anticoagulation was associated with a 39% reduction in the incidence of dementia.[14]

Screening Tools

A range of electronic devices are available to screen for AF. And the detection rate of silent AF improves as the duration of screening increases.

Following is the list of devices currently available:

- ECG
- Serial ECGs
- Holter monitoring (24–72 hours)
- Patch ECG monitors (external loop recorders)

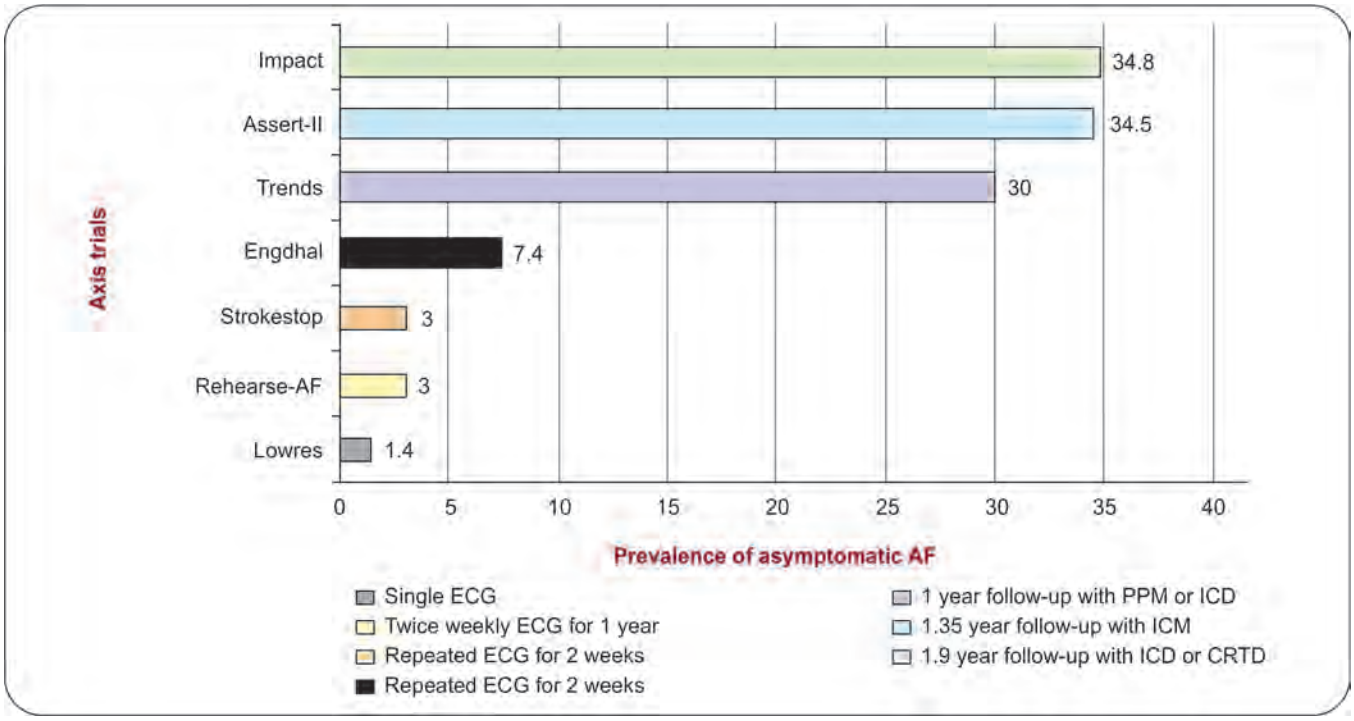

Fig. 2: Prevalence of asymptomatic atrial fibrillation by screening method and stroke risk score

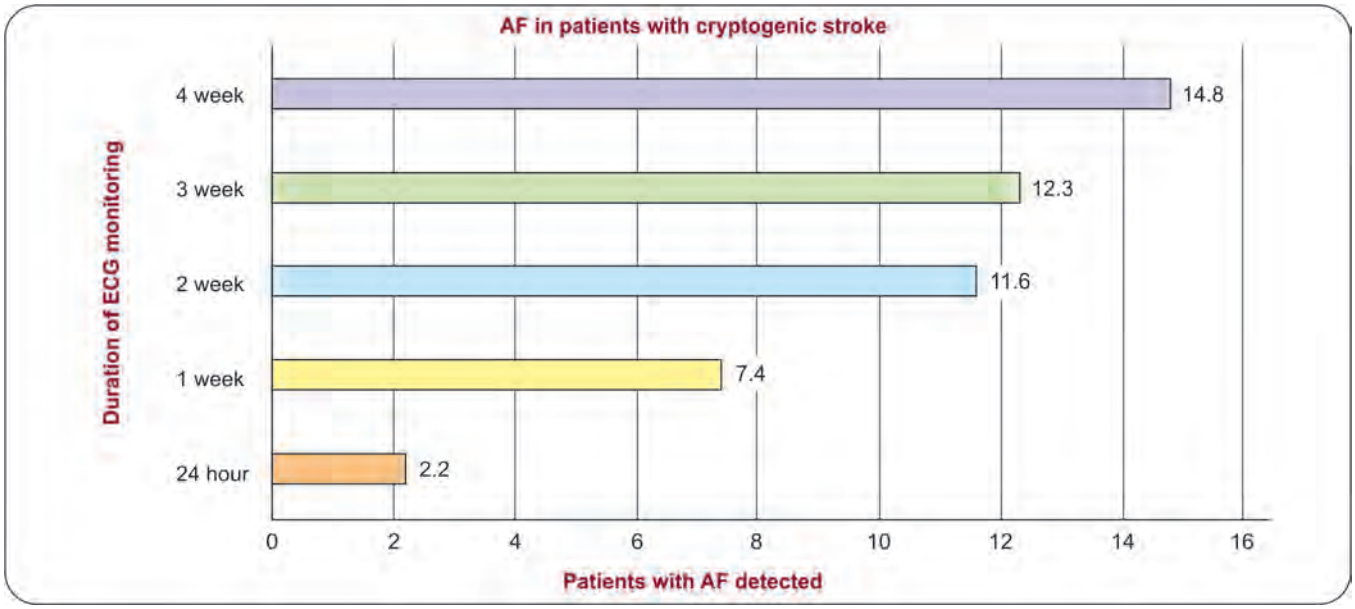

Fig. 3: Atrial fibrillation in patients with cryptogenic stroke

- Implantable cardiac loop recorder
- Pacemakers/ICDs
- Smartphone compatible ECG recorder
- Hand-held devices
- BP monitors
- Apple watch

mHealth devices have been categorized into the following three groups:

- App based, using Smartphone or tablet app, either by direct or indirect photoplethysmography (PPG). "Cardio Rhythm" is one of the most common Smartphone apps.
- "Wrist-Worn Wearables" like Apple Watch or HUAWEI Band 2.
- Hand-held devices like "AliveCor"

mHealth devices are convenient and have a high accuracy. However, after detection of AF by such devices, AF needs to be confirmed by standard 12-lead ECG Holter monitoring.[15]

Smartphones and smart watches have the sensitivity and specificity of above 90% for detection of AF.[16,17] Recently, the data of Apple Watch study, of nearly 420,000 people with no prior history of AF or on current anticoagulation was presented. Approximately 3% of the people above the age of 65 years received irregular pulse notification. The people who received the notification were advised to wear an ECG patch, 450 participants wore the patch and returned. Of which, 153 (34%) had AF detected showing the positive predictive value of 84% for irregular pulse notification.[18]

However, there are no randomized studies to compare the harm of systematic screening to no screening, but potential harms do exist from population screening.[19] Screening method which may have 95% specificity for AF diagnosis, can result in 50,000 false positive cases per million screened.[20] Unnecessary investigations, anxiety related to health, and the increased bleeding risk because of guideline directed anticoagulant therapy are the potential hazards. Further, cost-effectiveness by systematic population screening programs is always an area of big concern, hence systematic opportunistic screening has been recommended as the best strategy as on date.[7] All over the world, it has been noticed that anticoagulation has always remained suboptimal in large numbers of cases. The Risk-Stroke registry, having 94,000 people who suffered ischemic stroke, with over 22% AF population, only 16% received anticoagulation, 6 months prior to their stroke.[21] Cost-effectiveness of anticoagulation vis-à-vis economic impact of suboptimal anticoagulation in reducing stroke risk is burning issue and will be the area of future research. Changes in the stroke rates, major bleeding, and mortality are the areas of interest in the upcoming studies which are duly powered.[22]

Obesity, physical inactivity, and hypertension are preventable risk factors and control of hypertension and life style modification shall be advised regarding maintaining ideal body weight and doing regular exercise in general.

A large number of uncertainties have been pointed out and remain to be sorted:[2]

- Prevalence of undiagnosed AF.
- Which population to screen and how to screen?
- Stroke risk for people with AF detected via screening.
- Is screening the most effective way to reduce AF stroke incidence?
- What burden of AF is associated with significant stroke risk?
- Duration and frequency of screening
- Which screening device?
- What are the harms of screening?

Several ongoing trials, STROKESTOP, SCREEN-AF, IDEAL-MD, and D_2AF, in future will definitely be enlightening the physicians to deal with the issue of screening for asymptomatic AF and then the treatment strategy.

Conclusion

Atrial fibrillation is quiet a common arrhythmia and asymptomatic AF (subclinical AF) is also common and both AF and subclinical AF (SCAF) remain important risk factor for stroke and other thromboembolic complications and are growing health problem. Highly specific treatment strategies like anticoagulants are available, which can reduce this risk. Need to identify and treat SCAF to reduce the stroke risk and subsequent disability and death is logical, but with so many uncertainties, currently systemic population screening is not recommended. However, systematic opportunistic screening and screening of high-risk individuals need to be done. Large scale randomized trials are needed to understand the evidence gaps and cost-effective strategies to address SCAF management.

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CHAPTER

31 Prevention of CVD in Diabetes: Taming the Dragon

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Abstract

With better control of infective and metabolic complications, diabetes has become a cardiovascular disease (CVD). About 52–80% of diabetics die because of CVD and acute myocardial infarction accounts for 70% of deaths. The conventional anti-diabetic medications do not provide cardiovascular risk reduction but the two new block busters GLP-1 RAs and SGLT2 inhibitors are powered to improve cardiovascular and renal outcomes. The GLP-1 RA decreases atherosclerotic cardiovascular disease (ASCVD) but has no impact on heart failure. The SGLT2 inhibitors improve heart failure and renal outcomes. Besides this attention should be focused on lipid control with statins, ezetimibe, PCSK9 inhibitors, icosapent ethyl, etc., tight BP control, antiplatelet drugs in patients with high ASCVD risk, cessation of smoking, bariatric procedures, and lifestyle modification. A multipronged approach must be followed and this provides improvement in the outcomes on a long-term basis as shown STENO-2 trial and its extension follow-up.

Introduction

Diabetes is a den of cardiovascular disease (CVD). Globally, CVD occurs 10–15 years earlier in diabetics, is two times more common than non diabetics and a major chunk of diabetics succumb to CVD mainly acute myocardial infarction. Cardiovascular risk reduction (CVRR) is therefore of paramount importance and we are running a race against CVD for several decades. The conventional anti-diabetic agents do not provide CVRR but the two new anti-diabetic medications sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1 RA) has shown improved CV outcomes in several dedicated trials. Both these new antidiabetic medications are hitting the headlines in all current guidelines for diabetes. CVD in diabetes requires a multipronged approach targeting all risk factors like blood pressure, lipids, smoking cessation, weight management, lifestyle modification coupled with good and sustained glycemic control from early stage of the disease also utilizing the new antidiabetic medications.

New Antidiabetic Medications and Cardiovascular Risk Reduction

The conventional antidiabetic medications only provide glycemic control and do not offer cardiac protection. Among the new antidiabetic medications SGLT2 inhibitors and GLP-1 receptor agonist have shown cardiorenal protection in various cardiovascular outcome trials (CVOTs).

SGLT2 Inhibitors

These drugs are very useful in providing benefit to patients of heart failure (HF). They have been used in several subsets of patients.

High CV Risk Patients at Risk of Heart Failure

The three landmark trials EMPA-REG, CANVAS, and DECLARE TIMI-58 have shown decreased hospitalization for HF in patients at high risk both in the primary prevention group and in patients with preexisting CVD

(EMAPREG OUTCOME trial). The EMPAREG OUTCOME trial carried out in patients with preexisting CVD also showed decrease in cardiovascular mortality and all cause mortality. This was also shown in the subgroup analysis in patients with preexisting CVD in the CANVAS and the DECLARE TIMI-58.

Heart Failure with Reduced Ejection Fraction (HFrEF)

The DAPA HF trial[1] conducted in patients of HFrEF has shown improved CV outcomes. Patients with symptomatic HFrEF LVEF <40%, mean age 66 years, both diabetic (45%) as well as non diabetics were randomized to dapagliflozin 10 mg daily (n=2,373) versus placebo (n=2,371) with a follow-up 18.2 months. The N-terminal pro–B-type natriuretic peptide was ≥600 pg/mL. The trial showed a relative risk reduction of 26% (hazard ratio [HR] 0.74; 95% confidence interval [CI] 0.65-0.85), p<0.001 in the composite primary end point of CV death *or hHF or an urgent HF visit*. The CV death was reduced by 18% (HR 0.82, CI 0.69-0.98, p=0.029) and worsening HF component decreased by 30% (HR 0.70, CI 0.59-0.83, p=0.00003). The primary outcome was same in diabetic subset (HR 0.75, CI 0.63-0.90) compared to non-diabetic subset (HR 0.73, CI 0.60-0.88). Dapagliflozin also produced benefit on top of ARNI (HR 0.75, CI 0.50-1.13, without ARNI HR 0.74, CI 0.65-0.86), which was utilized in about 11% of patients in the trial. Several other trials with these agents in HFrEF are ongoing like EMPEROR-R and EMPIRE HF, CANDLE, etc.

Several trials of SGLT2 inhibitors are also ongoing in the subset of HFpEF like DELIVER, PRESERVED HF, EMPERIOR-P, EMPERIAL-P, but none of them have been completed as yet.

Renoprotection with SGLT2 Inhibitors

All SGLT2 inhibitors have shown renoprotection. Canagliflozin was tested in the dedicated chronic kidney disease (CKD) trial CANVAS.[2] The trial was carried out in 4,401 patients with canagliflozin compared to placebo in patients of T2D and established CKD. Half of them were put on canagliflozin and the remainder served as control. The duration of follow-up was 2.62 years. The trial was prematurely terminated because of immense benefit. The primary end point was end stage, kidney disease, doubling of serum creatinine, renal, or CV death.

The DAPA CKD trial with dapagliflozin was carried out in diabetic as well non-diabetic subset and has been terminated prematurely because of immense benefit. The top line results show that both diabetic and non-diabetic patient benefited from it. The EMPA CKD trial with empaglflozin is ongoing.

GLP-1 RAs Trials

Of the six completed CVOTs with GLP-1 RAs, four trials have shown positive results, that is, LEADER,[3] SUSTAIN-6, HARMONY, and REWIND in terms of reduction of primary end point of atherosclerotic MACE, that is, cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. The EXSCEL trial narrowly missed the primary end point while the ELIXA trial was negative.

The oral semaglutide was tested for its CV safety in a small trial in a dose 14 mg orally versus placebo. The trial was found to be non inferior in terms of atherosclerotic MACE. However, there was strong signal of reduction in cardiovascular death was by 51% (HR, 0.49; 95% CI, 0.27-0.92) and all cause mortality by 49% (HR, 0.1; 95% CI, 0.31-0.84). The oral semaglutide showed similar reduction in weight and HbA1c like the injectable semaglutide. The drug has been approved by FDA for treatment of diabetes and also going to be launched in India in near future. The CV OUTCOME trial SOUL with oral semaglutide is ongoing and is expected to complete by 2023/2024.

Lipid Control

Statins are the corner stone of treatment for diabetic dyslipidemia. All type 2 diabetics should be on moderate intensity statins. For high-risk patient the LDL-C goal is less than 70 mg/dL and he/she requires high intensity statins like atorva 80 mg or rosuva 40 gm. For the very high-risk patient the LDL-C goal is less than 55 mg/dL. If the goal is not achieved with high intensity statins than ezetimbe 10 mg/day can be added. If still the goal are not achieved PCSK9 inhibitors should be utilized. Bempedoic acid is not yet available in India but this can also be tried prior to initiation of PCSK9 inhibitors.

PCSK9 Inhibition

Monoclonal antibodies to PCSK9 have been tried in two CV OUTCOME trials.[4,5] The PCSK9 inhibitors produce an additional reduction of LDL-C by 40–60%, LP(a) is reduced by approximately 25% and other lipoprotein are also favorable altered. Both these molecules have been

approved for clinical use. Evolocumab is commercially available in India.

Evolocumab

This molecule was evaluated in FOURIER trial,[4] which compared evolcoumab with placebo in 27,564 patients with ASCVD having an LDL-C of more than 70 mg/dL with a median follow-up 2.2 years. There was a 15% relative risk reduction in the primary end point of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (HR, 0.85; 95% CI, 0.79-0.92; P<0.001).

In FOURIER study, LDL-C decreased from median base line value of 92 mg/dL to 30 mg/dL, i.e., approximately by 60% (P<0.001), 42% had LDL-C <25 mg/dL. Despite such low levels of LDL-C there was no evidence of muscle or liver toxicity, diabetogenecity or neurocognitive decline. The dedicated sub-study, EBBINGHAUS also confirmed lack of neurocognitive decline with its use. The only side effect which was more common with evolocumab was injection site reactions, 2.1% (evolocumab) versus 1.6% (placebo). The study therefore demonstrated incredible safety on top of statins. The benefit was seen across the range of LDL up to 20–25 mg/dL. All quartiles benefitted, highest as well as lowest. There was no J curve so lower is better is also validated for super low LDL-C. The FOURIER trial showed reduction in MI by 27% p≤0.001, stroke by 21%, p=0.01, and coronary revascularization by 22%, P≤0.001. There was no significant decrease in all cause or CV mortality.

It is available as 1 mL pen containing 140 mg. It is given in doses of 140 mg biweekly/420 mg monthly sc.

Alirocumab

The ODYSSEY OUTCOMES[5] alirocumab with placebo in post ACS patients 1–12 months after the acute event in 18,924 having LDL-C level of more than 70 mg/dL. The median duration of follow-up was 2.8 years. The composite primary end-point of ischemic event showed a relative risk reduction of 15% (hazard ratio, 0.85; 95% CI, (0.78-0.93; P<0.001). There was no statically significant decrease in CHD mortality or all cause of mortality. Patients with LDL-C >100 mg/dL benefited more and also showed decrease in all cause mortality.

This is approved for clinical use and is commercially available as 1 mL pen containing 75 mg, which is given every 2 weeks or 150 mg, which is given monthly.

BOX 1 Indications of PCSK9 inhibitors

- Failure to achieve LDL-C goals despite optimal doses of statins in patients with ASCVD
- Statin intolerance
- Familial hypercholesterolemia

The SPIRE 1 and 2 trial with bococizumab was prematurely terminated because of presence of neutralizing antibody in 29% and antidrug antibodies in 48% of patients taking the drug. This is because bococizumab is partially murine monoclonal antibody unlike evolocumab and alirocumab which are fully humanized monoclonal antibodies.

Although both SPIRE I and SPIRE II trials were prematurely terminated, the SPIRE II, which had LDL-C >100 mg/dL showed a reduction in CV events by 21% at 12 months hinting that the drug is also useful for primary prevention. The SPIRE I trial which enrolled cooperatively lower risk population (LDL-C >70) did not showed any benefit.

The current indications PCSK9 MoAbs are outline in **Box 1**.

Given the lack of long-term safety and efficacy data on these agents, they are not recommended for use for primary prevention except in patients with familial hypercholesterolemia. The data of PCSK9 for primary prevention like high-risk diabetics is yet to evolve out.

Role of Triglyceride (TG)

TG is commonly elevated in diabetes. All randomized trial of TG lowering with fibrates on top of statins has failed to show any CV benefit. The ACCORD LLA trial did not show benefit of fibrates on top of statins. The subgroup analysis of TG more 204 mg/dL and HDL-C <34 mg/dL has shown reduction in the CV events. This is hypothesis generating but is not yet tested in any randomized control trial. A meta-analysis of fibrates has shown benefit but all trials in this meta analysis were not done on top of statins. The REDUCE IT Trial[6] evaluated patients with established CVD or with diabetes and other risk factor who have been on statins with LDL-C levels of 41–100 mg/dL and TG levels were between 135 and 499 mg/dL. Icosapent ethyl 2 gm twice daily was compared with placebo over a period of 4.9 years and showed reduction of 25% in the composite primary end point of ischemic events (HR, 0.75; 95% CI,

0.68-0.83; P<0.001). Atrial fibrillation was more often seen with icosapent ethyl compared to placebo (3.1% vs. 2.1%, P=0.004). Serious bleeding was also observed in more number of patients with icosapent ethyl compared to placebo, 2.7 versus 2.1 (P=0.06). The trial was positive but subgroup analysis showed that the benefit was similar in groups with TG<150 mg/dL and >150 mg/dL indicating the mechanism of benefit is not related lowering of TG. Saroglitazar in dose of 4 mg/day has been used to treat hypertriglyceridemia, but there is no outcome data with it.

Newer Agents for Lipid Management

Besides PCSK9 inhibitors bempedoic acid is also approved for clinical use by US FDA and is likely to be available in our country in near future. It decrease LDL by 15–20% and is not associated with muscle toxicity. Inclisiran a small interfering RNA inhibits synthesis of PCSK9 and single injection of 300 mg decreases LDL-C levels by 50% and this remains there for 6 months. It is emerging as an important competitor for PCSK9 monoclonal antibodies but it is still undergoing evaluation. A single injection of PCSK9 vaccine decreases LDL-C by 50% which lasts for 12 months. If the human trial comes to out to be positive a yearly booster dose of this vaccine will be the new modality to target atherosclerotic cardiovascular disease (ASCVD).

Blood Pressure Control

The target for blood pressure control as per all current guideline is 130/80 mm Hg. RAAS blockers are the preferred agents but most of the diabetics in the long run require multiple drugs.

Antiplatelet Drugs

Currently antiplatelet drug are not recommended for primary prevention group unless the patient belongs to a very high risk group, that is, the 10-year ASCVD risk more than 10%. The three major trials released in 2018 have not shown any benefit in primary prevention of cardiovascular events.

Lifestyle Modification

All patients of diabetes must strictly adhere to lifestyle modification including cessation of smoking. The LOOK AHEAD Trial carried out with intensive lifestyle intervention, focused on weight loss, improved CV risk factors in T2D did not improve CV risk in T2D.

Bariatric Procedures

Bariatric surgery is recommended in obese diabetics and produces significant decrease in weight and blood glucose along with improvement in other concomitant risk factors. Currently great advances have been made in endoscopic bariatric procedure like intragastric balloon, endoscopic bypass, endoscopic gastroplasty, etc. The advantage of these procedures is that they are safe and have fewer complications than bariatric surgery.

Multipronged Approach

The STENO-2 trial[7] carried out a multipronged approach in T2DM patient and showed marked benefit in the long run. The composite endpoint of ischemic events decreased by 53% in this study and on follow-up after 5 year the benefit escalated to 59%. A 21-year follow-up of the trial showed a survival benefit of 7.9 years and CVD-free survival of 8.1 years.

Conclusion

Prevention of CVD in diabetes requires a multidisciplinary approach targeting all risk factors for ASCVD coupled with optimum glycemic control and increasing use of new antidiabetic medication like SGLT2 inhibitors and GLP-1 RA. Endoscopic bariatric procedures are also making their way in the treatment of obese diabetics and helps in CV risk reduction.

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CHAPTER

32 Heart Failure 2021

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Abstract

As we progress into 2021, health-care delivery, particularly for heart failure patients, becomes even more complicated and challenging. However, this poses opportunities in the path of an uncertain future. There has been remarkable progress in the science and management of heart failure recently. A key emerging theme in the science and medicine of heart failure is the need to identify and target specific causes of heart failure, defined by phenotype or genotype, which will respond to a particular intervention. QRS duration (a marker of cardiac dyssynchrony), mitral regurgitation, iron deficiency, and amyloidosis each identifies patients that will respond to a specific intervention. Although the evidence base for the treatment of HFrEF has expanded substantially, much work remains for the other forms of HF. New therapies for HF with preserved EF are under exploration, and the evidence base addressing HF with improved EF is just emerging. Adherence to recommendations can be enhanced by shared decision-making between health-care providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

Introduction

Heart failure (HF) can be defined in several ways, viz., ischemic and nonischemic cardiomyopathy based on the underlying cause and to determine outcomes. Of late, genetic information has been employed to sub-classify different forms of nonischemic cardiomyopathy. Iatrogenic forms of HF have also been recognized in patients undergoing cancer therapy.

However, the simplest and most widely used classification is based on left ventricular ejection fraction (LVEF) and, notably, it provides important diagnostic and prognostic information.

The usual HF is a condition with reduced ejection fraction (HFrEF), but it has been noted that patients with near normal or normal ejection fraction could also present with symptoms of HF, and this is known as HF with preserved ejection fraction or HFpEF, which remains an enigma and a challenge for clinicians. In between there is a gap, and this has been filled in the recent ESC Guidelines on Acute and Chronic HF[1] with the introduction of a novel category, that is, HFmrEF or HF with mid-range ejection fraction. Possibly, mild HFrEF may be much more appropriate terminology than HFmrEF.

As we progress into 2021, health-care delivery, particularly for HF patients, becomes even more complicated and challenging. HF has recently undergone major changes, while HFrEF is declining due to effective revascularization of patients with acute coronary syndromes, the prevalence and incidence of HFpEF, mainly characterized by diastolic dysfunction, is increasing due to ageing Indian societies.

Initiating Therapy

Established therapies for chronic HFrEF include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, loop diuretics, aldosterone antagonists, and hydralazine/isosorbide dinitrate (HYD/ISDN); with the exception

of loop diuretics, all have been shown in randomized controlled trials to improve symptoms, reduce burden of hospitalization, and/or provide survival benefit.[2] Recently, in addition to established guideline directed medical therapy (GDMT), an angiotensin receptor-neprilysin inhibitor (ARNI) and the hyperpolarization channel blocker ivabradine have been added to the treatment guidelines for HFrEF.[3]

ACEI or ARB initiation is usually better tolerated when patient is congested whereas beta-blockers may be better tolerated when patient is relatively dry with adequate resting heart rate. Only beta-blockers with evidence of benefit in HF should be used in HFrEF. In selected patients with HFrEF, low dose of a beta-blocker and an ACEI/ARB may be started; while in persistently symptomatic patients who tolerate an ACEI or ARB, switching to ARNI, would be recommended.

In one recent study[4] LVEF increased and cardiovascular mortality improved with beta-blockers in all groups in sinus rhythm except in those with a value of ≥50%. In patients with atrial fibrillation, beta-blockers increased LVEF when <50% at baseline, but did not improve prognosis. The data are most robust in HFrEF, but similar benefit was observed in HFmrHF. These relevant findings reinforce that HFrEF and HFmrEF are part of the same spectrum of HFrEF.

Mineralocorticoid receptor antagonists (MRAs) also improve HFrEF prognosis and possibly of HFpEF.[5] The role of MRAs in reducing inflammation and fibrosis, which cause progression of HF, is currently under investigation.

Angiotensin Receptor-Neprilysin Inhibition

Neprilysin, also known as neutral endopeptidase, is a zinc-dependent metalloprotease that inactivates several vasoactive peptides, including the natriuretic peptides, adrenomedullin, bradykinin, and substance P, each of which has an important role in the pathogenesis and progression of HF.[6] Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors raise angiotensin levels, which explains the rationale for coadministration of ARB. Neprilysin inhibitors are not combined with ACEI due to a higher risk of angioedema. When making the transition from an ACEI to ARNI, a 36-hour washout period should be strictly observed to avoid angioedema, a delay that is not required when switching from an ARB to ARNI. Starting dose of sacubitril/valsartan: 24/26 mg to 49/51 mg twice daily and target dose is 97/103 mg twice daily.

With accumulating clinical and research experience, there is a strong argument to consider them as first-line agents, in place of ACEI/ARB for the treatment of HFrEF. The benefits of sacubitril/valsartan are severely attenuated at LVEF above 60%, and therefore ARNI should not be used in HFpEF.

Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors

Although sodium glucose cotransporter 2 (SGLT2) inhibitors were developed for control of glycemia, but their cardiovascular benefits have caught the clinicians' attention. Dapagliflozin, reduced the combined risk of cardiovascular death and hospitalization for HF by 26% and the risk of cardiovascular death alone by 18% in the DAPA-HF trial.[7] SGLT2 inhibitors are presently being explored to treat HFrEF regardless of diabetic status of a subject in ongoing clinical trials. It is almost sure that, another drug would be added to the portfolio of cardioprotective agents. These disease-modifying drugs target important, but distinct, pathways that promote cardiomyocyte dysfunction and death.

Ivabradine

Ivabradine is a specific inhibitor of the *If* current involved in sinoatrial nodal activity and reduces the heart rate of patients in normal sinus rhythm without lowering blood pressure. In the SHIFT (Systolic HF Treatment with the If Inhibitor Ivabradine Trial) study, ivabradine therapy, when added to GDMT, resulted in a significant reduction in HF hospitalizations in stable, chronic, and HFrEF patients predominantly in NYHA class II and III.[8]

Ivabradine is recommended[3] to reduce the risk of HF hospitalization in patients with HFrEF (LVEF < 35%) already receiving GDMT (including a beta-blocker at maximally tolerated dose), and who are in sinus rhythm with a heart rate greater than 70 bpm at rest.

Biomarkers—When to Order Natriuretic Peptides

B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are the most studied biomarkers in HF. They play a role in diagnosis and prognostication. Higher concentrations of BNP or NT-proBNP in an ambulatory patient with HFrEF inform high risk, particularly when the concentrations

are rising. Current clinical practice guidelines give a Class I recommendation to measure NT-proBNP or BNP to support a clinical diagnosis of HF, to assess disease severity, or to establish prognosis.[2]

More recently, biomarkers have been examined for their role as a marker of clinical responsiveness to GDMT. This is, in part, due to the fact that a wide range of GDMT may reduce BNP and NT-proBNP concentrations, in parallel with the benefits of these therapies. Patients whose natriuretic peptide concentrations do not fall with GDMT (nonresponders) have a worse prognosis and more deleterious LV remodeling.[9] Therefore, measurement of BNP or NT-proBNP is useful to monitor risk, to assist in decision-making regarding the ordering of imaging studies to evaluate LV remodeling, to support clinical judgment with respect to prescription of GDMT, and to provide helpful objective data regarding decision-making for referral to advanced HF therapies. In the setting of worsening symptoms, the reassessment of BNP or NT-proBNP may be informative. However, serial assessment of BNP or NT-proBNP to guide aggressive titration of GDMT is not indicated and not warranted.[10] Severe renal dysfunction may interfere with the interpretation of natriuretic peptide concentrations.

While rising natriuretic peptide concentrations are correlated with adverse outcomes, this relationship can be confounded with the use of sacubitril/valsartan. Due to neprilysin inhibition, concentrations of BNP rise in patients treated with sacubitril/valsartan and tend not to return to baseline despite chronic therapy. In contrast, NT-proBNP concentrations typically decrease, as NT-proBNP is not a substrate for neprilysin.[11] Therefore, it may be more prudent to check only NT-proBNP in patients on ARNI. Also, transient increases in natriuretic peptide levels have been documented in the initial phases of beta-blocker initiation; such changes should not preclude up-titration of beta-blocker therapy, which should be guided by patient tolerance instead of asymptomatic change in natriuretic peptide levels.

Cardiac Resynchronization Therapy (CRT) and Implantable Defibrillator (ICD)

Cardiac resynchronization therapy is a key therapeutic strategy in eligible patients, but requires multiple lead implantations and a significant subset do not respond or technically cannot receive a coronary sinus lead. There is emerging evidence supporting His-bundle pacing using a single lead in the right ventricle as a means to provide resynchronization. Clinical trials comparing traditional resynchronization therapy with His-bundle pacing are ongoing.

Since the addition of ARNI to the already existing drug armamentarium and declining sudden death rates in HF, the requirement of prophylactic defibrillator implantation may require a rethink.

Functional Mitral Regurgitation in Chronic Heart Failure

Left ventricular (LV) remodeling and subsequent papillary muscle displacement resulting in mitral valve (MV) leaflet tethering, dilatation, and flattening of the mitral annulus and reduced closing forces can lead to functional mitral regurgitation (FMR)[12] in cases of chronic HF.

FMR is associated with HF symptoms, increased hospitalization rates and worse long-term prognosis of patients with chronic HF. However, it remains debated whether FMR is a central driving force of HF progression or rather a bystander, reflecting the severity of the disease. Nevertheless, driven by recent advances in percutaneous MV repair (PMVR), significant efforts are currently undertaken to reduce FMR in patients with HF in the hope to improve prognosis.[13] Similar to HF patients without FMR, it is recommended to prescribe optimized guideline-directed HF therapy (OMT) targeting LV dysfunction including cardiac resynchronization therapy.

However, whether OMT is able to counterbalance maladaptive processes and the adverse effects of FMR on long-term survival remain unknown.[14] Likewise, the impact of MV repair on outcome in HF patients with severe FMR by interruption of the presumed maladaptive effects is unknown.

The COAPT trial[15] suggested that a percutaneously delivered mitral clip could reduce functional (secondary) regurgitation with a subsequent substantial improvement in morbidity and mortality, while two-year follow-up of MITRA-FR suggested no benefit.[16]

Periodic longitudinal follow-up of patient populations with FMR will be needed to have a deeper understanding of its relation to long-term mortality in patients with various stages of HF, which in turn will help identify those that will benefit most from MV repair.

Left Ventricular Dysfunction in Cancer Treatment

Cancer therapies today have significantly improved survival but at the cost of treatment-related cardiovascular toxicity, including LV systolic dysfunction. Anthracyclines and radiation therapy were the only known cancer treatments with significant cardiotoxicity earlier. However, modern targeted cancer therapies, including HER2 inhibitors, tyrosine kinase inhibitors (TKIs), proteasome inhibitors, and immune checkpoint inhibitors, are known to have adverse cardiovascular events.

People with cardiomyopathy-related gene mutations may be more prone (7.5% compared to 1.1% of those without a titin gene mutation) to develop ventricular dysfunction after the administration of chemotherapy.[17]

Normal LVEF is a prerequisite for antineoplastic therapies, but it has limitations for risk prediction, and has prompted investigation of serum and imaging biomarkers in patients receiving cardiotoxic therapies. In patients receiving high-dose chemotherapy, early elevations in cardiac troponin I (cTnI)-predicted cardiac events at 3 years,[18] and troponin-guided initiation of enalapril in a similar cohort was associated with reduced risk of LVEF decline.[19] Decreases in global longitudinal strain (GLS), an echocardiographic marker investigated in breast cancer patients receiving doxorubicin and trastuzumab, have also been shown to predict subsequent LV dysfunction in combination with ultrasensitive cTnI.[20] In a systematic review, a 10–15% reduction in GLS predicted subsequent LV systolic dysfunction,[21] supporting the American Society of Echocardiography (ASE) recommendations to include GLS and cTnI in risk stratification of patients before and during treatment with anthracyclines or trastuzumab.[22]

Beta-blockers, ACEI, and ARBs have been mostly investigated in patients receiving lower anthracycline doses and overall have demonstrated feasibility, safety, and varying degree of LVEF decline attenuation, which has been the most common endpoint.

Conclusion

The prevalence of HF is escalating rapidly. Compounding this, HF is an illness that consumes significant health-care resources, inflicts significant morbidity and mortality, and greatly impacts quality of life. Important breakthroughs have redefined opportunities to change the natural history of the disease with a broad range of medical therapies, devices, percutaneous interventions along with different implants and care strategies, including readmission reduction programs and ambulatory outpatient disease management for those with more advanced disease.

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CHAPTER

33 Asymptomatic Left Ventricular Dysfunction

Asha Mahilmaran

Abstract

Asymptomatic left ventricular dysfunction (ASLVD) is more widely prevalent than overt clinical heart failure. ASLVD represents a huge opportunity but is under diagnosed and there are no clear cut trial data or guidelines for management. Symptomatic heart failure carries high morbidity and mortality and appropriate interventions to prevent or delay overt heart failure at the stage of ASLVD is critical in improving the prognosis.

Introduction

Heart failure is increasing in incidence as there is an increase of diabetes, hypertension, coronary artery disease and people surviving to advanced age. Heart failure continues to remain a major threat, an important cause of hospitalizations due to cardiac causes and mortality worse than many cancers despite advances in medical, interventional, and device therapy. The economic and social burden of the disease is immense and it is worthwhile to dwell upon early diagnosis at the asymptomatic stage of left ventricular dysfunction and if it is possible to prevent progression to overt heart failure.

Definition

Asymptomatic left ventricular dysfunction (ASLVD) is defined as depressed left ventricular dysfunction in the absence of overt symptoms and signs of heart failure.[1] The ejection fraction used as cut-off have varied in different studies, but we would use a left ventricular ejection fraction (LVEF) less than 50% as used in definition of heart failure reduced ejection fraction (HFREF).

American Heart Association Classification of Heart Failure

Stage A: At risk for heart failure like obesity, diabetes, hypertension, CAD, but no evidence of structural disease.

Stage B: Asymptomatic, but having structural abnormalities such as left ventricular dysfunction, left ventricular hypertrophy, and valvular lesions.

Stage C: Symptomatic heart failure.

Stage D: End stage heart failure.

ASLVD is classified as stage B heart failure and has the risk of progression to stage C or D heart failure.

Prevalence

The prevalence of ASLVD ranges from 7.3% to 23%. The heterogeneity is compounded by different cut-offs of LVEF used in various studies. The prevalence of ASLVD was 6.0% in men and 0.8% in women in the Framingham sub-study of 4,257 subjects who were followed for up to 12 years. Mild ASLVD-EF-40–50% was present in 61%, moderate

TABLE 1 Prevalence of ASLVD by age

Age	*Men (No.: 1860)*	*Women (No.: 2397)*
40–59	2.1	0.5
60–69	7.2	0.8
70–79	11.3	1.0
80+	14.3	1.9

EF-30–39% in 33%, and only 6% had severe ASLVD with EF less than 30% **(Table 1)**.

The risk of progression to overt heart failure was greater in patients with LVEF less than 40% as compared to mid-range ejection fraction of 40–50%.The relative risk of progression to clinical heart failure was 4.6 in patients with ASLVD in a meta-analysis of 11 studies comprising of 25,369 patients. The risk of progression was 1.7% in patients with asymptomatic left ventricular diastolic dysfunction (ALVDD). The major factors predicting an increased risk of progression from an asymptomatic stage were age, sex, blood pressure, diabetes, and body mass index. In the David-Berg study, patients with mild ASLVD had higher risk of overt HF on follow-up when there was associated diastolic dysfunction in patients with LVEF 40–52%. The HR for HF was 3.3 for patients with mild ASLVD (EF 40–50%), and HR of 7.8 for patients with moderate-to-severe ASLVD (EF < 40%) in the Framingham sub-study. The median survival of ASLVD was 7.1 years in this study **(Fig. 1)**.[2]

Etiology of Heart Failure

The major underlying causes of heart failure include hypertension, CAD, diabetes, obesity, and rheumatic heart disease (RHD). Quantitatively hypertension plays the most important contributing factor in isolation or alongside of CAD and RHD. A tight control of blood pressure is therefore one of the important early preventive intervention **(Fig. 2)**.[3]

Neuroendocrine Activation in ASLVD

Neuroendocrine activation has been shown to occur much earlier than symptomatic HF. In the SOLVD prevention arm, patients with asymptomatic LVEF less than 35% had higher plasma nor epinephrine levels than normal people, but lower than patients with clinical heart failure, the extent of nor epinephrine elevation correlated with future

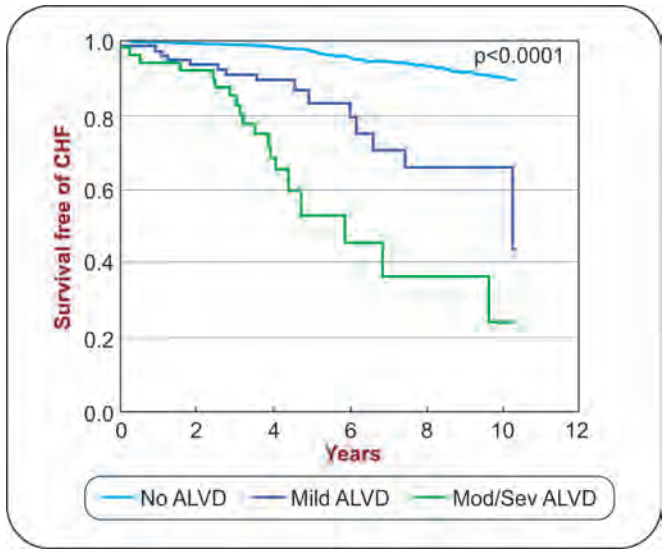

Fig. 1: Kaplan Meir survival curves of patients with no ASLVD and mild and moderate to severe ASLVD

death, overt heart failure development and ischemic events.[4] Plasma atrial natriuretic peptide, plasma arginine vasopressin levels were also increased but not plasma renin activity, suggestive that sympathetic activation occurs earlier than renin angiotensin system. This may help us plan strategy of treatment in ASLVD **(Fig. 3)**.

In the SAVE trial in patients with LVEF less than 40% following acute myocardial infarction (AMI), all neurohormones (PNE, PRA, AVP, and ANF) were all increased in asymptomatic patients, hence suggestion of benefit from early targeted therapy in ASLVD.[5-8] Neurohormonal modulation preemptively in the stage of ASLVD may prevent progression to overt heart failure.

Prognostic Significance of Preoperative ASLVSD and ASLVDD

In a study of 1,005 patients undergoing vascular surgery, both asymptomatic LV systolic dysfunction and diastolic dysfunction were associated with increased 30-day morbidity and long-term mortality. There was 17% incidence of non-fatal MI at 30 days, 10% in patients with normal LV function, 18% in ASLVDD, 23% in ASLVSD, and 49% in patients with symptomatic heart failure. Long-term follow-up revealed decreased survival in overt HF, HR-10.3, followed by ASLVSD HR-4.6, then ASLVDD, HR-3.0 as compared to normal LV function **(Fig. 4)**.[9]

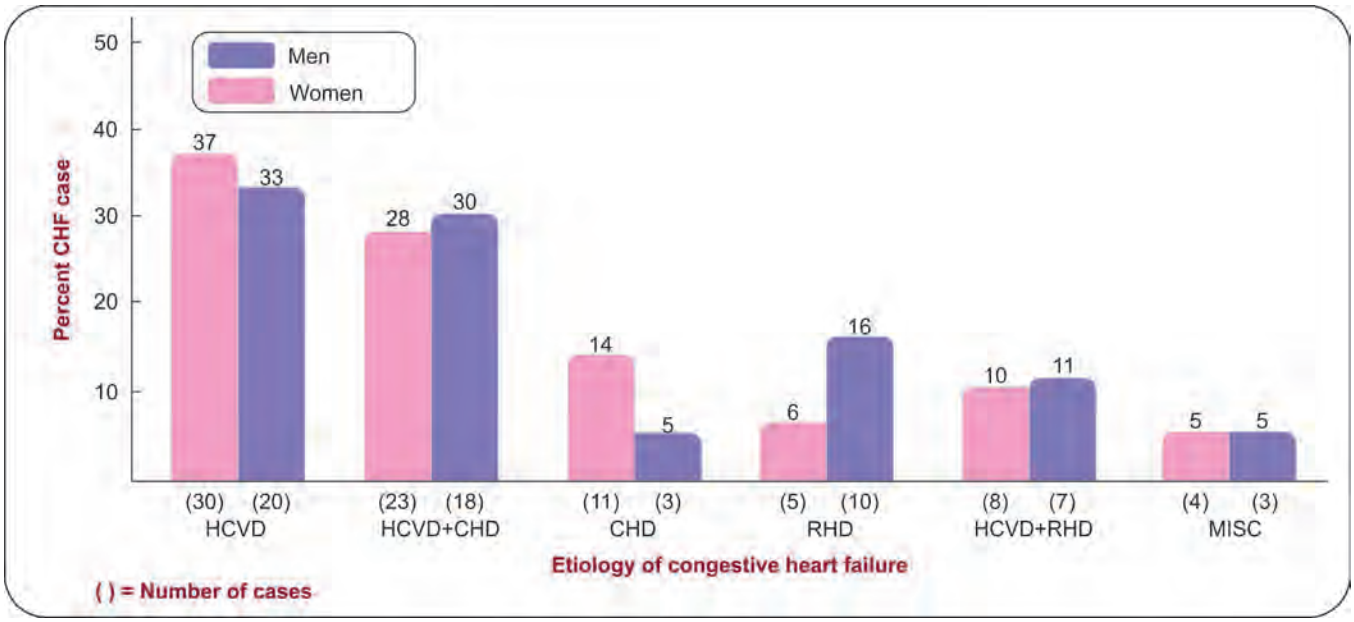

Fig. 2: Etiology of heart failure
HCVD, hypertensive heart disease; CHD, coronary heart disease; RHD, rheumatic heart disease

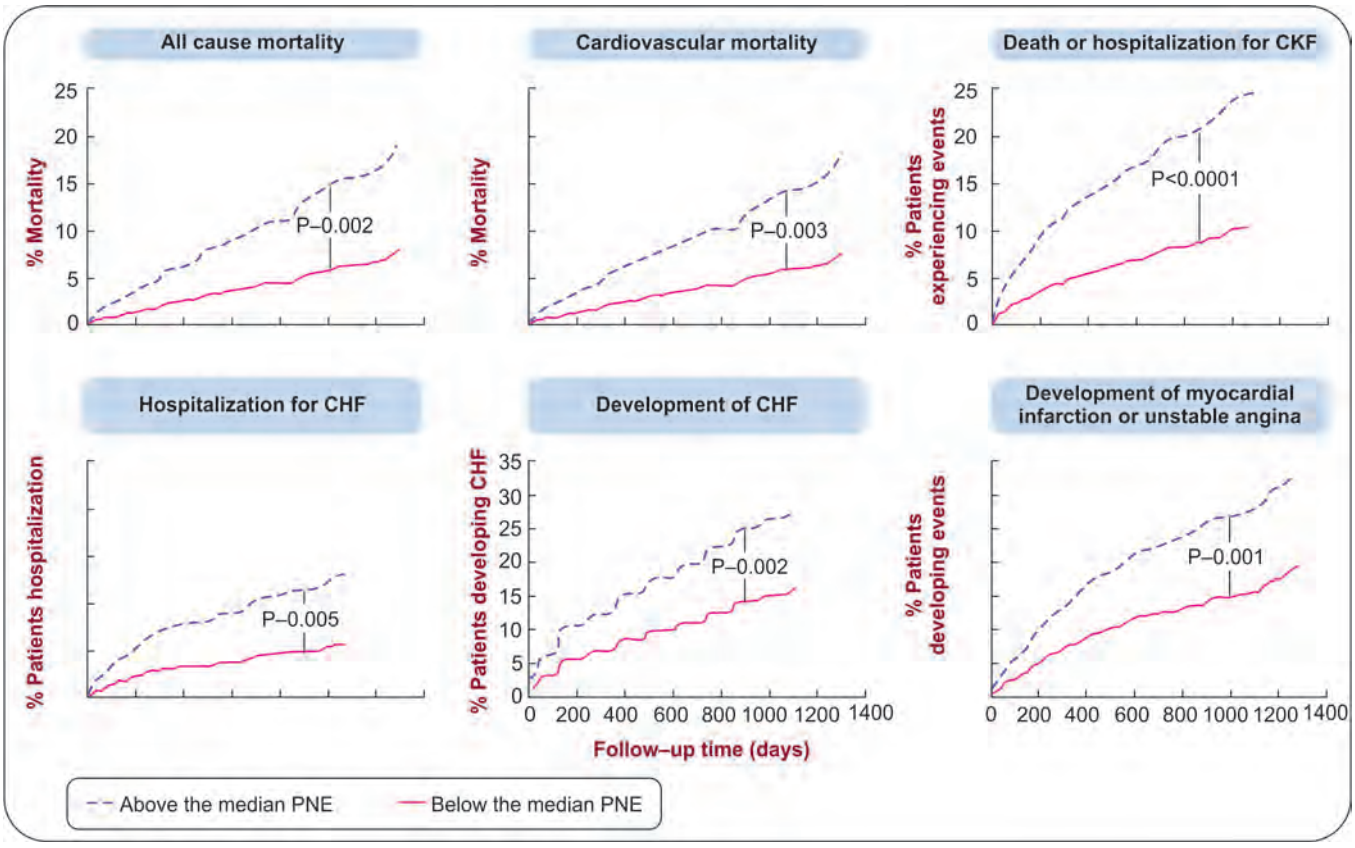

Fig. 3: Plasma norepinephrine levels and correlation to mortality and CV outcomes

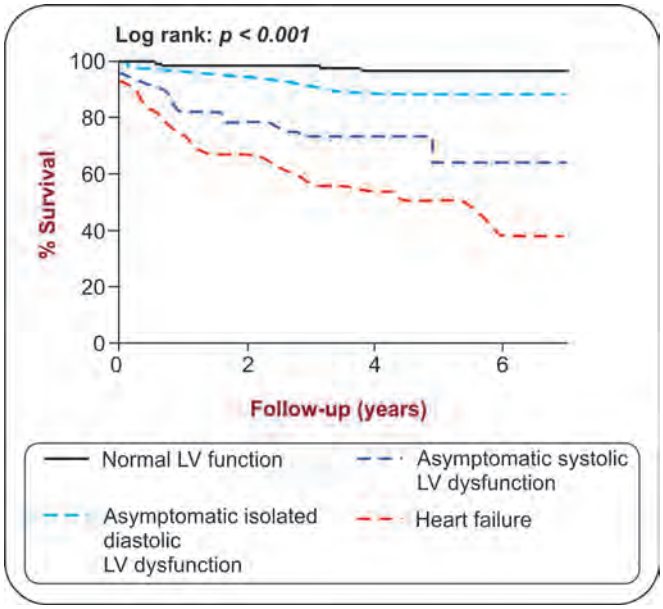

Fig. 4: Preoperative prevalence of asymptomatic isolated diastolic dysfunction, asymptomatic systolic LV dysfunction and heart failure and long term outcomes of patients undergoing vascular surgery[9]

Screening for ASLVD

Tests

ECG: Presence of Q-waves, old MI, left atrial enlargement, LVH, Conduction blocks, IVCD, and AF should prompt an evaluation of left ventricular function.

Chest X-ray: Presence of cardiomegaly, pleural effusion, pulmonary congestion, aortic calcification, posterior mitral annular calcification, aortic valve calcification merit further evaluation.

NT-ProBNP: Patients with elevation of NT-ProBNP had ASLVD in 6.6% of screened population in the SCREEN-HF study in a cohort of 3,550 patients with high risk for HF (AGE > 60 years with one other added risk factor for HF). In the David-Berg study, prevalence of ALSVD increased with age and CV risk. The prevalence was 5.3% and NT-ProBNP was more predictive than a combination of Framingham heart failure risk score (FHFRS) and ECG abnormalities.[10-12]

ECHO: ECHO screening should be done for patients with prior myocardial infarction, long standing DM, CKD, uncontrolled hypertension, presence of LVH, elderly patients above 60 years.

Global longitudinal strain (GLS): GLS is a more sensitive modality to diagnose early left ventricular function, it is load independent and less inter-observer variability is present. It is calculated by speckle tracking and GLS is the sum of peak longitudinal strain of 18 LV segments calculated from three standard two-dimensional ECHO views, apical long axis, Apical 4 chamber and Apical 2 chamber views. The normal value is -21 and a low value is ≤17. It is especially valuable in patients undergoing cancer chemotherapy as early detection may enable change of drug regime, initiation of early heart failure therapy. A decrease of 10–15% GLS is a reliable predictor of cancer chemotherapy induced cardiotoxicity. Low GLS has been noted in patients with uncontrolled hypertension, uncontrolled DM, obesity, hypercholesterolemia even with preserved LVEF. The low GLS is a predictor of future HF in these patients.[13]

Treatment of ASLVD

ACEI are the cornerstone of therapy of ASLVD. SOLVD prevention trial in patients with LVEF less than 35% had decreased HF hospitalization and overt HF when treated with enalapril as compared to placebo. SOLVD 12 year follow-up study showed decreased mortality in ASLVD patients on enalapril.[14] The SAVE trial, captopril in patients with ASLVD following AMI and in the TRACE trial following AMI, ASLVD patients on trandolapril were shown to have reduced CV events, HF, and mortality.

Angiotensin receptor blockers (ARB): ARB can be used in ACEI intolerant patients as shown in OPTIMAAL trial with losartan versus captopril and VALIANT trial with valsartan to be non-inferior to captopril in patients with LV dysfunction following AMI, a subset of whom were asymptomatic.

Beta blockers have been shown in the retrospective analysis of SOLVD and SAVE trials to have synergistic benefits when used with ACEI in ASLVD patients. In ANZ study and CAPRICORN trial, carvedilol has been shown to benefit post MI patients with LVEF less than 40%. In the REVERT trial, metoprolol has been shown to result in improvement in ejection fraction and ventricular remodeling in LV dysfunction of ischemic and non-ischemic etiology. Hence, beta blockers should be used in ASLVD to decrease the sympathetic over activation and slow progression of HF in both ischemic and non-ischemic etiologies.

Statin has been shown to reduce heart failure in patients with ischemia in the 4S study.

Diabetic patients with ASLVD had a higher risk of overt HF (HR-1.53) and HF hospitalization (HR-2.04) in the sub-analysis of SOLVD prevention trial patients with DM who developed HF had a mortality of 37% versus 29% in patients without DM. Sodium-glucose cotransporter inhibitor 2 (SGLT2) is the new class of diabetic drug, which prevents heart failure by 23% in a meta-analysis even in patients without pre-existing heart failure. The mechanism of benefit in heart is due to multiple modalities of action. They act by inhibiting glucose and sodium reabsorption in the proximal convoluted tubule causing glucosuria and natriuresis. The diuretic action of SGLT2 inhibitors is more on the interstitial fluid rather than intravascular fluid, so that there is no sympathetic activation and preload to heart is maintained. There is an increase in hematocrit by stimulation of erythropoietin, there is a uricosuric effect as well. The reduction in uric acid contributes to reduced oxidative stress. They inhibit NA^{+}-H^{+} ion exchanger in the heart resulting in prevention of cytosolic calcium excess which leads to apoptosis, shift the heart energy substrate to energy efficient ketone bodies instead of glucose. They also prevent cardiac fibrosis and hypertrophy and prevent adverse ventricular remodeling, which leads to progression of heart failure **(Flowchart 1)**.[16]

In addition, by increasing the sodium delivery in the distal tubule due to decreased proximal tubule reabsorption of sodium, through a tubule glomerular feedback, SGLT2 inhibitors lead to decreased glomerular pressure and have a renal protective effect as well, they also reduce renal fibrosis and hypoxia, which have favorable effects on the cardiorenal syndrome in HFREF **(Table 2)**.[16]

SGLT2 inhibitors have been shown to decrease HF hospitalization and CV mortality in the EMPAREG,

Flowchart 1: Mechanism of benefit of SGLT2 inhibitors

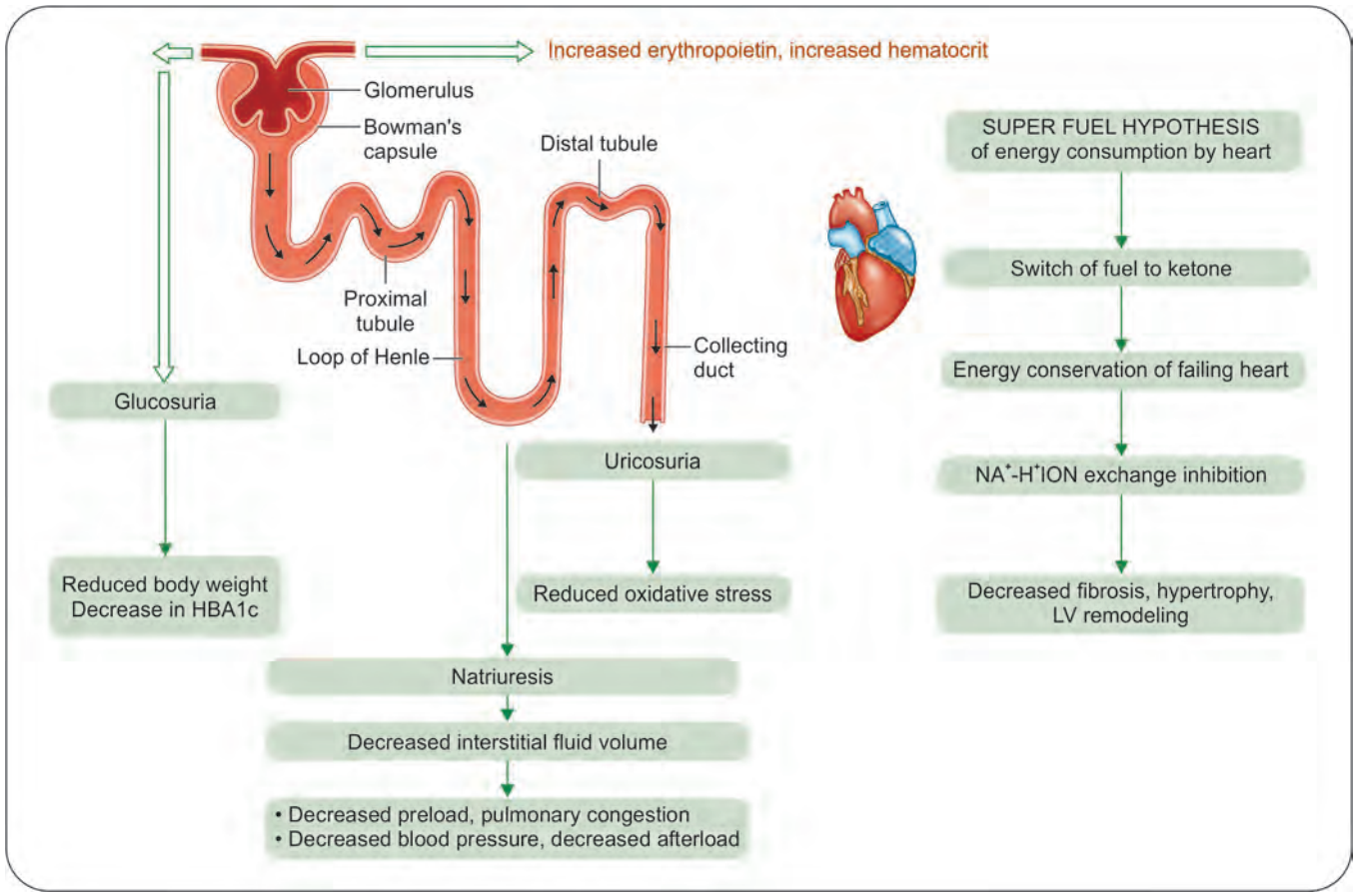

TABLE 2 Mechanism of cardiovascular benefits of SGLT2 inhibitors

Direct myocardial effects	Indirect systemic effects
Decreased NH exchanger	Decreased blood glucose
Decreased CAMKII	Natriuresis
Autophagy increased, lysosomal degradation increased	Increased hematocrit
Decreased inflammasome	Decreased plasma volume—greater decrease in interstitial fluid
Prevention of adverse cardiac remodeling	Increased uricosuria
Prevention of ischemia-reperfusion injury	Decrease in body weight
Decreasing of epicardial fat	Decrease in arterial pressure
Ketone utilization as substrate, more energy efficient	Decrease in arterial stiffness
Decreased SGLT1 activity	Improved renal function
	Increased vascular progenitor cells
	Inhibition of SNS
	Reduction of oxidative stress

CAMKII, calmodulin-dependent protein kinase II; NH, sodium hydrogen ion exchanger.

CANVAS, CREDENCE, and DAPA-HF trials. The DAPA-HF trial showed benefit in HFREF patients with or without DM. SGLT2 inhibitors added at the stage of A, B, or C has shown benefit and should be included for all diabetic patients with LV dysfunction with or without symptoms. It is probably worthwhile to explore their use in all patients with ASLVD with or without DM.[15,16]

Device Therapy

Patients with LVEF less than 30% for more than 1 month after an AMI have been shown to have survival benefit as shown in the MADIT II trial which included 40% of asymptomatic patients.

Cardiac resynchronization therapy (CRT) has been shown to reverse ventricular remodeling in REVERSE trial in patients with NYHA class II and III, but data not strongly showing benefit in NYHA class I patients.

The PACE trial showed better outcomes in patients with atrioventricular sequential pacing as compared to RV pacing in patients with LVEF less than 45%. Biventricular pacing has been shown to be superior to right ventricular pacing in patients with LVEF less than 50% in the BLOCK HF trial in patients with atrioventricular block with decreased combined end point of mortality, HF hospitalization or more than 15% increase in LV end systolic volume index.

His Bundle Pacing (HBP) is a new pacing strategy, which avoids the adverse consequences of RV pacing and ensures atrioventricular and intraventricular synchrony. It has been found to preserve left ventricular function and reduce mitral regurgitation in patients with heart failure and pacing indication. HBP is also being explored as an alternative to CRT in patients with LBBB and CRT indication.[15-18]

Conclusion

Asymptomatic left ventricular dysfunction occurs twice as common as overt heart failure. ASLVD carries a good prognosis until the development of overt HF and presents with a huge window of opportunity to implement therapy and mitigate the progression and adverse consequences of overt HF. Early screening with ECHO, GLS, and NT-ProBNP will help catching the patients early. RAAS inhibitors, Beta blockers, SGLT2 inhibitors, statins in patients with CAD prevent progression of heart failure and should be initiated in this stage. Avoidance of RV pacing, use of His bundle pacing in patients with left ventricular dysfunction improves LVEF.[19]

AICD prevents sudden death and decreases mortality in patients with LVEF less than 30% irrespective of their symptom status.

CRT and HBP are useful in patients with LBBB, broad QRS, and mitral regurgitation with LV dysfunction with stage C HF, but data not adequate in ASLVD. The use of ARNI also needs to be explored in ASLVD and if it is superior to ACEI in preventing adverse LV remodeling.

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CHAPTER

34 Cardiovascular Risk Assessment Tools

Ravikeerthy M

Abstract

Cardiovascular disease is the major non-communicable disease in both developed and developing countries. Its prevalence is increasing with the change in lifestyle factors. It is one of the preventable conditions. The disease remains asymptomatic till advanced stages in majority of the population. Early intervention with lifestyle changes and medication can prevent these cardiovascular events, need tools to identify the people at risk, and these tools are used to calculate an individual's risk of developing a CV event from risk factors obtained from history, physical examination, or investigations. There are several tools available for the risk assessment but very few tools like JBS3 identify the risk more accurately and this is applicable for Indian population also.

Introduction

Cardiovascular disease (CVD) has overtaken infection as a leading cause of death all over the world. It is the leading cause of not only mortality but also the morbidity, and is a major economic burden. With changing life styles and increased life span, the burden of disease is also increasing. India is no different from this because of the increase in its prevalence and that of CVD risk factors.[1]

The Global Burden of Disease study estimates suggest higher age-standardized CVD death rate of 272 per 100,000 population in India compared to the global average of 235 per 100,000 population.[2]

CVDs include coronary heart disease, cerebrovascular disease, peripheral artery disease, aortic atherosclerosis, and aneurysm of aorta (thoracic or abdominal).

Cardiovascular risk factors are divided into modifiable and non-modifiable risk factors. Modifiable risk factors are further classified as health conditions and life style factors **(Table 1)**.[3]

Various studies have shown that early intervention with lifestyle changes and medication can prevent these cardiovascular events. So accurate estimation of CV risk is important as it affects health behavior and medical decision-making, and helps improve patient compliance to the treatment.[4] As per the world health organization prevention is classified into the following type:

- Primordial prevention
- Primary prevention
- Secondary prevention
- Tertiary prevention
- Quaternary prevention

TABLE 1 Classification of CV risk factors

Non-modifiable risk factors	*Modifiable risk factors*	
	Health conditions	*Lifestyle factors*
• Age • Sex • Family history	• Hypertension • Dyslipidemia • Diabetes mellitus • Chronic kidney disease	• Smoking • Poor diet • Physical inactivity • Obesity • Psychosocial factors

The main aim should focus on Primordial or Primary prevention.[5]

Definition

Cardiovascular risk stratification by definition is the assessment to estimate the risk of developing cardiovascular event or estimating the risk of developing cardiovascular event during noncardiac surgery by perioperative risk assessment.

So we need tools to identify the people at risk and these tools are used to calculate an individual's risk of developing a CV event from risk factors obtained from history, physical examination, or investigations. Most guidelines recommend the use of risk scores to predict global risk rather than focusing on single risk modification. Studies from different parts of the world have reported that the rates of use of CV risk scores range from 17% to 65%. A study conducted in the United States, showed that 92% of physicians were aware of risk stratification tools; however, it was used in only 41% of patients, with only a part of the latter being used to guide the subsequent treatment decisions.

Studies have shown that subjective estimation of CV risk by doctors is inaccurate. Patients and doctors generally estimate risk by risk factor profile or risk factor counting as opposed to absolute risk calculation. However, focusing on individual risk factors or risk factor counting tends to underestimate risk in those who may have slightly elevated level of multiple risk factors that synergistically increase the overall absolute CV risk.[4,6]

Another study in primary care physicians in Canada demonstrated that almost one-third were not aware of the defining point for high CV risk (>20% 10-year FRS CV risk) which leads to misclassification of risk and underestimation of truly high-risk patients.

Risk Stratification Tools

There are many different tools available. Most important are listed below:

- Framingham Risk Score (FRS)
- Prospective Cardiovascular Munster Score (PROCAM)
- World Health Organization/International Society of Hypertension (WHO/ISH) CVD risk prediction charts
- Systemic Coronary Risk Evaluation (SCORE)
- American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equations
- 3rd Joint British Societies (JBS3) risk calculator
- Reynolds score
- Assign risk score
- Qrisk risk score
- Adult Treatment Panel III

Framingham Risk Score

It is the landmark study especially for the assessment of 10 years risk and most widely adapted. This is also used to assess the composite of all atherosclerotic cardiovascular events like angina, stroke, peripheral vascular disease, and heart failure. Paramaeters used for assessment are age, sex, diabetes, smoking, hypertension, total and HDL cholesterol.

Limitations—does not predict the true values in European and Asian people. Some important risk factors like family history of cardiovascular events, chronic kidney disease and body mass index are not included. Analysis of the study show both overprediction in low risk population and underprediction in high risk population. The study relies greatly on age as a predictor of cardiovascular risk; hence, in a young individual, the estimated 10-year CV risk is invariably low, even in the presence of multiple cardiovascular risk factors.

Systemic Coronary Risk Evaluation

This study was derived from 12 cohort studied involving more than 200,000 people in Europe and accuracy for European population is good. One major plus point of this study is its prediction of first fatal cardiovascular event.

Reynolds Risk Score

This was initially developed to assess the risk in healthy women and later applied to male population with slight modifications.[7] Around 25,000 healthy health professionals were involved in the initial study to assess the composite events like myocardial infarction, stroke, coronary revascularization, and cardiovascular death. Compare FRS and score tools, inclusion of HS CRP and parenteral premature cardiac events in this gives a better predictive value.

JBS3 Risk Calculator

The joint British societies released this risk score in 2014, and end points assessed are cardiovascular death, nonfatal MI, angina, stroke, TIA, and intermittent claudication.

This score estimates both 10-year risk and lifetime risk of CVD and also the "Heart Age."

This is a more extensive risk assessment tool compared to others. It includes several additional risk factors such as obesity and family history of premature CVD. This study also includes data on ethnic Indians and is more suitable for Indian population for the CV risk assessment.

Assign Risk Score

Assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network is developed in Scotland. The study group involved the asymptomatic CVD subjects aged between 30–74, both men and women. The study included most of the parameters as in other studies and a new risk factor that is social deprivation. One of the limitations of the study in not including obesity as a risk factor. This score predicted the 10-year risk of cardiovascular disease. It included all the discharges with the diagnosis of CVD and death.[8]

QRISK Risk Score

QRESEARCH cardiovascular risk algorithm a cohort of 1.3 million subjects, aged between 35–74 years and were free from diabetes and CVD. The following risk factors were considered in the study-age, sex, smoking status, systolic blood pressure, ratio of total to HDL-C, body mass index, family history of CHD, social deprivation, and antihypertensive treatment. The above score predicts the 10-year risk of CVD such as MI and also stroke, transient ischemic attack. Major limitation of the study is that it was validated on the same study subjects.[9]

The risk of CVD is classified into borderline (5–7.5%), intermediate risk (7.5–20%), and high risk (>20%) based on the different risk score. ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease-2019 recommends Cardiac Risk Assessment. By using the pooled cohort equations (PCEs), the physician should regularly assess cardiovascular risk factors and calculate 10-year risk of ASCVD of adults of age group 40–75 years. For adults 20–39 years of age, it is rational to assess traditional ASCVD risk factors at least once in 4–6 years. In adults at borderline risk (5% to <7.5% 10-year ASCVD risk) or intermediate risk (≥7.5% to <20% 10-year ASCVD risk), it is rational to use additional risk-enhancing factors to guide decisions about preventive interventions (e.g., statin therapy). In adults at intermediate risk (≥7.5% to <20% 10-year ASCVD risk) or selected adults at borderline risk (5% to <7.5% 10-year ASCVD risk), if risk-based decisions for preventive interventions (e.g., statin therapy) remain uncertain, it is rational to measure a coronary artery calcium score to guide clinician–patient risk discussion. For adults 20–39 years of age and for those 40–59 years of age who have <7.5% 10-year ASCVD risk, estimating lifetime or 30-year ASCVD risk may be considered.

The present understanding of the 10-year risk for atherosclerotic CVD identifies patients in higher-risk groups who are likely to have greater net benefit and lower number needed to treat for both statins and antihypertensive therapy. Lifetime CVD risk estimation, which measures the cumulative risk of developing the disease during the rest of an individual's lifespan, could provide a more accurate assessment of future risk of CVD than short-term risk estimates, more so in younger individuals who have low short-term risks. The guidelines now recommend stepwise stratification of disease-free and asymptomatic individuals into high short-term, low short-term/high lifetime, and low short-term/low lifetime CHD risk groups for targeting primary prevention strategies in all eligible individuals.[10]

Subclinical Atherosclerosis Assessment

Risk-scoring tools can improve the prediction of risk but their adoption in clinical practice is poor. Risk factor based approach estimate CV risk at population level and not at individual level. Hence, it is desirable to develop tools which could accurately identify individuals who are truly at risk. For example, 20% risk of cardiovascular events over 10 years means that out of 100 such individuals, 20 will develop a vascular event over 10 years; however, it is impossible to predict who are those 20 who might develop the event. Hence, all 100 patients need treatment.[11] Hence, inclusion of noninvasive tests that can identify subclinical atherosclerosis is required in improving the risk assessment.

Imaging techniques for sub-clinical atherosclerosis not only shows the evidence of sub-clinical atherosclerosis but also increases the probability of developing CVD later on, irrespective of cardiovascular risk factors and also helps benefit the patient by providing suitable preventive strategies and helps improving patient's treatment compliance.

The following is the list of tools available for the assessment of subclinical atherosclerosis:

- Carotid plaque assessment
- Carotid intima-media thickness (CIMT)
- Brachial artery flow-mediated dilatation
- Coronary calcium score (CCS)
- Ankle-brachial index
- Pulse wave velocity (PWV)
- Stress test/TMT

Coronary calcium score, carotid ultrasound imaging, and PWV are studied extensively in clinical practice. CCS is a computed tomography test which helps detect and quantify the amount of calcium in the coronary arteries. Presence of coronary calcium provides direct evidence of ongoing coronary atherosclerosis. CCS also provides prognostic information. CCS correlates with the extent of coronary artery disease in Indian subjects as well. The presence of atherosclerosis in carotid arteries shows high risk of coronary events also (since atherosclerosis is a generalized process). It can evaluate both intima-media thickness (CIMT) and carotid plaques. CIMT is associated with greater risk of vascular events, independent of common CV risk factors or FRS. CIMT is related to CV risk factors, presence of CAD, and the extent of CAD on angiography in Indian patients also. Aortic pulse wave velocity (PWV) is an indicator of arterial stiffness. It has greater value in the evaluation of pathophysiological states associated with arteriosclerosis, such as hypertension, ageing, and end-stage renal disease. A significant relationship between PWV and CV risk factors and incident CVD is shown in Indian subjects.

Other Markers of CV Risk Assessment

- High-sensitive c-reactive protein
- Lipoprotein a [Lp(a)]
- Apolipoproteins
- Inflammatory cytokines
- Fibrinogen

Indian Scenario

Indians are at a greater risk of CV disease as compared to other populations probably due to genetic make-up and early onset of conventional CV risk factors. A calibration method has been proposed to optimize cardiovascular risk estimates for Indians. A 10-year risk based on FRS can be recalibrated by multiplying the calculated risk with a correction factor. For rural Indians, the suggested correction factor is 0.8 for women and 1.0 for men, whereas for urban Indians it is 1.54 for women and 1.81 for men.[11]

WHO published series of risk prediction charts, which might be the only option available for populations for which prospective studies are not available. Another option is JBS3 risk calculator that allows separate risk assessment for people with Indian ethnicity. JBS3 risk calculator seems to have greater accuracy in Indian patients as it includes data on ethnic Indians and takes into consideration of many other risk factors such as obesity and family history of premature CVD. So it is more comprehensive risk assessment tool.[12]

Conclusion

Assessment of the risk of occurrence of future CV events is an important step in the management of the patients requiring primary prevention of CV disease. Using various risk assessment tools, people at high risk of CVD can be recognized. However, in clinical practice, cardiovascular risk assessment by primary care physicians frequently involves subjective evaluation rather than the use of risk assessment tools. Most of the cardiovascular risk assessment tools are not suitable for use in the Indian population. Therefore, there is a need for an optimal cardiovascular risk assessment tool in the Indian population. Although Framingham risk score is most widely used and accepted it is not suitable for the Indian population. Among the various risk assessment tools, the Joint British Societies (JBS3) risk calculator has been reported to provide a more accurate estimation of the cardiovascular risk in Indian population. Assessment of subclinical atherosclerosis enables more accurate identification of individuals who are at increased risk of CVD.

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CHAPTER

35

ARMOR–Arati's Regime for Management of Rheumatic Fever—Against Rheumatic Heart Disease—A Great Milestone

Arati Lalchandani, Prem Singh, Arvind Kumar, Taruni Lalchandani

Abstract

Rheumatic heart disease is a disease for which no significant progress has taken place as regards the diagnosis and the management for seven long decades; therefore, we find that physicians are struggling with the same dilemma in diagnosis and the age-old painful and ineffective prophylaxis with parenteral penicillin.

The ARMOR, i.e., Arati's Regime for Management of Rheumatic Fever – Against RHD will prove to be a great milestone in the management of Rheumatic Fever. The practice of ARMOR shall simplify and increase the sensitivity of diagnosis of RHD and make the treatment and prophylaxis of RHD safe, effective, and popular.

Introduction

ARMOR consists of:

I. **Diagnostic criteria for rheumatic fever (RF) rheumatic heart disease (RHD)—arthralgia or arthritis, cardiac involvement typical of RF, Echo-Doppler findings typical of RF RHD, with history of sore throat.**

II. **Use of newer anti-inflammatory drugs for arthritis of RF—aceclofenac 200 mg BD or any NSAID for 5 days or longer.**

III. **Primary prevention, treatment, and secondary prophylaxis of RF RHD with tablet azithromycin 500 mg 1 daily for 5 days followed by 1 tablet once a week for 1 year only.**

Azithromycin must be started with 500 mg/day each time even when changing over from other drugs.

Since more than five decades physicians have been struggling with the very same weapons against RF/RHD although there have been great strides in management of infections especially over past two decades.

RHD is no doubt a heart disease, but it is well established that it begins as an infection of the tonsils/sore throat which later, by still largely unexplained mechanism, destroys the heart valves irrevocably thus shortening the life span of the individual.

Since 1940s though several attempts were made to bring about changes to Jones Criteria for diagnosis and management of RF RHD, the dire changes needed were not made.

The Major Problems with Application of Jones Criteria

I. *Very complicated confusing criteria for diagnosis:* RHD is a simple disease with very typical symptoms and consistency of clinical features; therefore, should be very easy to diagnose by any practitioner. Moreover, since the introduction of Echocardiography Doppler study, a very definite diagnosis can be made by viewing the heart under direct vision.

The ARMOR regime therefore in its diagnostic limb only includes typical migratory arthritis affecting the medium and large joints, transient, recovering completely, endocarditis of heart valves resulting in regurgitant or stenotic valves, pericarditis with minimal fluid with full recovery, myocarditis with MR TR, cardiomegaly, heart failure, very often even

irreversible heart valve damage—mitral stenosis, mitral regurgitation, aortic regurgitation, aortic stenosis, tricuspid regurgitation.

The heart lesions typical of RF RHD can be easily and definitively confirmed by Echo Doppler study, which is now available as easily as X-ray of yesteryears.

The other clinical features of RF RHD viz chorea, subcutaneous nodules, and erythema marginatum have been given too much importance as major Jones criteria.

In a study of 200 patients of RF by Lalchandani et al. it was shown that out of all the Jones criteria only arthritis, arthralgia, and carditis were found in the majority of patients whereas there were no patients with chorea, erythema marginatum, or subcutaneous nodules.[1]

Since it is well known that chorea in RF occurs as an isolated feature and almost never with cardiac involvement; therefore, it should not be a major diagnostic criterion for RF. Also a patient of chorea does not have the evidence of Streptococcal infection; therefore, chorea could very well be a separate entity called Sydenham's chorea.[2,3]

The incidence of chorea has been very low in western literature and very rare in Indian patients. A patient of chorea who does not have other features of RF should not be labeled as patient of ARF as there are many other causes of chorea.

According to Jones criteria only one major and two minor criteria along with essential association of GABHS is required for diagnosis so subcutaneous nodules and erythema marginatum, which have so many other causes cannot be considered as major criteria.

The clinical profile of 550 cases of RF RHD was studied by Ravisha et al. in India where arthritis and carditis was found in 169 (67.6%) and 105 cases (42%) chorea in 47 (18.8%) and erythema marginatum in 4 only.[4]

As regards *minor criteria of Jones* they are mostly the features of infection and inflammation, which are common to many other diseases.

By thus simplifying the diagnosis of RF RHD sensitivity of ARMOR would be high compared to Jones and would help in starting early prophylaxis and curing the cases before serious organic heart disease.

It is pointed out here that even ARF can be picked up on echocardiography-echocardiographic criteria for diagnosis of RF by Dr Anita Saxena and Dr IB Vijaylaxmi.[5,6]

II. *A majority of literature on RF RHD advocate an extremely dangerous drug—aspirin as the drug of choice for rheumatic arthritis:* It is really flummoxing that even after the discovery of an array of anti-inflammatory analgesic drugs with excellent safety profile and availability the textbooks continue to advocate Aspirin. Aspirin is a very toxic drug causing peptic ulcer, hemorrhage from gastric and other sites, rhinitis, bronchial asthma, Reye's syndrome and even death.

Aspirin has been recommended in a very high dose of 8–12 g/d for 6 weeks to 6 months and needs to be tapered over weeks to avoid rebound relapse.

Therefore, Aspirin should be replaced with the newer anti-inflammatory aceclofenac 200 mg twice a day or Nimesulide 200 mg twice a day, which needs to be given only for 5 days or more according to discretion of physician. These are very safe effective easily available and can be given for very short duration without rebound or relapse.[7]

III. *The antibiotic of choice till today continues to be the age-old BPG (Benzathine Penicillin):* The mainstay of prevention and treatment of RHD is an antibiotic effective against GABHS. BPG the gold standard is given as a stat dose IM AST in a dose of 1.2 m units for treatment. For secondary prophylaxis BPG 1.2 m units is given IM AST every 21 days.

Today the best drug for GABHS is azithromycin which if started within 9 days of symptom of sore throat, almost all cases of RF can be prevented.

Azithromycin can be used for primary prevention treatment and also to prevent recurrent attacks of ARF as well as secondary prevention because of its accessibility safety, efficacy, affordability, tolerability, and oral mode of dispensation.

All cases of sore throat whether of viral or bacterial etiology resolve in 3–5 days but full course of azithromycin 500 mg or 12 mg/kg once daily for 5 days must be given to all cases to prevent RF RHD in the developing countries.[8]

BPG must be replaced with azithromycin due to the following reasons:

- Severe fatal reaction may occur with BPG in as many as 1:10000 patients, which is a considerable number

as 20 million people may be having RHD in the world today.[9]

Only a well-equipped emergency setup can deal with anaphylaxis due to BPG.

- The demand of BPG hugely outnumbers the supply.
- BPG has to be given AST each time.
- After an injection BPG the patient suffers from same features of RHD like pains, aches, and fever.
- BPG is an oily injection given deep IM 2–5 mL in quantity to cachectic patients of RHD.
- Patients have transient valvulitis of MV AV after BPG so that benefit of BPG is not seen.[10]
- Commonly co-prescribed drugs like warfarin, aspirin, diuretics interact with penicillin.
- Accidental IV can cause cardiac arrest and death.
- Severe allergic reactions are common.
- Pseudomembranous colitis can occur.
- Clostridium difficile associated diarrhea increases mortality and morbidity.

Many studies have shown that relapse and recurrence and progression of RHD is not much influenced by regular administration of BPG as substantiated in Pediatric Cardiology 2010 Division of Cardiology, University of Virginia in retrospective review of patients of ARF less than 21 years, which showed recurrence rate of 38% in 144 patients of RHD, compliance with BPG 59% and recurrence of ARF in 57%.[11]

The recurrence rate of RF from various studies is 3–8% over 5–6 years with BPG and consistently less than 3% with azithromycin.[12]

Penicillin concentration in serum of more than 0.02 μgm/mL is required to prevent recurrence compared to azithromycin, which persists in therapeutic concentration in tissues.

Azithromycin is the drug of choice in ARMOR due to the following reasons:

- Azithromycin is an azalide, chemical name is 9-deoxy-9-za9-a-methyl-9-a homoerythromycin, Molecular weight 749.
- Azithromycin if started with 500 mg OD for 5 days has to be given only weekly thereafter as its persistence in the tissues continues for about 6 days, therefore, needs to be given on the 7th day, that is, weekly dose.
- It has autoimmune suppressant and anti-inflammatory effect.
- It is acid stable so oral dose is well absorbed and is readily absorbed.
- Time to peak concentration is 2.1–3.2 hours.
- The drug is concentrated in phagocytes and actively transported to infection site thereafter released at the site of infection in large quantities.
- Concentration of azithromycin is 50 times higher in tissues than in plasma due to ion trapping and high solubility of drug. Concentration in lung and tonsils exceeds MIC 90 even after a single dose. A single large dose can eradicate the bacteria completely.
- It acts by binding to 50s ribosomal subunits and prevents translocation of peptides thus inhibiting bacterial protein synthesis.
- After single dose of 500 mg of azithromycin its concentration in plasma declines in polyphasic pattern with a plasma clearance rate of 630 mL/minute and terminal elimination half-life 68 hours due to property of large uptake and sustained slow release of drug from tissues.
- It is freely available, safe, cost-effective with excellent antistreptococcal activity.
- Has to be given with caution in renal impairment.
- Safe in hepatic impairment.
- Safe in pregnancy.

Azithromycin discovered in 1991 is extensively used for GAS with great results by physicians and ENT surgeons.

In a systematic review of 21 RCTs azithromycin 20 mg/kg/day for 3 days achieved GABHS eradication in 95% cases in streptococcal tonsillopharyngitis.[13]

In a study by Lalchandani et al., 730 patients were given azithromycin for ARF in dose 500 mg once daily for 5 days followed by 500 mg on 2 consecutive days in a week. No patient had relapse or reinfection or worsening of cardiac valve disease. Compliance was 100% and patients who had no new problem attributable to RF were given prophylaxis for 1 year only.[12]

In a correspondence with Prof A Lalchandani, Dr Stephen Marko of World Heart Federation, University of Connecticut, expressed concern over use of BPG due to alarming issues of quality and quantity of drug stating that treatment guidelines be modified by individual circumstances.

After detailed deliberations over the GABHS infection, its persistence in the bloodstream, sensitivity to the drug, a possible time-interval for causation of autoimmune

damage, the time gap between infection and carditis progressing to organic heart valve disease, conclusion is that there is no basis for RHD prophylaxis for greater than 1 year after sore throat, recurrence, or relapse or ARA.[14]

In a study by Dr BL Agarwal in 1986 the mean duration of symptoms before admission to hospital in a series of 100 cases of initial attack was 6.47±3.4 weeks, in children without carditis it was 5.0±4.03 weeks after onset of illness while in those with uncomplicated carditis it was 5.95±5.26 weeks.[15]

In view of the above facts RHD prophylaxis exceeding 1 year seems devoid of reasoning. Even in poststreptococcal reactive arthritis VHD patients should be given appropriate prophylaxis for up to 1 year (Class IIb, LOE C-AHA Scientific Statement).

Conclusion

In anticipation of infection lifelong prophylaxis with antibiotic is not only absurd but extremely harmful; that too with a drug which has to be tested each time for sensitivity, the risk incurred being greater than benefit reaped. With azithromycin prophylaxis for 1 year the disease progression is checked and even reversed.

For the past more than 12 years azithromycin is being given exclusively for treatment and prophylaxis of RF RHD in GSVM Medical College, Kanpur, with excellent miraculous results which have been documented in theses of PG students over several years. Many studies have shown azithromycin to be a much superior drug to BPG when GABHS is culprit organism of RF.[16,17]

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CHAPTER

36 Evaluation and Management of Chronic Stable Angina: Physicians' Perspective

Vibhu Khanna, Ankush Gupta, Sanya Chhikara

Abstract

Chronic stable angina, while being a widely used term, is part of a much wider spectrum of chronic coronory syndromes (CCS). This spectrum consists of a dynamic and progressive disease course rather than a stable one, and hence requires thorough risk stratification and management. Risk stratification includes analyzing the demographics and clinical presentation of the patient to decide further management and testing. While ECG is the first step in making the diagnosis, there are several other modalities available to us today that supplement the ECG. These include both functional and anatomical imaging techniques like Echocardiography, Cardiac Magnetic Resonance Imaging, Coronary CT Angiography and various stress tests as well as invasive techniques like Percutaneous Coronary Angiography. The mainstay of treatment for CSA and CCS remains medical treatment. There are a variety of drug classes available that can be tailored depending on individual patient requirements. In addition to medical management, myocardial revascularization can also be attempted in specific cases using percutaneous coronary intervention or surgery.

Introduction

Coronary artery disease (CAD) or ischemic heart disease (IHD) covers a wide spectrum of syndromes that occur due to imbalance between myocardial oxygen demand and supply. The underlying pathology is most often the atherosclerotic involvement of the epicardial vessels, with varying degrees of obstruction. While the disease itself is chronic and progressive, presentation varies widely. Patients may be asymptomatic, present with a chronic stable course, or present acutely.

The most widely accepted classification of symptomatic patients includes stable coronary artery disease (SCAD) and acute coronary syndrome (ACS). Recent literature has recommended the use of the term chronic coronary syndrome (CCS) as an alternative to SCAD so as to retire the use of "Stable" and emphasize the progressive nature of the condition. The 2019 guidelines on CCS by the European Society of Cardiology (ESC) provide a comprehensive outlook on this new terminology as well as clinical practical guidelines on the approach and management of CCS.[1]

The ACS spectrum includes unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). SCAD/CCS also includes a variety of presentations, one of which is chronic stable angina (CSA). This is an episodic clinical syndrome caused due to transient myocardial ischemia. CSA occurs due to gradual progression of atherosclerosis in the epicardial vessels or due to supply/demand mismatch caused increased myocardial oxygen demand.[2]

Presentation

Angina refers to chest pain/discomfort attributable to myocardial ischemia. Elements of history that are critical to making the diagnosis of angina include four main categories as shown in **Table 1**.

TABLE 1 Anginal chest pain

Category	*Description*
Location	Chest pain, often retrosternal, with radiation to the epigastrium, arms, shoulders, neck and throat, jaw, and rarely interscapular *Levine sign:* Placing a clenched fist over the precordium to describe the pain
Quality	Often described as: squeezing, pressure, constricting, strangling, burning, chest fullness, band-like sensation, ache, heavy weight on chest
Duration	Classically for 2–5 minutes but usually lasts not more than 20–30 minutes
Other exacerbating or relieving factors	Provoking factors: Increased myocardial oxygen demand due to exercise, cold, emotional stress, sexual intercourse, meals, or lying down Relieving factors: termination of the provoking factor or administration of nitroglycerin

TABLE 2 Clinical classification of angina

Typical	• Substernal chest discomfort with characteristic quality and duration • Provoked by exertion or emotional stress • Relieved by rest or nitroglycerin
Atypical	Meets two of the above characteristics
Non-cardiac	Meets one or none of the typical angina characteristics

Source: Knuuti, J. et al.[1]

Symptomology can be classified on the basis of history taking into typical, atypical, or noncardiac chest pain **(Table 2)**. Atypical presentation is often seen in women and elderly.

Angina can be graded into various classes depending on severity **(Table 3)**.

TABLE 3 Canadian Cardiovascular Society grading of effort angina

Grade	*Description of angina severity*	
I	Angina only with strenuous exertion	Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs)
II	Angina with moderate exertion	Slight limitation of ordinary activities when they are performed rapidly, after meals, in cold, in wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions
III	Angina with mild exertion	Having difficulties walking one or two blocks, or climbing one flight of stairs, at normal pace and conditions
IV	Angina at rest	No exertion needed to trigger angina

Evaluation

In addition to laboratory investigations and biochemical tests to identify possible causes of ischemia and risk factors, the diagnosis of CAD can be made with the help of the several modalities. The choice of diagnostic tests should made after giving due consideration to pretest probability and the patients be stratified as high-, intermediate-, and low-risk groups. For example, a young woman presenting with atypical angina would be classified as a low-risk patient and does not warrant additional testing for CAD if the baseline ECG is normal.

Resting Electrocardiography

While a normal ECG is often recorded, ongoing angina may be accompanied by dynamic ST segment changes making this modality crucial for diagnosis of CAD. Other findings that may be indicative of underlying pathology include evidence of previous infarction (Q waves or an R wave in V1 or persistent ST-T wave inversions), conduction blocks (LBBB, AV blocks), and LV hypertrophy.

Resting Echocardiography

Echocardiography utilizes ultrasound waves to assess cardiac function and structure. In patients with CAD, ischemic myocardial damage can be correlated with LV ejection fraction (LVEF) as well as regional wall motion abnormalities (RWMA). It may also help in identifying alternative causes of chest pain like heart failure, valvular abnormalities (like aortic stenosis) or cardiomyopathies. CMR is a relatively new alternative to echocardiography and can be helpful in defining cardiac anatomy and function, especially in patients with poor acoustic windows.

Exercise Electrocardiography

Exercise ECG (Ex-ECG) is a widely utilized initial diagnostic test for SCAD and CSA. It is often conducted using a Treadmill test (TMT). The presence of exercise induced ST-T changes or chest pain is an indicator of coronary obstruction. The Duke Treadmill Score can also be of valuable diagnostic and prognostic importance, and combines multiple predictors into one composite index. Ex-ECG has a sensitivity and specificity of 68% and 77% respectively, for detection of CAD.[3] However, the diagnostic performance of Ex-ECG is inferior as compared to diagnostic imaging tests. Hence, there may be limited benefit of doing Ex-ECG testing without the addition of imaging. Other limiting factors to its use include patients who are unable to reach target heart rate and the existence of baseline ECG abnormalities that might interfere with the interpretation of ST-T changes, for example, LBBB, paced rhythm, WPW syndrome, or baseline ST depression. Nevertheless, careful interpretation of Ex-ECG in selected patients may be of considerable benefit in resource limited conditions and non-availability of imaging.

Stress Echocardiography/Stress CMR

New or worsening RWMA or LV function during, immediately before, and after stress are the diagnostic outcomes in stress echo. This stress, that is, reaching a target heart rate, can be achieved using either exercise or pharmacologic agents. In patients who have difficulty in exercising, stress can be induced by pharmacological agents, of which dobutamine is most commonly used. Alternatives are vasodilators like adenosine, dipyridamole, and regadenoson.[4] Stress echocardiography has a sensitivity of 70–85% for exercise and 85–90% with pharmacological agents and specificity of 77–89% for exercise and 79–90% with pharmacological agents.[2]

Nuclear Myocardial Perfusion Imaging (MPI)

Nuclear MPI is an excellent noninvasive modality that provides assessment of stress induced reversible perfusion defect (RPD) in the myocardium. RPD refers to decrease in myocardial perfusion after stress, which may be exercise or pharmacologically induced. The sensitivity of stress nuclear MPI ranges from 82% to 88% for exercise and 88% to 91% for pharmacological MPI, whereas the specificity ranges from 70% to 88% for exercise and 75% to 90% for pharmacological stress nuclear MPI.[2] Stress CMR MPI can also be used to assess MPI.

Coronary CT Angiography (CCTA)

CCTA is a noninvasive diagnostic test using intravenous contrast to provide a highly accurate definition of coronary artery lumen. CCTA, along with functional noninvasive imaging like nuclear MPI or Stress Echo, is recommended as the initial diagnostic test for diagnosing CAD by guidelines.[1] CCTA's high sensitivity (values ranging 93–97%) and negative predictive value make it an excellent modality to rule out CAD.[2]

Invasive Testing

Invasive coronary angiography is considered the "gold standard" for diagnosis of CAD and may be used in cases where noninvasive tests are either inconclusive or indicate a high likelihood of severe IHD. It may also be used as an initial diagnostic test in patients with high clinical likelihood of CAD or angina with minimal exertion or symptoms unresponsive to medical therapy.[1]

Treatment

Management of CSA involves a multidisciplinary approach using general measures like lifestyle management, promotion of medical adherence, and support for managing lifestyle risk factors in conjunction with medical or interventional management. Lifestyle recommendations include smoking cessation, dietary changes, regular physical activity, maintaining a healthy weight, as well as management of risk factors like hypertension, diabetes, and hypercholesterolemia.

Medical Management

This is the mainstay of treatment in CSA for both symptomatic relief and coronary event prevention. The drugs used are mentioned in **Table 4**.

Revascularisation: Myocardial revascularization should be considered in patients of CSA who are symptomatic despite medical therapy. While there is no mortality benefit of revascularization in CSA,[5,6] some patients continue to be symptomatic despite optimal medical treatment. Such patients may benefit from revascularization, leading to improvement in quality of life and endurance with

TABLE 4 Medical management of chronic stable angina[1]

	Drug	***Indication***	***MoA***
Antiplatelet	Aspirin	All patients for even prevention	Irreversible COX-1 inhibition
	• Clopidogrel • Prasugrel • Ticagrelor	• Patients in whom DAPT is recommended (e.g., Post-PCI, history of PAD/TIA/Ischemic stroke) in combination with aspirin • Clopidogrel pretreatment in patients requiring PCI	Block the platelet $P2Y_{12}$ receptor, thus inhibiting platelet activation and preventing the development and propagation of arterial thrombus
Anti-anginal drugs	**Beta-blockers** *β_1 selective:* Metoprolol Bisoprolol Atenolol Non β_1 selective: Carvedilol	Patients with recent MI or chronic heart failure	Reduce heart rate, contractility, and atrioventricular conduction, thus reducing myocardial oxygen demand and time-to-angina onset during exercise
	Calcium Channel Blockers *DHP:* Nifedipine Amlodipine	• Hypertensive patients with angina usually with a beta-blocker • Exercise induced ischemia	DHP: Reduction in peripheral vascular resistance due to arterial vasodilation
	Non-DHP: Verapamil Diltiazem	All types of angina (exercise, vasospastic, or unstable), SVTs, and hypertension. Avoided in heart failure or in patients on beta-blockers	Decrease heart rate and myocardial inotropism
	Nitrates *Short acting:* Sublingual/Spray nitroglycerin	• Acute effort angina • Prophylaxis before physical activities	Dilatation of peripheral veins, with corresponding reductions in systemic vascular resistance, coronary blood flow redistribution, and preload
	Long acting: Isosorbide mononitrate Isosorbide dinitrate	Angina prophylaxis in cases where beta-blockers or non-DHP CCBs are contraindicated, poorly tolerated or provide insufficient symptom control	
	Ivabradine	2nd line drug	Decreases heart rate and consequently myocardial oxygen demand. No effect on contractility or BP
	Nicorandil	2nd line drug	Stimulates the ATP-sensitive potassium channels of the vascular smooth muscle resulting in systemic venous and coronary vasodilation
	Ranolazine	2nd line drug in patients with refractory angina	Inhibition of calcium overload in cardiomyocytes, without substantial changes in heart rate or BP
	Trimetazidine	2nd line drug	Targets deranged cellular energetics, particularly in ischemic myocardial tissue. Improves HbA1c and glycemia in diabetics
Lipid lowering drugs	*Statins:* Atorvastatin Rosuvastatin Simvastatin	Moderate to high dose statin therapy is indicated in all patients irrespective of LDL/Cholesterol levels	HMG-CoA reductase inhibition

Contd...

Contd...

	Drug	*Indication*	*MoA*
RAAS blockers	ACEI/ARB	Patients with coexisting hypertension, LVEF ≤40%, diabetes, or CKD	Reduce mortality, MI, stroke, and HF
	Spironolactone Eplerenone	Post-MI patients who: • Are on an ACEI/ARB plus beta-blocker, • EF ≤35%, and • DM or HF	Aldosterone receptor blockers

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; DAPT, dual anti-platelet therapy; DHP, dihydropyridine; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

reduced pharmacological and mental burden on the patients. Other indications of revascularization include multivessel disease, reduced ejection fraction, significant coronary artery stenosis, and large area of ischemia (>10% of LV). Revascularization may be achieved percutaneously or with CABG.

Conclusion

A patient with history of chest pain presents a diagnostic challenge for physicians because of the wide variety of causes and variability in presentation. Therefore, careful history taking and guideline dictated testing is essential for identifying possible cardiac causes without subjecting the patient to unnecessary testing and monetary burden.

While chronic stable angina often presents as a "stable" disease, it is important to carefully evaluate patients for progressive disease or risk of imminent ischemic event. Lifestyle modification and medical therapy are the mainstay of treatment of CSA. Revascularization may be considered in addition to these in selected patients with careful consideration.

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CHAPTER

36 Evaluation and Management of Chronic Stable Angina: Physicians Perspective

Vibhu Khanna, Ankush Gupta, Sanya Chhikara

Abstract

Chronic stable angina, while being a widely used term, is part of a much wider spectrum of chronic coronory syndromes (CCS). This spectrum consists of a dynamic and progressive disease course rather than a stable one, and hence requires thorough risk stratification and management. Risk stratification includes analyzing the demographics and clinical presentation of the patient to decide further management and testing. While ECG is the first step in making the diagnosis, there are several other modalities available to us today that supplement the ECG. These include both functional and anatomical imaging techniques like Echocardiography, Cardiac Magnetic Resonance Imaging, Coronary CT Angiography and various stress tests as well as invasive techniques like Percutaneous Coronary Angiography. The mainstay of treatment for CSA and CCS remains medical treatment. There are a variety of drug classes available that can be tailored depending on individual patient requirements. In addition to medical management, myocardial revascularization can also be attempted in specific cases using percutaneous coronary intervention or surgery.

Introduction

Coronary artery disease (CAD) or ischemic heart disease (IHD) covers a wide spectrum of syndromes that occur due to imbalance between myocardial oxygen demand and supply. The underlying pathology is most often the atherosclerotic involvement of the epicardial vessels, with varying degrees of obstruction. While the disease itself is chronic and progressive, presentation varies widely. Patients may be asymptomatic, present with a chronic stable course, or present acutely.

The most widely accepted classification of symptomatic patients includes stable coronary artery disease (SCAD) and acute coronary syndrome (ACS). Recent literature has recommended the use of the term chronic coronary syndrome (CCS) as an alternative to SCAD so as to retire the use of "Stable" and emphasize the progressive nature of the condition. The 2019 guidelines on CCS by the European Society of Cardiology (ESC) provide a comprehensive outlook on this new terminology as well as clinical practical guidelines on the approach and management of CCS.[1]

The ACS spectrum includes unstable angina, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). SCAD/CCS also includes a variety of presentations, one of which is chronic stable angina (CSA). This is an episodic clinical syndrome caused due to transient myocardial ischemia. CSA occurs due to gradual progression of atherosclerosis in the epicardial vessels or due to supply/demand mismatch caused increased myocardial oxygen demand.[2]

Presentation

Angina refers to chest pain/discomfort attributable to myocardial ischemia. Elements of history that are critical to making the diagnosis of angina include four main categories as shown in **Table 1**.

TABLE 1 Anginal chest pain

Category	*Description*
Location	Chest pain, often retrosternal, with radiation to the epigastrium, arms, shoulders, neck and throat, jaw, and rarely interscapular *Levine sign:* Placing a clenched fist over the precordium to describe the pain
Quality	Often described as: squeezing, pressure, constricting, strangling, burning, chest fullness, band-like sensation, ache, heavy weight on chest
Duration	Classically for 2–5 minutes but usually lasts not more than 20–30 minutes
Other exacerbating or relieving factors	Provoking factors: Increased myocardial oxygen demand due to exercise, cold, emotional stress, sexual intercourse, meals, or lying down Relieving factors: termination of the provoking factor or administration of nitroglycerin

TABLE 2 Clinical classification of angina

Typical	• Substernal chest discomfort with characteristic quality and duration • Provoked by exertion or emotional stress • Relieved by rest or nitroglycerin
Atypical	Meets two of the above characteristics
Non-cardiac	Meets one or none of the typical angina characteristics

Source: Knuuti, J. et al.[1]

Symptomology can be classified on the basis of history taking into typical, atypical, or noncardiac chest pain **(Table 2)**. Atypical presentation is often seen in women and elderly.

Angina can be graded into various classes depending on severity **(Table 3)**.

TABLE 3 Canadian Cardiovascular Society grading of effort angina

Grade	*Description of angina severity*	
I	Angina only with strenuous exertion	Presence of angina during strenuous, rapid, or prolonged ordinary activity (walking or climbing the stairs)
II	Angina with moderate exertion	Slight limitation of ordinary activities when they are performed rapidly, after meals, in cold, in wind, under emotional stress, or during the first few hours after waking up, but also walking uphill, climbing more than one flight of ordinary stairs at a normal pace, and in normal conditions
III	Angina with mild exertion	Having difficulties walking one or two blocks, or climbing one flight of stairs, at normal pace and conditions
IV	Angina at rest	No exertion needed to trigger angina

Evaluation

In addition to laboratory investigations and biochemical tests to identify possible causes of ischemia and risk factors, the diagnosis of CAD can be made with the help of the several modalities. The choice of diagnostic tests should made after giving due consideration to pretest probability and the patients be stratified as high-, intermediate-, and low-risk groups. For example, a young woman presenting with atypical angina would be classified as a low-risk patient and does not warrant additional testing for CAD if the baseline ECG is normal.

Resting Electrocardiography

While a normal ECG is often recorded, ongoing angina may be accompanied by dynamic ST segment changes making this modality crucial for diagnosis of CAD. Other findings that may be indicative of underlying pathology include evidence of previous infarction (Q waves or an R wave in V1 or persistent ST-T wave inversions), conduction blocks (LBBB, AV blocks), and LV hypertrophy.

Resting Echocardiography

Echocardiography utilizes ultrasound waves to assess cardiac function and structure. In patients with CAD, ischemic myocardial damage can be correlated with LV ejection fraction (LVEF) as well as regional wall motion abnormalities (RWMA). It may also help in identifying alternative causes of chest pain like heart failure, valvular abnormalities (like aortic stenosis) or cardiomyopathies. CMR is a relatively new alternative to echocardiography and can be helpful in defining cardiac anatomy and function, especially in patients with poor acoustic windows.

Exercise Electrocardiography

Exercise ECG (Ex-ECG) is a widely utilized initial diagnostic test for SCAD and CSA. It is often conducted using a Treadmill test (TMT). The presence of exercise induced ST-T changes or chest pain is an indicator of coronary obstruction. The Duke Treadmill Score can also be of valuable diagnostic and prognostic importance, and combines multiple predictors into one composite index. Ex-ECG has a sensitivity and specificity of 68% and 77% respectively, for detection of CAD.[3] However, the diagnostic performance of Ex-ECG is inferior as compared to diagnostic imaging tests. Hence, there may be limited benefit of doing Ex-ECG testing without the addition of imaging. Other limiting factors to its use include patients who are unable to reach target heart rate and the existence of baseline ECG abnormalities that might interfere with the interpretation of ST-T changes, for example, LBBB, paced rhythm, WPW syndrome, or baseline ST depression. Nevertheless, careful interpretation of Ex-ECG in selected patients may be of considerable benefit in resource limited conditions and non-availability of imaging.

Stress Echocardiography/Stress CMR

New or worsening RWMA or LV function during, immediately before, and after stress are the diagnostic outcomes in stress echo. This stress, that is, reaching a target heart rate, can be achieved using either exercise or pharmacologic agents. In patients who have difficulty in exercising, stress can be induced by pharmacological agents, of which dobutamine is most commonly used. Alternatives are vasodilators like adenosine, dipyridamole, and regadenoson.[4] Stress echocardiography has a sensitivity of 70–85% for exercise and 85–90% with pharmacological agents and specificity of 77–89% for exercise and 79–90% with pharmacological agents.[2]

Nuclear Myocardial Perfusion Imaging (MPI)

Nuclear MPI is an excellent noninvasive modality that provides assessment of stress induced reversible perfusion defect (RPD) in the myocardium. RPD refers to decrease in myocardial perfusion after stress, which may be exercise or pharmacologically induced. The sensitivity of stress nuclear MPI ranges from 82% to 88% for exercise and 88% to 91% for pharmacological MPI, whereas the specificity ranges from 70% to 88% for exercise and 75% to 90% for pharmacological stress nuclear MPI.[2] Stress CMR MPI can also be used to assess MPI.

Coronary CT Angiography (CCTA)

CCTA is a noninvasive diagnostic test using intravenous contrast to provide a highly accurate definition of coronary artery lumen. CCTA, along with functional noninvasive imaging like nuclear MPI or Stress Echo, is recommended as the initial diagnostic test for diagnosing CAD by guidelines.[1] CCTA's high sensitivity (values ranging 93–97%) and negative predictive value make it an excellent modality to rule out CAD.[2]

Invasive Testing

Invasive coronary angiography is considered the "gold standard" for diagnosis of CAD and may be used in cases where noninvasive tests are either inconclusive or indicate a high likelihood of severe IHD. It may also be used as an initial diagnostic test in patients with high clinical likelihood of CAD or angina with minimal exertion or symptoms unresponsive to medical therapy.[1]

Treatment

Management of CSA involves a multidisciplinary approach using general measures like lifestyle management, promotion of medical adherence, and support for managing lifestyle risk factors in conjunction with medical or interventional management. Lifestyle recommendations include smoking cessation, dietary changes, regular physical activity, maintaining a healthy weight, as well as management of risk factors like hypertension, diabetes, and hypercholesterolemia.

Medical Management

This is the mainstay of treatment in CSA for both symptomatic relief and coronary event prevention. The drugs used are mentioned in **Table 4**.

Revascularisation: Myocardial revascularization should be considered in patients of CSA who are symptomatic despite medical therapy. While there is no mortality benefit of revascularization in CSA,[5,6] some patients continue to be symptomatic despite optimal medical treatment. Such patients may benefit from revascularization, leading to improvement in quality of life and endurance with

TABLE 4 Medical management of chronic stable angina[1]

	Drug	***Indication***	***MoA***
Antiplatelet	Aspirin	All patients for even prevention	Irreversible COX-1 inhibition
	• Clopidogrel • Prasugrel • Ticagrelor	• Patients in whom DAPT is recommended (e.g., Post-PCI, history of PAD/TIA/Ischemic stroke) in combination with aspirin • Clopidogrel pretreatment in patients requiring PCI	Block the platelet $P2Y_{12}$ receptor, thus inhibiting platelet activation and preventing the development and propagation of arterial thrombus
Anti-anginal drugs	**Beta-blockers** *β_1 selective:* Metoprolol Bisoprolol Atenolol Non β_1 selective: Carvedilol	Patients with recent MI or chronic heart failure	Reduce heart rate, contractility, and atrioventricular conduction, thus reducing myocardial oxygen demand and time-to-angina onset during exercise
	Calcium Channel Blockers *DHP:* Nifedipine Amlodipine	• Hypertensive patients with angina usually with a beta-blocker • Exercise induced ischemia	DHP: Reduction in peripheral vascular resistance due to arterial vasodilation
	Non-DHP: Verapamil Diltiazem	All types of angina (exercise, vasospastic, or unstable), SVTs, and hypertension. Avoided in heart failure or in patients on beta-blockers	Decrease heart rate and myocardial inotropism
	Nitrates *Short acting:* Sublingual/Spray nitroglycerin	• Acute effort angina • Prophylaxis before physical activities	Dilatation of peripheral veins, with corresponding reductions in systemic vascular resistance, coronary blood flow redistribution, and preload
	Long acting: Isosorbide mononitrate Isosorbide dinitrate	Angina prophylaxis in cases where beta-blockers or non-DHP CCBs are contraindicated, poorly tolerated or provide insufficient symptom control	
	Ivabradine	2nd line drug	Decreases heart rate and consequently myocardial oxygen demand. No effect on contractility or BP
	Nicorandil	2nd line drug	Stimulates the ATP-sensitive potassium channels of the vascular smooth muscle resulting in systemic venous and coronary vasodilation
	Ranolazine	2nd line drug in patients with refractory angina	Inhibition of calcium overload in cardiomyocytes, without substantial changes in heart rate or BP
	Trimetazidine	2nd line drug	Targets deranged cellular energetics, particularly in ischemic myocardial tissue. Improves HbA1c and glycemia in diabetics
Lipid lowering drugs	*Statins:* Atorvastatin Rosuvastatin Simvastatin	Moderate to high dose statin therapy is indicated in all patients irrespective of LDL/Cholesterol levels	HMG-CoA reductase inhibition

Contd...

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	Drug	*Indication*	*MoA*
RAAS blockers	ACEI/ARB	Patients with coexisting hypertension, LVEF ≤40%, diabetes, or CKD	Reduce mortality, MI, stroke, and HF
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ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; DAPT, dual anti-platelet therapy; DHP, dihydropyridine; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

reduced pharmacological and mental burden on the patients. Other indications of revascularization include multivessel disease, reduced ejection fraction, significant coronary artery stenosis, and large area of ischemia (>10% of LV). Revascularization may be achieved percutaneously or with CABG.

Conclusion

A patient with history of chest pain presents a diagnostic challenge for physicians because of the wide variety of causes and variability in presentation. Therefore, careful history taking and guideline dictated testing is essential for identifying possible cardiac causes without subjecting the patient to unnecessary testing and monetary burden.

While chronic stable angina often presents as a "stable" disease, it is important to carefully evaluate patients for progressive disease or risk of imminent ischemic event. Lifestyle modification and medical therapy are the mainstay of treatment of CSA. Revascularization may be considered in addition to these in selected patients with careful consideration.

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CHAPTER

37 Optimal Therapy in ST-elevation Myocardial Infarction Patients Presenting after 24 hours

Gaurav Singhal, Dinesh Gautam, Sanjiv Maheshwari, Shekhar Kunal, Shyam Sunder

Abstract

The management of ST-elevation myocardial infarction (STEMI) has undergone a paradigm shift from the initial days of thrombolysis to balloon angioplasty and percutaneous coronary intervention (PCI) along with stenting. Patients with STEMI have a time dependent myocardial injury leading to grim outcomes in delayed presenters. It has been clearly demonstrated that there is a remarkable benefit in opening of the infarct-related artery in order to salvage the ischemic myocardium within 12 hours of chest pain. There are also evidences that patients do not get benefit who present after 12 hours of STEMI. However, if patient presented with ongoing chest pain, signs of cardiogenic shock, or persistent ST-elevation, patient should be managed actively by PCI and stenting.

Guidelines also say about routine pharmacoinvasive therapy in 3–24 hours of STEMI. Most of the clinical trials either based on fibrinolysis or PCI and stenting showed suboptimal outcome after 24 hours of STEMI. Asymptomatic and stable patients do not get benefit by any reperfusion intervention after 24 hours.

Case Scenario

Case 1: A 64-year-old never smoker diabetic female presented to the cardiology outpatient emergency with complaints of a single episode of retrosternal chest pain lasting for 15 minutes a day prior to her presentation. She had initially consulted a local physician who after a thorough evaluation had got an ECG done which he interpreted to be abnormal, and hence referred her to a cardiologist. However, since the patient thought her symptoms had abated, she planned a routine visit to a cardiologist in the nearby city the day later. On evaluation, the patient was pain free, hemodynamically stable with a 12-lead ECG showing anterior wall myocardial infarction. The Cardiologist now has to make a decision regarding the treatment of this late presenter of STEMI.

Case 2: A 59-year-old former smoker hypertensive male presented in the emergency department with symptoms of chest pain (angina in character) for the past 2 days. On examination, the patient was drowsy but arousable, with tachycardia (pulse: 120/min, regular), blood pressure of 80/50 mm Hg with bibasilar crepitations. ECG on presentation was suggestive of an extensive ST-segment elevation MI. 2D echocardiogram reported severely depressed left ventricular ejection fraction with akinesia of the anterior wall with mild mitral regurgitation and no evidence of pericardial effusion. The emergency physician consulted the cardiologist on call who has to decide the further treatment plan in this patient with STEMI, cardiogenic shock, and delayed presentation.

Both the clinical scenarios presented above are not something new but reflects the problems faced by clinicians in everyday practice.

Introduction

Management of ST-elevation myocardial infarction (STEMI) is based on timely reperfusion of the occluded vasculature in order to salvage the ischemic myocardium.[1] However, a significant number of patients present late (beyond 12–24 hours) and constitute what we know as "late presenters." Data from the Western countries reveal that nearly 11% patients in the GRACE registry[2] and up to 40% patients in the TETAMI study[3] were classified as late presenters. However, the data from India is somewhat limited and showed that one third to half of STEMI patients presented to non percutaneous coronary intervention (PCI) centers and managed there conservatively and then referred to higher center.[4] A study from Lucknow (single center) is showing nearly a third of their cases were late presenters.[5] Patients presented after 24 hours of STEMI has different spectrum of presentation including totally asymptomatic to mild symptoms to cardiogenic shock (CS). Late presenters with CS constitute a subset of patients with extensive myocardial damage and poor clinical outcomes. In a another single center study from India, the in-hospital mortality rates of late presenters with CS was as high as 42.9%.[6] Hence, prompt identification of STEMI followed by urgent revascularization should be the goal of therapy. These late presenters may have completed occluded artery or may have patent infract-related artery (IRA) or severe stenosis in one, two, and three vessel disease. They can present with mechanical complication like rupture chordae, ventricular septal perforation, acute mitral regurgitation (MR), etc.

So the management of such a spectrum of presentation cannot be done in one way. Treatment strategy in such cases should be individualized with use of existing, but limited guidelines and experience. Many studies have suggested to perform primary PCI in late presenters with hemodynamic or electrical instability irrespective of time of presentation. But guidelines are not clear regarding the management of stable late presenters and there is an unmet need for well-planned clinical trials in order to have a clear understanding of the treatment algorithm in these patients. In this chapter we have discussed about management of patients presented after 24 hours of STEMI.

Reasons for Late Presentation

Multiple reasons can be laid down for late presentation in STEMI patients, which include:

- Lack of awareness or denial of the symptoms or presence of atypical symptoms
- Failure to or refusal to seek medical attention or use of alternative system of medicine
- Poor access to health care
- Incorrect diagnosis including atypical presentation
- Presentation in a non-PCI hospital[7]
- Financial issues

Proposed mechanism underlying the beneficial effects of late reperfusion: Clinical trials and meta-analysis showed the beneficial effects of reperfusion up to 12 hours from the onset of MI. After that there is no benefit to open the artery because of formation of mature thrombus and myocardial necrosis. However, this is not applicable to every patient.

There are some factors like presence of collaterals, ischemic preconditioning, subtotal occlusion, and spontaneous reperfusion, which delay the progression of infract size and prevent ventricular dysfunction.

Therapy in patients with STEMI presented after 24 hours: The goal of early management of STEMI by thrombolysis or by PCI with stent is to restore the myocardial perfusion, reduce microvascular damage, to limit infract size, and reduce mortality. It has been seen that spontaneous recanalization of occluded IRA occur in one third of patients started at 12–24 hours.[1] This delayed spontaneous reperfusion may enhance left ventricular function because it reduces infract size, prevents ventricular remodeling. In addition, interventions like thrombolysis or PCI accelerates the healing of infract. The efficacy of pharmacological agents decreases as coronary thrombus mature overtime. For every 30 minute delay in reperfusion, there is increase 8% relative risk of mortality per year.[2]

- *Thrombolysis in patients presented after 24 hours of STEMI:* Thrombolysis is based on clot lysis and establishment of the patency of the IRA leading to the salvage of the ischemic myocardium. Most of the landmark trials[8-10] on fibrinolysis in STEMI revealed that a majority of benefit is seen in patients who present early and the role of thrombolysis is limited to patients presenting within 12 hours. The meta-analysis of nine major trials (FTT Collaborative Group meta-analysis)[11] evaluated the role of fibrinolysis in 58,600 patients presenting with STEMI. The authors reported a significant decrease in mortality among patients

presenting early (up to 12 hours) post-STEMI, but no benefit in late presenters.

- *Reperfusion PCI in patients beyond 24 hours of STEMI:* Primary PCI is considered as the treatment of choice in patients with STEMI presenting within 12 hours of symptom onset. However, if patients have ongoing pain, persistent ST elevation, CS, decision of either thrombolysis or PCI should be taken accordingly and it is case dependent. A multi-centric RCT Occluded Artery Trial (OAT)[12]—involving 2,166 stable patients with total occlusion of the IRA 3–28 days post an episode of acute MI along with the presence of a high-risk criterion (i.e., LVEF <50% or a proximal occlusion of a coronary artery). The primary outcome was a composite of death, re-infarction or NYHA class IV heart failure (HF) with the exclusion criteria being (a) CS, (b) NYHA class III/IV HF, and (c) severe ischemia or left main involvement or triple vessel disease. The primary endpoint was achieved among 17.2% patients in the PCI group as compared to 15.6% of the medical therapy group with a higher re-infarction rate in the PCI group. In addition, there was no difference in event-free survival between groups with a median follow-up of 3.2 years. This trial showed no benefit of routine PCI in stable late presenters with STEMI.

  Barve II study[13] enrolled patients who were presented more than 12 hours but without any chest pain. There was significant reduction in infract size in the invasive group compared to medical therapy group but no mortality benefit. Four-year results of this study showed mortality benefit in PCI group but results of this study cannot be applied to all patients because of limitations of this study. A meta-analysis (Abbate et al.[14]) evaluated 10 RCTs comparing PCI of IRA with medical therapy in patients with delayed presentation (>12 hours–60 days) following acute MI. The PCI arm had significantly lower mortality as compared to the medical therapy arm [PCI arm: 112 (6.3%) vs. medical therapy: 149 (8.4%); OR: 0.49; P=0.03]. In addition, favorable benefits were reported in terms of significantly improved LVEF in PCI arm (4.4% increase post PCI; P=0.009).

Risk Stratification in Late Presenters after STEMI

- *Clinical:* In patients with late presentation following STEMI, clinical parameters pointing to a high risk include hemodynamic or electrical instability, and hence prompt revascularization should be performed in these patients.
- *LV ejection fraction (LVEF):* Most of the guidelines recommend assessment of resting LVEF as an integral component of risk stratification in late presenters.[15] Multiple imaging modalities including echocardiogram or cardiac MRI can be used to determine the LVEF. There is an increased cardiac mortality in patients with LVEF below 40%.[16]
- *Myocardial viability:* In clinically stable late (>72 hours) presenters myocardial viability should be assessed before a decision to revascularize is taken. A spectrum of imaging modalities, such as Thallium-201 or Technetium-99m SPECT, FDG-PET, Dobutamine stress echo (DSE), Contrast-enhanced cardiac MRI, and Dobutamine stress cardiac MRI, can be used to assess myocardial viability. The Viability-Guided Angioplasty after Acute Myocardial Infarction (VIAMI)[17] trial showed that PCI was associated with a significant reduction in ischemic event rates in patients with viability reported on low-dose DSE performed 48–72 hours post-STEMI. A decision to revascularize the ischemic myocardium should be made based on the presence of viability. CMR can very well characterize acute myocardial injury and determine the infarct size, hence has become the imaging modality of choice for the assessment of patients post-STEMI.
- *Stress testing:* Exercise testing in late presenters of STEMI is useful in determining the exercise capacity, identifying persistent ischemia as well as for future risk stratification. This has been proven in the DANAMI-I[18] and the SWISSI-II[19] trials where a beneficial effect was seen post PCI in late presenters with evidence of ischemia on stress testing. Stress testing can be combined with an imaging modality to identify high-risk patients who would benefit from delayed revascularization.

Recommendations for management of "unstable" late presenters: This subgroup of patients (clinical scenario: Case B) present with ongoing angina, CS or electrical instability following acute MI. These subgroup of patients requires the highest attention and timely revascularization in these patients, often alter the natural course of the disease.[20] Most of the guidelines[20,21] are in unison regarding the recommendations in these group of patients.

Recommendations for management of "stable" late presenters: The clinical scenario in the initial part of the chapter regarding Case A reflects the problems faced by clinicians and interventionists in deciding the tricky approach regarding revascularization in these asymptomatic/"clinically stable" late presenters following STEMI. The 2013 ACCF/AHA STEMI[20] guidelines clearly states that "Delayed PCI of a totally occluded infarct artery greater than 24 hours after STEMI should not be performed in asymptomatic patients with 1- or 2-vessel disease, if they are hemodynamically and electrically stable and do not have evidence of severe ischemia" (Class: III, LOE: B). The guidelines defined clinical stability as "absence of low cardiac output or hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia."

The 2017 ESC guidelines on STEMI[21] management states that "In asymptomatic patients, routine PCI of an occluded IRA >48 hours after onset of STEMI is not indicated" (Class: III, LOE: A). A more practical approach in this subgroup of patients would be coronary angiogram with an intent to revascularize in clinically stable early "late presenters" (<48 hours), while in patients presenting beyond 48 hours, stress or viability testing should be performed followed by a decision to revascularize.

Indian Guidelines: The 2017 Cardiological Society of India position statement[22] for the management of STEMI in India states that in late presenters of STEMI (>24 hours) with evidence of shock, pulmonary edema, electrical instability or ongoing ischemia, coronary angiogram with an intent to revascularize should be done as soon as possible. In addition, clinically stable patients with diabetes and LVEF below 40% should undergo a coronary angiogram with PCI if subtotal occlusion is there. In cases of total occlusion, myocardial viability needs to be established prior to PCI. Hemodynamically stable patients without high-risk features should undergo a stress test prior to discharge based on which a decision to revascularize should be made. Very late presenters (>72 hours) with a total occlusion and clinically stable do not have significant improvement following revascularization as seen in the OAT trial.

Conclusion

Asymptomatic STEMI patients after 24 hours should be managed conservatively, and intervention can only be done when signs and symptoms of ischemia appears. If there are complications like CS, ongoing pain, and other signs of ischemia, then intervention should be done to restore the flow. Further availability of various stress tests and myocardial viability tests would help in management of such late presenters.

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CHAPTER

38 Management of Heart Failure in 2021—What Physician Must Know?

Alok Kumar Singh

Abstract

Heart failure (HF) is the final common pathway for many diseases that affect the cardiovascular system, if left untreated in the early course of disease. The lifetime risk for developing HF is about 20% for both men and women. Increasing prevalence of cardiac risk factors, such as hypertension, diabetes, and dyslipidemia as well as improved survival of patients with acute cardiovascular diseases, have resulted in HF becoming a major public health problem, across the world. The fundamental hemodynamic changes present in HF are increased pulmonary capillary wedge pressure, increased central venous pressure, and reduced cardiac output. Fluid and salt restriction (< 5 gm) is indicated in congested symptomatic HF patients in spite of diuretic therapy. RAS inhibition, beta blockade, and mineralocorticoid receptor antagonists (MRAs) are the main pillars of medical therapy of HF. At present angiotensin receptor neprilysin inhibitor (ARNI) (sacubitril/valsartan) is preferred over isolated RAS inhibition. Cardiac resynchronization therapy (CRT) and implantable cardiac defibrillator (ICD) should be utilized judicially at proper time in the disease course of HF. LV-assist devices should be considered in refractory heart failure as bridge to transplantation or as destination therapy.

Introduction

Heart failure (HF) is the final common pathway for many diseases that affect the cardiovascular system, if left untreated in the early course of disease. The lifetime risk for developing HF is about 20% for both men and women. Increasing prevalence of cardiac risk factors, such as hypertension, diabetes, and dyslipidemia, as well as improved survival of patients with acute cardiovascular diseases, have resulted in HF becoming a major public health problem, across the world. There is no exact data on HF burden in India is available at present, because of the absence of disease surveillance systems in India. A rough estimate[1] on the community-level prevalence of HF in the adult population in India is about 1%. As per the European Society of Cardiology, HF is best defined as "A clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress." In this chapter we restrict our discussion in the context of chronic HF only.

Pathophysiological Basis of Heart Failure

The three fundamental hemodynamic changes present in HF are increased pulmonary capillary wedge pressure, increased central venous pressure, and reduced cardiac output. Lung congestion, secondary to increase left sided cardiac filling pressure, responsible for breathlessness at rest or exertion, paroxysmal nocturnal dyspnea, orthopnea, or rales in lung during chest examination. Increased CVP secondary to left sided heart disease, or isolated right heart disease, leads to systemic congestion, leads to

clinical features such as ascites, anorexia (secondary to gut congestion), elevation of liver enzyme (sometimes can mimic viral hepatitis) and generalized body swelling. Reduced forward cardiac output secondary to ventricular dysfunction occurs relatively late in the natural history of chronic HF, although in acute HF it may occur in minute to hours. In chronic HF, as the ejection fraction decreases, heart increases stroke volume by increasing end diastolic volume of the left ventricle, until or unless ejection fraction very low (<20%), so this may be the reason, why some patients are relatively asymptomatic for longer time in chronic HF with left ventricular with systolic dysfunction.

Chronic maladaptive activation of sympathetic nervous system (SNS) and renin angiotensin system (RAS) in HF leads to ventricular remodeling. The complex alterations in the ventricle in response to various mechanical and neurohormonal stressors on the heart, resulting in alterations in volume, wall thickness and/or shape (from ellipsoid to spherical in case of left ventricle) is defined as ventricular remodeling. As a result of myocardial stretch in HF, the gene coding for brain natriuretic peptide (BNP) is activated and the prohormone pro-BNP is produced. This is cleaved to the biologically active BNP and the biologically inert but stable NT-proBNP. BNP induces natriuresis, vasodilatation, and vascular smooth muscle relaxation, because of their sympatho-inhibitory action. These three systems (SNS, RAS, and NP) are the targets of modern medical therapy, which have changed the natural history of HF by inducing reverse remodeling.

Classification of Heart Failure

HF can be classified in multiple ways,[2-5] depending on left ventricular ejection fraction **(Table 1)**, depending on presentation **(Table 2)**, and functional class **(Table 3)**. These classifications are important for management strategies as well as prognostic point of view. The NYHA functional classification has been used to describe the severity of symptoms and exercise intolerance. The symptom stages are clearly related survival, yet they correlate poorly with LV function. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) classification[3,4] describes stages of HF development based on structural changes and symptoms have been described in **Table 4**. The ACC/AHA staging is invaluable in holistic management of HF, from prevention to appropriate intervention at appropriate time.

TABLE 1 The classification of heart failure based on LVEF

Type of HF	*Characteristics*
Heart failure with reduced ejection fraction (HFrEF)	• Symptom ± sign of heart failure • LVEF < 40%
Heart failure with preserved ejection fraction (HFpEF)	• Symptom ± sign of heart failure • LVEF > 49% • Elevated level of natriuretic peptide* • Minimum one additional echo criteria – Relevant structural heart disease such as LVH and LAE – Evidence of diastolic dysfunction
Heart failure with midrange ejection fraction (HFmrEF)	• Symptom ± sign of heart failure • LVEF 40–49% • Elevated level of natriuretic peptide* • Minimum one additional echo criteria – Relevant structural heart disease such as LVH and LAE – Evidence of diastolic dysfunction

*BNP—35 pg/mL or NT-proBNP > 125 pg/mL.

TABLE 2 The classification of heart failure based on time course

Type of heart failure	*Definition*
Acute decompensated heart failure (ADHF)	Term for patients presenting acutely with HF, which can be defined as "the sudden onset of the signs or symptoms of heart failure requiring unplanned hospitalization, or emergency room visits, or unplanned office consultation"
Chronic heart failure	Term for patients presenting with insidious onset of symptom and signs of heart failure
A new-onset/de novo HF	Term used for HF patients, presenting with symptoms of heart failure in an acute or sub-acute (gradual) fashion for the first time
Stable heart failure	A treated patient of heart failure with unchanged symptomatic status for at least 1 month is said to be "stable"
Advanced HF	Term refers to patients with severe cardiac dysfunction, recurrent decompensation, and severe symptoms despite optimal standard medical therapy
Asymptomatic LV systolic dysfunction	Term used for an asymptomatic patient with reduced LVEF who never exhibited typical signs and symptoms of HF

TABLE 3 The NYHA classification of heart failure

NYHA class	*Description*
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF
IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

TABLE 4 The ACC/AHA staging of heart failure

Stages	*Description*	*Example*
A	At high risk for HF but without structural heart disease or symptoms of HF	Risk factors for HF like hypertension, diabetes, and dyslipidemia
B	Structural heart disease but without signs or symptoms of HF	Asymptomatic patient with structural heart disease such LV hypertrophy and LV dysfunction
C	Structural heart disease with prior or current symptoms of HF	Current or prior symptomatic (NYHA classes I to IV) patients with objective evidence of cardiac dysfunction
D	Refractory HF requiring specialized interventions	End stage HF—unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest

Diagnosis of Heart Failure

Clinical Features

Breathlessness on exertion or at rest, orthopnea, and paroxysmal nocturnal dyspnea may be the presenting symptom of HF. Anorexia, generalized swelling of body, fatigue, oliguria, and altered sensorium may be the presenting feature of advanced HF. S3, S4, and murmur on cardiac auscultation may be present in HF patients. Presence of rales (usually absent in chronic HF) may be present on lung examination. Presence of raised jugular venous pressure, hepatomegaly, anasarca, and ascites may point toward the diagnosis of HF. ECG is must in all cases of HF. ECG may give clue to the etiology of HF. Perfectly normal ECG is highly unlikely in HF, although some time may be present. If history, physical examination, and ECG are suggestive of HF, then echo should be done to establish the diagnosis and classification of HF. If echo is not available at site, then assessment of cardiac biomarker followed by echocardiography can be done. For patients presenting with chronic HF, the optimum exclusion cut-off point is 125 pg/mL for NT-proBNP and 35 pg/mL for BNP, whereas for patients presenting with acute HF, the ideal exclusion cut-off point is proposed to be 300 pg/mL for NT-proBNP and 100 pg/mL for BNP. It needs to be understand that the negative predictive value of BNP/NT-pro-BNP is very high (0.94–0.98), while the positive predictive value is low (0.64–0.67), making them a good test to rule out HF but a poor tool to establish diagnosis.

Echo is invaluable in diagnosing specific valvular pathologies, pericardial diseases, and specific type of cardiomyopathies. Assessment of diastolic dysfunction (E/A ratio, E/e, Left Atrial volume, LV mass) is must for establishing the diagnosis of HFmrEF and HFpEF.

Presence of pulmonary artery hypertension is indicative of poor prognosis in HF, so it should be looked for in every case of HF.

In select cases CT or invasive coronary angiography is recommended for ruling in or out coronary artery disease. Magnetic resonance imaging is also having important role in establishing the diagnosis of specific cardiomyopathies and determining the viability in ischemic cardiomyopathy before proceeding to revascularization. Complete blood count (Hb, TC, DLC, and ESR), serum electrolyte, and serum creatinine, liver function test, and thyroid profile should be done in all cases of HF.

Treatment of Heart Failure

Fluid and salt restriction (<5 gm) is indicated in congested symptomatic HF patients, in spite of diuretic therapy. Exercise should be encouraged in early phases of HF, but in

advance stage it may not be advised. If any specific etiology is responsible for HF should be treated accordingly, such as valvular hear diseases by valvular intervention, ischemic heart disease by revascularization and pericardiectomy for constrictive pericarditis. Diuretics are recommended to relieve lung as well as systematic congestion and symptomatic benefit only. No specific therapy have been found to change the natural history of HF in HFpEF population till date, so only symptomatic treatment and associated comorbidities such as hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease (COPD), and rhythm disorders such as atrial fibrillation should be treated. The major objective of therapy in HFrEF is to improve functional class, symptomatic status, and prevent recurrent hospitalizations and reduce mortality. It is recommended to treat HFrEF patients with ACE inhibitor [or angiotensin receptor blocker (ARB)] and beta blockers to the maximum tolerated dosages. If patient is still symptomatic and LVEF less than 35%, then mineralocorticoid receptor antagonists (MRAs) should be added. Once MRAs and angiotensin converting enzyme) inhibitors (ACEIs) or ARB are combined, then close monitoring of serum potassium and creatinine

TABLE 5 All-cause mortality reduced by treatments recommended in HFrEF

Therapy	*Number needed to treat (For 5 years)*
Beta blocker	8
ARNI	11 (compared to placebo), 21 (compared to ACEI)
MRA	15
ACE	18
ARB	24
ICD	14
CRT	14

TABLE 6 Dosages and side effects of drugs approved in heart failure

Drug class	*Dosages*	*Side effects*
Beta blockers	Metoprolol succinate (12.5–200 mg od) Carvedilol (3.125–25 mg bd) Bisoprolol (1.25–10 mg od)	Hypotension, Bradycardia, AV-block, Fatigue
ACEIs	Enalapril (2.5–20 mg bd) Ramipril (2.5–10 mg od) Captopril (6.25–50 mg tds) Lisinopril (2.5–35 mg od)	Cough, dizziness, angioedema, hypotension, renal impairment, and hyperkalemia
ARBs	Losartan (50–150 mg od) Valsartan (40–160 mg bd) Candesartan (4–32 mg od)	Same as above
ARNI	Sacubitril/Valsartan (49/51–97/103 mg bd)	Same as above
MRAs	Spironolactone (25–50 mg od) Eplerenone (25–50 mg od)	Hyperkalemia, Gynecomastia (more common with spironolactone)
If channel inhibitor	Ivabradine (5–7.5 mg bd)	Bradycardia, development of AF and rarely torsade ds pointes, visual symptoms (phosphenes)
Digoxin	(125 mg od to .25 mg od)	Nausea, vomiting, anorexia, arrhythmias (ectopic and re-entrant tachycardias with AV block), visual disturbances, disorientation, and confusion
Hydralazine and isosorbide dinitrate	(25/20–75/40 mg tds)	Headache, dizziness, and non-specific gastrointestinal complaints
Loop diuretics	Furosemide (20–240 mg od) Bumetanide (0.5–5 mg od) Torsemide (5–200 mg od)	Hypokalemia, fluid depletion, azotemia, ototoxicity
Thiazides	Hydrochlorothiazide (12.5–100 mg od) Metolazone (2.5–10 mg od) Indapamide (2.5–5 mg od)	Hyperuricemia, hyponatremia, hypokalemia, hypomagnesemia, hypercalcemia, and fatigue

is recommended, because both can increase serum potassium. If HF patient able to tolerate ACEIs or ARB, and still symptomatic and LVEF less than 35%, then ACEIs or ARB should be replaced with angiotensin receptor neprilysin inhibitor (ARNI) (Sacubitril/valsartan). ARNI should be started after 36 hour of stopping ACEIs because of increased risk of angioedema, if both are combined together. If patient is still not improving and in sinus rhythm and heart rate greater than 70, then channel current inhibitor (ivabradine) should be added. After all pharmacological treatment exhausted (3–6 months of optimal medical therapy), patient still symptomatic, LVEF less than 35%, QRS duration greater than 130 milisecond and LBB morphology, then cardiac resynchronization therapy (CRT) is recommended. If there is a history of ventricular tachycardia or fibrillation or patient LVEF is less than 35% despite optimal medical therapy, then implantation of implantable cardiac defibrillator (ICD) is recommended to prevent sudden cardiac death. As evidenced by recent analysis, among all guideline directed therapies, beta blockers are most effective in reducing mortality and promoting reverse remodeling in HF[6] **(Table 5)**. The dosages and side effect of drugs recommended in HF are summarized in **Table 6**. If patient is still symptomatic and refractory to all described therapies, then patient should be referred to specialized center for ventricular-assist devices or cardiac transplantation. Based on the result of DAPA-HF trial[7] of the US FDA dapagliflozin (SGLT-2 inhibitor) approved for the treatment symptomatic HF of LVEF 40%. Drugs known to adversely affect the clinical status of patients of HFrEF should be avoided, whenever possible (e.g., most antiarrhythmic drugs), most calcium channel blocking drugs (except amlodipine), NSAIDs, or TZDs (pioglitazones).

Conclusion

HF is the final common destination of untreated cardiovascular diseases. As the population is aging worldwide, prevalence of HF is increasing. RAS inhibition and beta blockade is the main pillar of medical therapy of HF. At present ARNI is preferred over isolated RAS inhibition. CRT and ICD should be utilized judicially at proper time in the disease course of HF. LV-assist devices should be considered in refractory heart failure as bridge to transplantation or as destination therapy.

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CHAPTER

39 Atherosclerotic Cardiovascular Prevention in 2020: Consideration of Gray Areas and Ways to Remedy It

Amarendra Kumar Sinha, Ashish Sinha, Nitin Kumar Sinha

Abstract

The most important way to prevent atherosclerotic vascular disease, heart failure, and atrial fibrillation is to promote healthy lifestyle throughout life. Coronary artery disease (CAD) risk equivalents, like atherosclerotic changes in carotid artery, peripheral artery, and abdominal aortic aneurysm, should receive serious attention to prevent established atherosclerotic cardiovascular disease. A diligent search should be made to detect apparent risk and silent risk factors like coronary artery calcium (CAC) and inflammatory status (increased hs-CRP, IL-6, especially associated with visceral adiposity, etc.). Guidelines should be shorter, crisp, and user friendly. A team-based care approach is an effective strategy for prevention of cardiovascular disease. Health literacy is essential for implementation of guideline.

Introduction[1]

In the developed nations and to some extent also in developing nation, coronary artery disease (CAD) is a major cause of death and disability. Although mortality rates related to CAD have continued to decline over past years, CAD remains accountable for about one third of all deaths over the age of 35 years. Majority of CAD are due to atherosclerosis (ASCVD), which involves other major large arteries like cerebral and peripheral artery. Obviously it has huge impact on finances and health care system.

Most Americans, who have had myocardial infarction (MI), had unfavorable level of at least 1 Cardiovascular (CV) risk factor before their ASVCD event. In 2010, American Heart Association (AHA) defined "ideal CV health" and referred to as "Life's simple 7".

Risk Factors and CAD Risk Equivalents[1]

CAD Risk Equivalents

Some individuals without known CAD have risk of major CV events that is equivalent to that of patient with established CAD. They should be managed aggressively like patient of established CAD. They are:

- Atherosclerotic disease status in carotid artery, peripheral artery, abdominal aortic aneurysm. In such situation 10 years risk of developing CAD exceeds 20%.
- Diabetes mellitus (DM), insulin resistance, hyperinsulinemia, and elevated blood sugar are associated with ASCVD. The all-cause mortality risk associate with DM is comparable to all-cause mortality risk associated with prior MI.
- Hyperglycemia without overt DM correlates with CV risk.
- Chronic kidney disease (CKD) even with mild to moderate renal dysfunction is associated with substantial increase in CAD risk.

Traditional Risk Factors for Atherosclerosis

- High blood pressure
- High total cholesterol
- High LDL cholesterol

- Low HDL cholesterol
- Hypertriglyceridemia
- Increased non-HDL cholesterol
- Increased lipoprotein (a)
- Increased apolipoprotein-B
- Increased apolipoprotein C-III
- Small dense LDL particles
- Glucose intolerance
- Smoking
- Family history of premature CAD
- High BMI
- Age
- Physical inactivity
- Obesity
- Psychosocial factors, (depression, anger, stress, and other factors). They lead to premature CAD, acute coronary syndrome (ACS), and sudden cardiac death (SCD).

Novel and Emerging Risk Factors

- High Hs-CRP (high-sensitivity C-reactive protein)
- High IL-6 (interleukin) and membrane bound IL-6
- Increased level of leukocyte enzyme myeloperoxidase
- HIV-positive status
- Mediastinal and chest wall radiation
- Metabolic syndrome
- Microalbuminuria
- Remnant lipoproteins

Novel risk factors like Hs-CRP, IL-6, leukocyte enzyme myeloperoxidase denote inflammatory changes in atheroma formation and progression. They have opened new pathway for treatment. The association of microalbuminuria and CAD is established but mechanism remains unclear.

Genetic susceptibility to CAD is seen in 40–60% cases. Currently 33 genetic variants have been identified, which increase patients risk for CAD.

Borderline CAD Risk[2]

Among adults with 10 years borderline risk (5% to <7.5%) and intermediate risk (>7.5% to <20%) risk, one may consider searching additional individual risk-enhancing clinical factors. This will help to revise the 10 years ASCVD risk estimate.

Risk-enhancing Factors[2]

- Family history of premature ASCVD (male: <55 years; female: <65 years)
- Primary hypercholesterolemia
- Metabolic syndrome (MS)
- Chronic kidney disease (CKD)—eGFR 15–59 mL/min/1.73 m^2
- Chronic inflammatory conditions. Example, psoriasis, RA (rheumatoid arthritis), lupus, or HIV/AIDS
- History of premature menopause (before 40 years) or preeclampsia
- High-risk ethnicity. Example, South Asian Ancestry
- Lipid/Biomarkers associated with increased ASCVD risk
  - Persistently elevated LDLC > 160 mg/dL
  - Persistently elevated primary hypertriglyceridemia >175 mg%—non fasting
  - High Hs-CRP (≥2.0 mg/L)
  - High lipoprotein (a) (≥50 mg/dL)
  - Elevated apolipoprotein B (≥130 mg/dL)
  - ABI (<0.9)

Risk Assessment and Detection of Asymptomatic Atherosclerosis

Status of CAC[2]

Coronary artery calcium (CAC) detection by high-resolution computer tomography (CT) or CT angiography. CT angiography is burning topic, as these have additional power of treating ASCVD.

Recent evidences support that measurement of CAC is predictive of coronary heart disease death or MI at 3–5 years. Current evidence also suggests that use of CAC is independently predictive of outcome over and above traditional cardiac risk factors.

CAC scoring has been evaluated as noninvasive diagnostic technique for detecting obstructive CAD. CAC may be used as an effective filter before undertaking invasive diagnostic procedure. Score less than 100 are associated with low probability. No calcium means zero score.

Use of CAC score are not recommended for follow-up of lesion due to cost and radiation hazard.

Atheroma Progression, Regression, Vulnerable Plaque: Impact of Serial CAC and Statin[3-5]

A trend toward increasing atheroma calcification following statins use has been reported. Aside from lipid regression within plaques following long-term potent statin therapy, statin mediated atheroma calcification may improve plaque stability.

Recent research suggests that plaques containing low proportion of microcalcifications actually rupture. With more confluent and dense plaque calcification, plaque stability is improved due to low-wall stress. Cardiac CT angiography (CCTA) provides direct visualization of vessel wall, thus providing good assessment of the atherosclerotic burden. The goal is to identify vulnerable plaque, responsible for most ACS. Plaque measured by wall component is classified in Hounsfield Units (HU), as soft or lipid rich (30–60 HU), fibrous (70–120 HU), or calcified (>350 HU).

In a study of 1,059 patients, who underwent CCTA, the investigators found that those with plaques showing positive remodeling and low attenuation on CCTA were at higher risk for ACS during 27-month mean follow-up compared with patients without these characteristic.

Atherosclerosis, Inflammation, and Thrombosis

Inflammation most likely plays a causal role in plaque rupture. Vulnerable plaque has thin cap fibroatheroma (TCFA). These have very high density of macrophages (approximately 14%) in contrast to stable fibroatheroma (approximately 2.0% macrophages). These can be assessed by CCTA.[6]

Detection of inflammatory markers as discussed earlier has opened a new avenue for treating atherosclerosis and preventing impending thrombosis. Two trials are worth mentioning:

- *The Cantos Trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study)*:[7] Inclusion criteria: History of MI, High Hs-CRP (≥2), Duration of study 3.7 years, Targeted level of Hs-CRP, IL-6, IL-18, IL-B. Dose of 150 mg daily was effective in preventing adverse cardiac event after median of 3.7 years with hazard ratio 0.68. Mechanism of benefit is due to decrease in Hs-CRP likely. Could not be used in practice due to cost, duration, and complication of infection.
- *Colcot Trial*:[8] Efficacy and safety of low dose colchicines after MI. A small dose of 0.5 mg daily was used in recent MI. Endpoint was composite death from CVS cause, MI, stroke, angina, cardiac arrest. Result was 5.5% in treated group versus 7.1% in placebo, with hazard ratio of 0.77.

How should we Approach Preventing ASCVD?[2]

ACC/AHA guideline (2019) on the primary prevention of CVD aims to promote the delivery of patient-centered care:

- Team based care approach for control of risk factors associated with ASCVD. (COR:1).
- Shared decision, after discussion about best strategy to reduce ASCVD risk (COR:1).
- Social determinants of health will guide better implementation of plan for prevention of ASCVD.

Assessment of Cardiovascular Risk

Tool is available online at ACC/AHA site:

- For adult 40–75 years—should routinely assess traditional CV risk factor and calculate 10 years risk of ASCVD.
- For adults 20–39 years—Assess risk every 4–6 years.
- In adult at borderline risk (5% to <7.5%) or in intermediate risk (≥7.5% to <20% 10 years risk) assess risk *enhancing factors* to guide about preventive therapy (like statin).
- In adult with intermediate risk or in borderline risk, if decision about statin remains uncertain, measure CAC for clarification (Class IIa).

Assessment of Risk Factors

- One should look for all traditional and emerging risk factors in each cases but the clinical scenario will guide the situation.
- At the same time risk-enhancing factors should be searched and assessed.

Assessment of Social Determinants of Health

This will guide us about implementation of preventive strategy in each case at grass root level:

- Psychological stressors

- Health literacy
- Social barriers of heart healthy diets
- Neighborhood environment. Facility of exercise
- Concept about health, body weight, and obesity
- Concept of lifestyle counseling for weight loss, sleep, psychosocial stressors
- Job status, family life, and mutual relation, history of depression
- Personal habits, viz. tobacco, alcohol
- Diabetes mellitus—controlled on diet, exercise of drugs? Education to maintain sugar level
- Hypertension—controlled on drug? Does he understand benefit of low-sodium diet, exercise, and proper sleep

It cannot be overemphasized that health literacy will go long way to prevent ASCVD.

Detection of Inflammatory Status and Asymptomatic Cases of ASCVD

This has already been discussed earlier in this chapter. It is very important to prevent ACS. This concept is the need of hour and is oriented toward saving life of patient. This involves detection of inflammatory marker and study by CCA or CCTA for vulnerable plaque.

Management Issues[2]

All risk factors should be dealt with as per guideline. Few very relevant points will be discussed here:

- Diet
- Exercise and physical activity (PA)
- Cholesterol management (lipids)
- Hypertension (HTN)
- Diabetes mellitus
- Tobacco abstinence
- Prophylactic ASA (aspirin) therapy

- *Diet:* It should be followed as per guideline. Salient points are:
  - Encourage vegetables, fruits, legumes, nuts, whole grain and fish
  - Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats
  - Low in cholesterol and sodium
  - Avoid processed meats, refined carbohydrate, and sweetened beverages
  - Red meat should be eliminated. It increases systemic levels of TMAO (Trimethylamine N Oxide) a mocrobiome-dependent metabolite. It has been associated with increase CV risk[9]
  - Trans fats should be avoided
- *Exercise and physical activity:*
  - Should be routinely counseled in health care visits about need of active lifestyle
  - Adult should engage in at least 150 minutes per week of moderate exercise or 75 minutes per week of vigorous-intensity aerobic exercise
  - Even less than ideal goal is beneficial

  Definitions of different intensity of physical activity:
    - Sedentary, 1–1.5 mets—sitting, lying, watching TV
    - Light, 1.6–2.9—walking slowly, cooking, light household work
    - Moderate, 3.0–5.9—brisk walking (3.8–6 km/hr), biking (8–14 km/hr), active yoga
    - Vigorous ≥6—jogging, running, biking >16 km/hr, single tennis, swimming laps
- *Cholesterol management:*[2,10] Few accepted facts as per 2018 cholesterol guidelines:
  - Adults with intermediate (7.5% to <20%) risk of 10 years ASCVD—moderate intensity statin.
  - In intermediate risk LDL-C should be reduced by 30% or more.
  - In high risk 10 years group (20% or more)—LDL-C should be reduced by 50% or more.
  - In adult, 40–75 years of age with diabetes, regardless of estimated 10 years risk, moderate intensity statin is indicated.
  - In patients of 20–75 years age with LDL-C level 190 mg/all maximum tolerated dose of statin should be given.
  - In DM with multiple ASCVD risk factors. High intensity statin should be prescribed. Goal should be to reduce LCL-C by 50% or more.
  - In intermediate risk (≥7.5% to <20%) presence of risk enhancing factors favor initiation or intensification of statin therapy.
  - In intermediate or borderline risk, if CAC is measured—CAC is zero—withhold statin.

    CAC is 1–99—start statin in 55 years age or more.

    CAC is 100 or higher—initiate statin.

  - In borderline risk (5% to <7.5%), presence of risk enhancing factors justify statin.
- *Hypertension:* Principles of management as per guideline:
  - Non-pharmacological interventions:
    - Weight loss
    - Heart healthy dietary pattern
    - Sodium restriction
    - Dietary potassium supplementation
    - Increased physical activity and exercise
    - Limited alcohol (1–2 drink daily) (1 drink means 14 gm pure alcohol)
  - BP target of less than 130/80 mm Hg
  - In CKD and DM, treatment initiated at 130/80
  - If ASCVD 10 years risk is less than 10%, antihypertensive drugs are initiated at 140/90 or more choice of drug as per guidelines.
- *Diabetes mellitus (T2DM):*
  - One should look for diabetes specific risk enhances in DM (T2DM). These are independent of other risk factors:
    - Long duration—more than 10 years in T2DM, more than 20 years in T1DM.
    - Albuminuria + >30 mcg albumin/mg of creatinine.
    - eGFR <60 mL/min/1.73 m^2
    - Retinopathy
    - Neuropathy
    - ABI <0.9

  Such patients required high-intensity statin therapy.
  - After appropriate diet therapy and exercise cum physical activity plan, one should proceed to drug therapy:
    - Metformin is a first-line drug. It reduces 32% reduction in micro and moreover vascular DM related outcome, 39% reduction in MI, and 36% reduction in all-cause mortality rate.
    - In addition two class of drug: SGLT-2 inhibitors reduce incidence of heart failure. GLP-1R agonist reduces ASCVD events.

  Drug management of DM should be done as per guideline protocol.
- *Achieve tobacco abstinence:* It should be firmly emphasized. It is important to encourage patients to seek help from trained staff. All adult and adolescents should avoid secondhand smoke exposure to reduce ASCVD risk.
- *Prophylactic aspirin:*
  - In primary prevention:
    - Benefit seen in DM. Major vascular events decreased by 12%.
    - Between age 40 and 70 years only Class IIb recommendation. Individual approach by clinician and risk of bleeding to be considered.
    - Beyond 70 years, not recommended.
  - In secondary prevention:
    - Prophylactic ASA (aspirin) is recommended in setting of elevated ASCVD risk.
    - ASA suggested when risk is more than 10% at 10 years ASCVD risk.
    - Recent clinical trials also allow us to use low dose ASA among patient with high ASCVD risk.
    - Dose of ASA can be adjusted as per body weight.

Conclusion

- ASCVD events are avoidable through primordial prevention (i.e., prevention of risk factor development) and control of traditional CV risk factors.
- Tobacco avoidance is critically important for ASCVD prevention.
- Exercise and physical activity along with dietary management are absolutely essential.
- All these factors are better implemented with basic health education and how best dedicated persons are involved in counseling. Without these, it will go waste.
- The intensity of preventive efforts should match with individual's absolute risk of future ASCVD event.
- The clinician must balance the benefit and risk.
- Assessing appropriateness of pharmacotherapy may require search of "Risk enhancing factors" in borderline situation.
- At this point, use of "CAC" measurement can help in decision-making for cholesterol lowering or antihypertensive medication use in intermediate risk individuals.
- CCTA or CAC is now the most accurate in invasive tool for the assessment of ASCVD with highest concordance to invasive coronary angiography (CAG). CCTA is widely utilized in accurate and rapid assessment in cases of chest pain in emergency department (ED). The visualization of subclinical atherosclerosis (on either coronary calcium scanning or seeing non-obstructed plaques on CCTA) allows for targeted anti-atherosclerotic treatment strategies and improved adherence to these treatment. Possible diagnosis of vulnerable plaque is another achievement to prevent ACS.

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- Inflammatory markers should also be taken care of to halt atherosclerosis progress and possibly prevent ACS.

There are additional challenges specific to prevention realm.

AHA in 2011 in their policy statement described about value of primordial and primary prevention in CVD:

"Assessing the value of prevention in apparently healthy patients is generally more difficult than evaluating therapy for established disease because the time horizon to the clinical manifestation of disease is generally long, many decades in the young. Thus, it is difficult, perhaps impossible, to assess long-term effectiveness in terms of survival or quality-adjusted life-years (QALYs) or associated costs because of increasing uncertainty about outcome, the further one tries to look into the future."

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CHAPTER

40 SGLT2 Inhibitors in Heart Failure

NS Prasad

Abstract

The occurrence of heart failure (HF) is on the increase globally and in India. The coexistence of diabetes (DM) and HF increases the mortality risk. Various CVOT trials have proven SGLT inhibitors to reduce the hospitalization for heart failure (HHF) and CV mortality. SGLT inhibitors have proven to be useful in heart failure regardless of diabetic status.

Introduction

Patients with coexisting conditions of type 2 diabetes mellitus (T2DM) and heart failure (HF) tend to have increased mortality risk when compared to people who do not have either DM or HF.[1-3] This association of DM and HF is mainly due to mistimed and asynchronous handling of glucose and free fatty acids by the cardiac system. Another hypothesis is that the effect on heart and blood vessels, caused directly by the metabolic derangements seen in patients with diabetes mellitus (DM) may also play a vital role in this coexistence. Also, use of certain anti-diabetic agents (mainly DPP-4 inhibitors and pioglitazone) can potentiate hospitalization for HF.[4]

As high as 20% of the population is expected to develop HF at some point during their lifetime.[5] It is a global pandemic affecting an estimated 26–37.7 million people worldwide.[6,7] The burden of HF in India has become an important public health concern because of very high mortality. HF exerts a high-economic burden mostly due to hospitalizations.[8] India is the highest spending country on HF in South Asia with a total expenditure amounting to 1.7% of total health expenditure of India.[9] Recent studies have clearly shown that the prevalence of HF with preserved ejection fraction (HFpEF) is mounting significantly when compared to that of HF with reduced ejection fraction (HFrEF). Available statistics further suggest that in the year 2020, only 35% of patients with HF have reduced EF<40%, and over 65% have a preserved EF>40%.[10] Atherogenesis and endothelial damage play a very crucial role in pathophysiology of HF in DM. Insulin resistance and hyperinsulinemia cause left ventricular hypertrophy which is frequently linked to T2DM.[11] Hyperglycemia results in cardiac muscle stiffness and leading to non-compliance of the myocardium. Therefore, drugs decreasing insulin resistance and aggressively controlling the hyperglycemia should be part of therapy in order to reduce the incidence of HF in T2DM.[12] T2DM could potentially cause cardiomyopathy independent of atherosclerotic ischemia, and there is evidence of cardiomegaly in T2DM patients. Hence, therapy targeting such pathology,[13] for example, sodium/glucose cotransporter-2 inhibitors (SGLT2i), might be useful.[14,15]

Cardiorenal Association

Heart and kidney are closely related when it concerns the physiological functions and pathological conditions of both systems. Acute or chronic disorders of one of these organ systems are capable of having a deleterious effect on the other. This closely linked interplay is often called as the cardiorenal association.[16] Studies have indicated that

anywhere between 20% and 67% of patients with HF will also have chronic renal impairment as an association.[17,18] HF can also directly or indirectly lead to renal impairment or CKD. This may be due to a low cardiac output and increased venous pressure. On the other hand, renal impairment may also worsen HF. This can happen via enhanced water and sodium retention, potentiated atherosclerosis, anemia, inflammation, uremic toxins, and activation of the neurohormonal pathways.[19,20]

Evidence for Use of SGLT2i in HF Prophylaxis

SGLT2i have shown positive results when it comes to hospitalization for the sake of heart failure (HHF) and CV or overall mortality across several cardiovascular outcome trials. These favorable results have been demonstrated both in patients with and without history of pre-existing cardiac ailment. A meta-analysis has confirmed robust advantages with SGLT2i on HHF and CV mortality even in patients without CVD or HF, indicating benefits in the early HF stages as well.[21]

Empagliflozin in the EMPAREG OUTCOME study[22] and dapagliflozin in DECLARE-TIMI 58[23] study revealed a significant reduction in HHF. Analysis of the CANVAS trial[24] also exhibited a significant fall in HHF rates in both prevention groups—primary and secondary. In line with these results, the US regulatory authority has approved empagliflozin for lowering CV mortality and canagliflozin for lowering major adverse cardiac events—MACE in patients with DM who also have coexisting cardiac disease. The results of DECLARE-TIMI 58 have proven significantly lower rates of cardiovascular mortality or HHF. Further, they also mildly suggested that it may apply to primary prevention also, since clinical mortality benefits were seen in patients who did not have cardiac disease or HF at the baseline. DECLARE TIMI results when stratified by cardiac ejection fractions showed an HHF reduction.[25] Patients with previous cardiac disease had a greater absolute relative risk in DECLARE-TIMI 58.[26-30] DAPA HF trial[31] results have also shown significant fall of mortality with the use of dapagliflozin (both with and without DM). Dapagliflozin[32] significantly reduced the overall composite endpoints of CV mortality/HHF/urgent HF visit, when compared with standard arm (both with and without DM). The quality of life was also significantly improved as measured by KCCQ score.[32]

Major trials that are currently underway (such as the EMPEROR employing the use of empagliflozin) may further show the path toward SGLT2i use in patients with or without DM for HF treatment or prevention.

Safety of SGLT2i

One of the most common side effects of SGLT2i is genital infections.[22,23,33,34] DKA can also typically occur in patients treated with SGLT2i, although rare.[22,23,33,34] Current recommendations suggest that treatment should be discontinued as soon as DKA sets in.[35,36] CANVAS trial showed that lower limb amputation frequency was significantly greater in the arm with canagliflozin.[33] Accordingly, regulators have highlighted practicing doctors' need for caution when they use SGLT2i. This is more so pertinent in patients who have a history of or high risk of amputation.[37] Another major concern with canagliflozin was the higher risk of fractures in CANVAS. However, this was not replicated in the trials with other SGLT2i.[22,23,33]

Can SGLT2i be Beneficial in the Treatment of HF?

Efficacy in HF prevention need not mean that SGLT2i are also useful in HF treatment.[38,39] Dapagliflozin significantly lowered primary composite end point of CV mortality or HHF. This was more evident in patients with HFrEF than in HFpEF.[25] Patients who had reduced EF (EF<30%) had significantly higher benefit.[25] Also, CV mortality benefits in patients with HFrEF were seen in those treated with ARBs, ACEIs, and beta-blockers.[25]

Role of SGLT2i in Patients without DM

As mentioned earlier, SGLT2i might serve to be useful regardless of DM status and EF percent. While several mechanisms have been hypothesized for their cardiac benefits, the following are backed with considerable evidences:

- Reduction of cardiac preload leading to an improvement in ventricular loading (facilitated predominantly due to increased osmotic diuresis and sodium loss in urine).[40]
- Sodium/hydrogen (Na^+/H) exchanger inhibitor in the myocardial tissues.[41]

As all these mechanisms have been elucidated both in patients with and without DM,[42-44] SGLT2i may benefit all groups of patients.[45-48]

Future Directions

Impending results of the currently progressing trials on SGLT2i in HF are required to fully analyze and study the treatment/preventive ability. This will apply to all patients, irrespective of DM status and EF percent. DAPA-HF, DELIVER, EMPEROR-Reduced and EMPEROR-Preserved may help in this regard. The EMPA-HEART study showed that empagliflozin causes a significant decrease in LV mass regression, which probably suggests potential reverse cardiac remodelling.[49] SOLOIST-WHF trial, which is testing sotagliflozin (a dual SGLT1/SGLT2i), may reveal drug-specific effects due to the difference in receptor selectivity and specificity. If this class of drugs sees clinical efficacy, then there is a likelihood of moving from a multidrug-containing polypill to a single pill that will be able to target multiple pathways at the same time.[50]

Conclusion

HF and T2DM are major public health threats across the globe. SGLT2i have emerged as a potential drug group for the prophylaxis of HF in individuals with DM. Accumulating evidence suggests that SGLT2i may produce coupled renal and cardiac effects, thus ensuring promise for the treatment of HF in patients irrespective of DM status and EF percent. We will have to play the waiting game to see if this promise turns into reality in the coming times, with the results of ongoing trials in these categories.

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CHAPTER

41 Dual Antiplatelet Therapy: Current Status

Sudha Vidyasagar

Abstract

The role of dual antiplatelet therapy (DAPT) has come into vogue, in the last two decades, after several clinical trials proved their superiority to aspirin alone, in the prevention of vascular events, especially in the coronary and cerebral circulations. In the heart, their use has been extensive, especially after the use of drug eluting stents for acute coronary events. In the brain, their efficacy has to be balanced against their tendency to cause dangerous intracranial hemorrhage. Several scoring systems have been devised to address this risk benefit ratio. Judicious use of these combination therapies for the appropriate duration will prevent a significant number of recurrent vascular events, without dangerous bleeding risk.

Introduction

Atherosclerosis leading to vascular complications of heart and brain are important causes of morbidity and mortality. Platelet activation has a very important role in the occurrence of ischemic events in atherosclerosis. This makes antiplatelet drugs an essential part of the armamentarium the physician has to reduce these events. Currently they are being used in cardiology for acute coronary syndromes and vascular pathologies, and in neurology for the prevention of stroke and transient ischemic attacks (TIAs). In addition, their role in the management of prevention of thromboembolism in atrial fibrillation is also to be defined.

In this chapter we will review the current status of dual antiplatelet therapy (DAPT), in cardiac and cerebral events, keeping in mind the data available on this subject, and the current guidelines on the use of DAPT.

Review of Literature on DAPT

Brief History

The concept of using DAPT therapy began when it was shown two decades ago, that they decreased vascular events, especially in the context of coronary intervention.[1] The choice of anti-platelet therapy has also changed from ticlopidine to the safer clopidogrel and more potent drugs like ticagrelor and prasugrel.

Role in Acute Coronary Syndrome

ST-Elevation Myocardial Infarction (STEMI)

In STEMI, the aim of antiplatelet therapy is to reduce the thrombotic tendency at the site of plaque rupture, and also prevent further thrombosis due the intervention in the coronaries. This has to be efficient and fast in order to serve this purpose. Hence, the combination of heparin, aspirin (325 mg, non-enteric coated, crushed or chewed for early action) and a second antiplatelet drug like prasugrel or ticagrelor is recommended. The concept of preloading before stenting is not recommended any more, based on the results of the ATLANTIC trial, which did not show any advantage in patients who received anti platelet therapy in the ambulance.[2]

The current focused update of European Society of Cardiology (ECS) recommends that ticagrelor 90 mg BD be used, along with aspirin in all patients undergoing

percutaneous coronary angioplasty (PCI). If the patient has been on clopidogrel, it is recommended to stop it and switch to ticagrelor because of its superior efficacy.[3] In STEMI patients who undergo thrombolysis, clopidogrel 300 mg loading, with 75 mg OD should be continued. In patients in whom bypass surgery is anticipated early, DAPT is avoided, and only aspirin is given.

In Unstable Angina

In NSTEMI, the need for antiplatelet therapy is to stabilize the ruptured plaque. The patient is usually taken up for intervention over the next 1–2 days. When they undergo PCI, it is advised to give DAPT, preferably ticagrelor or prasugrel with aspirin. These need not be given upfront, as the ACCOAST trial,[4] did not find any advantage in using the second antiplatelet at arrival, and in fact showed that it increased chances of bleeding.

In patients who need only medical management for acute coronary syndrome (ACS), it is advised to give ticagrelor along with aspirin for a period of 1 year. Clopidogrel is a second choice.

In Stable Angina

For stable angina patients, who are managed medically, DAPT is not needed, as shown by the CHARISMA trial.[5] For those who undergo coronary stenting, clopidogrel can be added to aspirin and continued further for 6 months. The loading dose would be 600 mg, followed by 75 mg OD along with aspirin. If they have a high risk of bleeding, DAPT can be brought down to single drug at 1 month.

Role of DAPT after Stenting

The problem of prevention of stent thrombosis encouraged the use of DAPT. The change from bare metal stents to the use of drug eluting stents further increased the danger of stent thrombosis, which led to the usage of more potent drugs. However, here, DAPT has a dual role. It serves to prevent stent thrombosis, but also prevented atherosclerotic events as a whole in the body. Ticagrelor fitted the bill adequately and is hence recommended for prevention of stent induced thrombosis.

Duration of DAPT after Stenting

The fear of stent thrombosis with DES has also come down as the stents now have thinner struts and are more biodegradable. Hence, the duration of DAPT therapy has also come down from 12 months to 6 months and even 3 months in suitable patients. The TWILIGHT trial found that 3 months of DAPT followed by ticagrelor monotherapy for 1 year, is non inferior to 1 year of DAPT.[6]

The duration of therapy needed after stenting is a delicate balance between the risk of thrombosis and recurrence of ACS, versus the danger of bleeding. The current ECS recommendations are for 6 months in patients with drug eluting stents, if they are stable. However, for patients with ACS, the risk of recurrence is higher, and hence DAPT is extended for 1 year. This can be reduced to 6 months if bleeding risk is high.

To balance the ischemic and bleeding risk, various scores have been put forth. The ischemic risk is calculated by patient characteristics and what is defined as the complexity for the coronary lesion as given below, using the DAPT score. If this score is more than 2, a longer duration of DAPT is advised.

The PRECISE-DAPT score assesses the bleeding risk. A PRECISE-DAPT score of more than 25 would indicate a high bleeding risk and may call for shortening duration of DAPT **(Table 1)**.[7]

In a meta-analysis of 9,000 patients, the PCI complexity was assessed by six interventional factors: three-vessel PCI, implantation of three or more stents, three or more complex coronary lesions, bifurcation stenting, total sent length more than 60 mm, and treatment of a chronic total coronary occlusion.[8] Further, if the LAD is involved, the duration of therapy is extended even beyond 12 months keeping in mind the recurrence risk.[9]

The bleeding risk can also be calculated by the CRUSADE score and the HAS-BleD scores to decide on duration of therapy. Treatment will have to be individualized, as has been recommended by all major guidelines.[10] In addition, all patients who require DAPT for any indication, and have a high bleeding risk, should be given proton pump inhibitors along with them. **Table 2** summarizes current recommendations.

DAPT in Patients with AF

Between 6–8% of patients who are on anticoagulation may need PCI. In such patients, the duration of DAPT plus an anticoagulant can be given up to 6 months if their bleeding risk is low and shortened to 1 month if it is high. However, prasugrel and ticagrelor are best avoided, as they

TABLE 1 Risk scores validated for dual antiplatelet therapy duration decision-making

	PRECISE-DAPT score	***DAPT score***
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)
Score calculation	HB ≥12 11-5 11 10-5 ≤10 WBC ≤5 8 10 12 14 16 18 ≥20 Age ≤50 60 70 80 ≥90 CrCl ≥100 80 60 40 20 0 Prior bleeding No Yes Score points 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	Age 75 −2 pt 65 to <75 −1 pt <65 0 pt Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Praclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +2 pt
Score range	0 to 100 points	−2 to 10 points
Decision-making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT
Calculator	www.precisedeptscore.com	www.daptstudy.org

TABLE 2 Drug of choice and duration of treatment for various vascular conditions

Clinical condition	***DAPT-aspirin + Drug of choice***	***Duration of DAPT***
MI with PCI	Prasugrel/ticagrelor	1 year
MI with thrombolysis	Clopidogrel	1 year
NSTEMI with PCI	Prasugrel/ticagrelor	1 year
NSTEMI with medical treatment	Ticagrelor	1 year
Stable angina with PCI	Clopidogrel	6 months
Stable angina with medical management	Only aspirin	Lifelong single drug

are unpredictable and cause major bleeding along with anticoagulants. There is some data, that using NOACs like apixaban and rivaroxaban may cause less bleeding risk; however, treatment is best individualized.[5]

Surgery on DAPT

Stopping DAPT for elective surgery should be a collective decision between departments involved and cardiologist. If aspirin can be continued, stopping DAPT for few days will not be difficult. If aspirin is discontinued, bridging with tirofiban or eptifibatide may be needed.

Intervention on DAPT: If a patient needs PCI on DAPT, radial access is preferred over femoral one, and aspirin can be continued. The additional use of a PPI is recommended.

DAPT in Neurology Practice

DAPT in Transient Ischemic Attacks

TIAs are the forerunners of strokes but leave no permanent neurological deficit. They give an opportunity to give antiplatelet therapy to prevent further vascular events. The risk of stroke increases with the characteristics of the TIA, which can be categorized by clinical features. Patients with TIA are risk stratified according to ABCD^2 score (age, blood pressure, clinical features, duration of TIA, and presence of diabetes). A score of more than or equal to 4 denotes a high-risk TIA and such patients are prone for recurrent stroke of up to 8%, especially in the first 48 hours.

Two major trials addressed the question of DAPT and its duration in high risk TIAs and minor strokes with National Institutes of Health Stroke Scale (NIHSS) score of

less than or equal to 3. The CHANCE (Clopidogrel in High-Risk Patients with Acute Non-Disabling Cerebrovascular Events) trial done in China, showed for the first time, that aspirin and clopidogrel for 21 days, and then only clopidogrel until 90 days decreased the subsequent ischemic events.[11] However, the POINT trial, which was conducted in North America, Australia, and other countries, did not find lesser ischemic events with DAPT, and had more bleeding events.[12]

This difference has been attributed to the different patient populations used and the varying causes of ischemic events in these groups. The POINT showed more risk of bleeding, which could be due the longer duration of DAPT used (90 days as opposed to 21 days in CHANCE). Further the Asian population in CHANCE did have genetic differences which could account for the lesser bleeding risk. The absorption of clopidogrel depends on the presence of a transporter in gut called ABCB1, which affects its efficacy but not bleeding risk. Hence, the different results may be due to ethnic variation.[12]

However, most analysis recommend the use of DAPT in high risk TIA with aspirin (160–325 mg loading dose, followed by 50–100 mg daily) plus clopidogrel (300–600 mg loading dose, followed by 75 mg daily) in the first 21 days of therapy,[13] as this is the most vulnerable period for recurrent ischemic events. From day 22 to 90 days, the ischemic events were less, and the bleeding risk was unnecessarily increased as seen in a meta-analysis including CHANCE and POINT trials. In fact, the first 10 days after TIA are crucial to prevent recurrence, though most guidelines recommend DAPT up to 21 days.[14] The bleeding risk with DAPT is minimal till 21 days, and this does not compromise the benefits of prevention of stroke. If the TIA happens on a single antiplatelet drug, the second one can be added up to 21 days as advised.

The choice of the antiplatelet drug, which should be continued after day 21, till 90 days, has been clopidogrel in most studies, anticipating aspirin resistance. However, the Indian guidelines on stroke do not specify this, and mention that either aspirin or clopidogrel can be continued based on the choice of the physician, as aspirin resistance is not well documented in the Indian population. There is also a small improvement in functional scores after DAPT in minor strokes, which may recommend their use.

Further triple therapy (aspirin, dipyridamole, and clopidogrel) was also tried in the TARDIS trial and given up, as it gave rise to more bleeding and less advantage with ischemic events. Of late, newer DAPT therapy using ticagrelor[15] and prasugrel are also undergoing trials to check their efficacy and safety. The SOCRATES trial,[16] compared the efficacy of clopidogrel to ticagrelor, and found it is non inferior, but caused more bleeding risks in the ticagrelor arm.

DAPT in Secondary Prevention of Strokes

The CAPPRIE trial was the first to demonstrate the efficacy of additional clopidogrel in secondary prevention of strokes. This was followed by the MATCH trial, which actually showed higher bleeding risk in patients on DAPT. Following this the CHARISMA trial used aspirin, versus aspirin with clopidogrel, and found DAPT to be useful in preventing ischemic events though with increase in bleeding. So DAPT is recommended for patients with acute ischemic stroke with an NIHSS score of less than 3. As of now, there is no role for DAPT in acute ischemic stroke with a higher score. In these patients, a single antiplatelet, which is aspirin in a dose of 325 mg stat, followed by 75 mg daily after that is given lifelong.

As of now, there is no evidence for continuing DAPT beyond 90 days, in any neurological situation as it results in more bleeding and less efficacy for prevention.[17]

DAPT in Lacunar Strokes

Antiplatelet therapy has no major role in lacunar strokes. However, in high risk TIAs and those with early neurological deterioration in lacunar infarcts, a study showed better functional outcomes of short duration DAPT for 5 days.[18]

DAPT in Intracranial Large Artery Thrombosis

DAPT decreases stroke and death in patients in this subgroup, if aspirin and clopidogrel are given in the first 90 days in symptomatic patients with 70–99% stenosis as shown in the SAMMPRIS trial.[19] But this is useful only when the NIHSS score is less than 3. Beyond this, there is a fear of hemorrhagic transformation and aspirin alone is recommended.

DAPT in Vascular Disease

DAPT has been used in symptomatic carotid stenosis, which is severe, for the prevention of stroke for at least 3 months. In patients with asymptomatic intracranial stenosis, DAPT can be given for 1 month, followed by single antiplatelet, if patients have TIA and minor stroke.

TABLE 3 Summary of indication on antiplatelet treatment from ESC guidelines, 2017

District	*Monotherapy (aspirin or clopidogrel)*	*DAPT (aspirin plus clopidogrel)*
LEAD		
Asymptomatic	Class III A	–
Symptomatic	Class IA	–
Endovascular revascularization	From 1 month after procedure: class IIa C	For 1 month after procedure: class IIa C
Surgical revascularization	Class IIb B	–
Carotid artery disease		
Asymptomatic (>50% carotid artery stenosis, low bleeding risk)	Class IIa C	–
Symptomatic	Class IA	–
Endovascular revascularization	From 1 month after procedure: class IA	For 1 month after procedure: class IA
Surgical revascularization	Class IA	–

ESC, European Society of Cardiology; LEAD, lower extermity

TABLE 4 Antiplatelet reversal recommendations

Reversibility	*Recommendations*
Irrversible binding agents	**Platelet transfusion** *Intracranial hemorrhage:* Platelet transfusion for patients NOT undergoing a neurosurgical procedure is associated with worse functional outcome and death with no change in volume growth **Desmopressin 0.4 µg/kg IV for 1 dose** Desmopressin can be considered for patients on antiplatelet therapy that binds irreversibly. For those undergoing a neurosurgical procedure DDAVP can be used in addition to platelet transfusaion
Reversible binding agents	**Platelet transfusion** *Neurosurgical procedure:* Allow 3–5 half-lives from the last administration of the antiplatelet agent before administering platelet transfusion to prevent inhibition of infusing platelets **Desmopressin 0.4 µg/kg IV for 1 dose** When used in combination with platelet transfuion, desmopressin may be beneficial prior to emergent procedures

In the CASPAR (Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Artery Disease) study, subjects underwent below-knee femoropopliteal bypass received either DAPT or aspirin alone. This study showed that the patients with prosthetic grafts on DAPT did benefit.[20]

Currently, DAPT is advised for both carotid stenosis and peripheral vascular disease, for 1 month, after revascularization. If asymptomatic, there is no indication for DAPT in lower extremity atherosclerotic disease or mild to moderate carotid stenosis **(Table 3)**.

In patients with cardioembolic stroke with contraindication to anticoagulants, DAPT has been tried as an alternative, with some success, though this is not the first choice.

DAPT and Correction of Bleeding

There is always a danger of bleeding during any neurosurgical procedure for patients on DAPT for any indication. In this instance, platelet transfusion and desmopressin can be used as summarized in **Table 4**.

Conclusion

To conclude, DAPT has a definite role to play in the prevention of ischemic events in the coronary and cerebral circulation. Their efficacy in decreasing mortality and morbidity is evident from results from various trials. However, they must be used judiciously to avoid bleeding risks, for the minimum period of time, to be useful and safe.

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CHAPTER

42 Novel Oral Anticoagulants: Which, When, and Where?

Vishwanath Krishnamurthy

Abstract

The new oral anticoagulants (NOACs) developed to address these limitations are backed by good trials. Beginning with Dabigatran in 2010, currently two classes of NOACs are available, the oral direct thrombin inhibitors (e.g., dabigatran) and direct factor Xa inhibitors. They have a distinct advantage of having rapid onset of action, fixed dosing, and absence of need of regular monitoring compared to VKA. Prediction tools like SAMe TTR2 score can be used in the decision-making between NOAC and VKA. In this chapter a brief description of different NOACs and its use in several situations have been highlighted. With the correct knowledge about these drugs, choosing the right patient and following the principle of therapeutic humility the benefits of these novel drugs can be passed on to the patients for better efficacy.

Introduction

Vitamin K antagonists (VKAs) have been the main treatment modality for the prevention of thrombotic episodes in atrial fibrillation (AF). Despite its significant impact to prevent strokes, there have been many limitations in its use from benign one to more serious ones. In the last several years, the new oral anticoagulants (NOACs) developed to address these limitations are backed by good trials. Beginning with Dabigatran in 2010 leads to creation of another novel oral anticoagulant rivaroxaban. Further with development of apixaban, edoxaban they changed the name to direct oral anticoagulants and is currently the term used by ISTH (International Society of Thrombosis and Hemostasis).[1]

There are several advantages and disadvantages of NOAC Vs VKA **(Table 1)**, with the correct knowledge and decision making the right NOACs can be given to the right patient.

Mechanism of Action

Currently two classes of NOACs are available, the oral direct thrombin inhibitors (e.g., dabigatran), which directly bind to thrombin, thus prevent cleaving of fibrinogen to fibrin and direct factor Xa inhibitors (e.g., rivaroxaban, apixaban, and edoxaban), which prevent factor Xa from cleaving prothrombin to thrombin. Unlike VKAs, which block the formation of vitamin K-dependent coagulation factors (factors II, VII, IX, and X), these drugs block a particular step in coagulation cascade.

Approved Indications for NOAC[3,4]

- Reduce risk of embolization events (e.g., stroke) in patients with non-valvular AF.
- Treatment of DVT and pulmonary embolism (PE).
- Reduction in risk of recurrent DVT, PE in patients at risk after initial treatment.
- Prophylaxis of DVT.

TABLE 1 Advantages and disadvantages of NOAC over warfarin

Feature	*Warfarin*	*NOAC*
Onset of action	Slow	Rapid
Dosing schedule	Variable	Fixed
Food interaction	Yes	No
Interactions	Many	Fewer
Monitoring	Yes	No
Offset	Long	Shorter
Frequency	Once daily	Once/Twice
Monitoring	INR	Uncertain
Clearance	Non renal	Renal (25–80%)
Antidote	Vit K	Idaricuzumab/Andexanet alpha/?Dialysis[2]
Familiarity	Extensive	Minimal

TABLE 2 Table showing SAMeTTR2 score[5,6]

Factor	*Point*
Sex (Female)	1
Age (<60 years)	1
Medical history(H/O more than two of the following: HTN, Diabetes, CAD, PAD, Heart failure, Stroke, Pulmonary hepatic, or Renal disease)	1
Treatment (Interacting medications, e.g., amiodarone)	1
Tobacco Use (within 2 years)	2
Race (non-caucasian)	2

Score	*Action*
0–2	Patients likely to achieve a high TTR VKA may be beneficial
≥2	NOAC would be better initial option

Emerging Indications

- Use of NOACs before and after cardioversion and catheter ablation in AF.
- Prevention of further cardiovascular events in patients after ACS.
- NVAF undergoing PCI.
- In stable CV disease and peripheral vascular disease.
- Prevention of venous thromboembolism (VTE) in acutely ill medical patients.

Considerations when starting/choosing a NOAC—think ABCDE:

A—Low weight (dose reduction might be needed)

B—Bleeding risk (GI bleeding)

C—Creatinine clearence (renal function)

D—Drug interactions (p-glycoprotein, CYP450, e.g., reduced verapamil dose with dabigatran)

E—Elderly (dose reduction might be necessary)

SAMe-TT2R2 Score (Table 2)

It is a prediction tool that predicts the quality of vitamin K antagonist anticoagulation therapy as measured by time in therapeutic INR range (TTR).It can be used in the decision-making between NOAC and VKA. It can be used in patients with CHA2DS2VASc score ≥1 where oral anticoagulation is recommended.[5,6]

Brief Description of NOACs

Dabigatran

Dabigatran belongs to group of direct thrombin inhibition, after oral ingestion inactive drug is converted to active form and reaches peak plasma levels within 2–3 hours. Onset of action is 1–2 hours, with a half-life of 12–17 hours, and is predominantly excreted by the kidneys (80%)

RE-LY trial compared dabigatran 110 mg BID or 150 mg BID with warfarin in 18,113 patients with AF with a mean CHADS score of 2.1.[7] The primary endpoints assessed were occurrence of stroke and systemic embolism. Study showed that dabigatran 150 mg BID was superior to warfarin with no significant differences in major bleedings. However, GI bleeding was found to be more with dabigatran (150 mg BID). Dabigatran 110 mg BID was non-inferior to warfarin for the primary endpoint, with a reduction of 20% in major bleedings.

An extension of RE-LY study called the RELY-ABLE study was conducted where the cases enrolled in the earlier RE-LY study were further followed up for another 2 years and 3 months from the original study period. This study confirmed the results of RE-LY and gave information on the long-term effects of dabigatran use in both the doses.

Another two studies (RE-COVER)[8,9] and RE-COVER II, which were a comparison of dabigatran and warfarin in venous thromboembolism showed that dabigatran was non-inferior to standard treatment of VTE with reduced bleeding risk (1.4%) with no differences in major bleeding.

Rivaroxaban

It is a dose-dependent direct inhibitor of factor Xa and the second NOAC approved by the FDA[10] based on the ROCKET AF study.[11]

Rivaroxaban in comparison to warfarin is effective in prevention of stroke in AF, and also in treatment and prevention of DVT with reduced risk of serious bleeding complications.[12]

The ROCKET AF[11] was a double-blinded study which showed noninferiority of rivaroxaban to warfarin in the prevention of stroke or systemic embolism; however, rivaroxaban failed to show superiority over warfarin in the intention to treat analysis. Fatal bleeding occurred less frequently in the rivaroxaban group, with no differences in the risk of major bleeding. GI bleeding and transfusion requirements were greater with rivaroxaban. The EINSTEIN DVT[13] trial showed rivaroxaban was noninferior to warfarin for DVT with similar bleeding risk among both.

Apixaban

It is a direct, reversible, competitive, and selective inhibitor of factor Xa in patients of AF. It is approved for stroke prevention. Among the NOACs, apixaban is least cleared from the kidneys and is metabolized predominantly by the liver, and hence its use in renal failure patients.[14]

The ARISTOTLE[15] study showed apixaban was better than warfarin, with fewer primary outcomes (overall strokes and systemic emboli). Apixaban was compared with aspirin in the AVERROES study. But after a mean follow-up of 1.1 years, the study was prematurely stopped as there was a clear benefit of apixaban. The primary outcome of stroke or systemic embolism was significantly lower in the apixaban group versus aspirin, with similar bleeding risk (major bleeding and intracranial bleeding) between the two.[16] The APPRAISE study assessed the effect of apixaban with placebo in addition to antiplatelets following ACS. It was stopped as it was found to have more risk of bleeding with less benefit after 8 months.[17]

Edoxaban

It is once daily dosing drug. In comparison with warfarin, once daily Edoxaban had similar efficacy to warfarin in stroke prevention and treatment of DVT AND PE with lesser risk of bleeding complications.[18] ENGAGE AF TIMI 48 trial[19] showed that both low dose (30 mg) and high dose (60 mg) were noninferior to warfarin and a dose-related reduction in bleeding as compared to warfarin.

Bleeding while Using an NOAC

Unlike in VKA fresh frozen plasma cannot be used when there is serious bleeding for reversal ,instead can be used only for volume expansion, Drugs like andexanet alfa (a recombinant human FXa analogue that competes for the FXa inhibitors with FXa), idarucizumab, (humanized antibody fragment that specifically binds dabigatran) prothrombin concentrates, can be used depending on the availability and latest evidence More importantly we have to inquire about the dosing regimen, the time of last dose as it is expected that after stopping the treatment, haemostasis is expected within 12–24 h after the last taken dose, as plasma half-life is around 12 h for most NOACs .Thus in most non serious bleeding conditions a wait and watch principle can be used.[25]

Switching from Heparin/VKA to NOAC

While Changing from heparin to NOAC, in case of conventional heparin they can be started after stopping the conventional heparin,in case of LMWH it has tob

TABLE 3 NOAC in renal disease[22]

Drug	*Criteria*	*Dose modification*
Dabigatran	Creatinine clearance <50 mL/min <30 mL/min	110 mg BD & as per ESC guidelines should not be used
Rivaroxaban	Creatinine clearance <50 mL/min	15 mg OD
Apixaban	Two of these factors: Age >80, creatinine >1.5, weight <60	2.5 mg BD
Edoxaban	Creatinine clearance <50 mL/min	30 mg OD

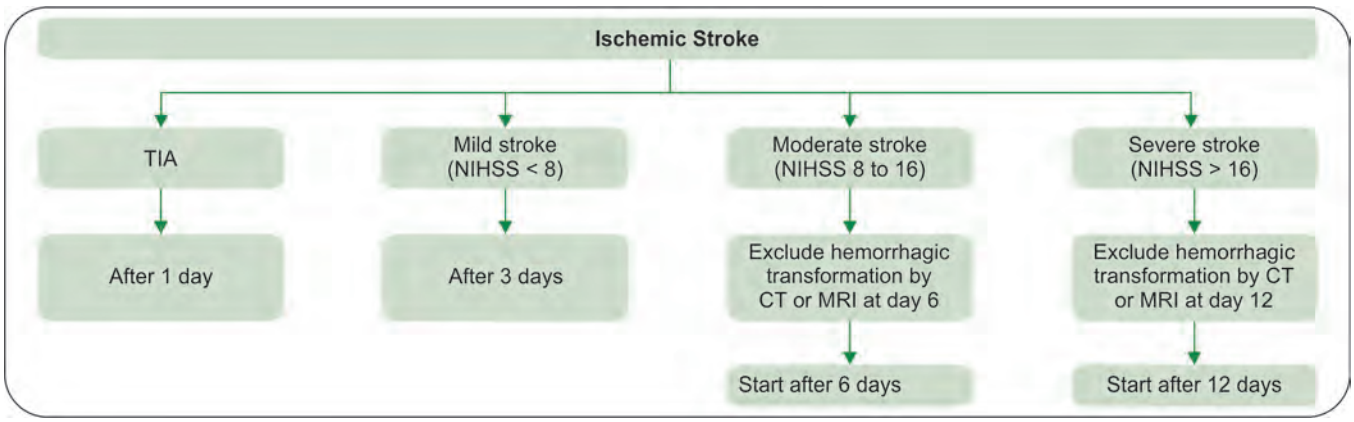
TABLE 4 NOAC before surgery[23]

Drug	*Renal function*	*Minor surgery*		*Major surgery*	
		PREOP	*POST-OP*	*PRE-OP*	*POST-OP*
Dabigatran	CrCl >50	Stop 2 days before surgery	Restart 1 day after surgery	Stop 3 days before surgery	Restart 2 days after surgery
	CrCl <50	Stop 3 days before surgery	Restart 1 day after surgery	Stop 4–5 days before surgery	Restart 48 h after surgery
Rivaroxaban	CrCl >30	Stop 2 days before surgery	Restart 24 h post-surgery	Stop 3 days before surgery	Restart 48 h after surgery
Apixaban	CrCl >30	Stop 2 days before surgery	Restart 24 h post-surgery	Stop 3 days before surgery	Restart 48 h after surgery

TABLE 5 Coagulation profile and NOAC[24]

Test	*Factor Xa inhibitors*	*Dabigatran*
Qualitative (Present/Absent)	PT (Riva>Edoxa>Apixaban)	TT>aPTT
Quantitative test	Chromogenic Anti Xa levels (Requires specific calibration to drug)	Dilute TT, Anti IIa (specific calibration)

Flowchart 1: NOAC in stroke[26]



started 2 hours prior to stopping LMWH. When it has to be changed back from NOAC to parental anticoagulants we can start 12 h after Apixaban or Dabigatran dose and after 24 hrs of last Rivaroxaban dose. From warfarin to NOAC depending on the INR (Dabigatran/Apixaban if INR <2.0 , Rivaroxaban when INR <2.5) it can be started after stopping warfarin.[27]

NOAC in Special Situations

Refer **Tables 3 and 4, Flowchart 1**.

NOAC in Asian Population

A meta-analysis which included 5 NOAC trials, 21 observational Cohort showed that NOAC were associated with decreased rates of systemic embolization, ischemic stroke, myocardial infarction, major bleeding among Asian population with consideration of rivaroxaban for myocardial infarction.[20,21]

Coagulation Profile and NOAC[24]

NOAC does not require routine monitoring of coagulation profile. However, they can significantly be affected and pose a difficulty in presence of acute overdose or significant bleeding.

Normal PT or aPTT does not guarantee absence of anticoagulant activity. Quantitative tests are not standardised or approved. Depending on the clinical situations decision on switching between anticoagulants have to be taken **(Table 5)**.

Conclusion

With increase in the armamentarium of drugs used for antithrombotic effect, it is imperative that as clinicians we need to know the mechanism of action, adverse events, studies backing the NOAC, and importantly the situation where these drugs have to be used and when are they contraindicated. We should never forget the important third dimension in the treatment which is the financial consideration as it is one of the important aspects in our setup. As most of these drugs' costs are higher compared to VKA with the correct knowledge and use of these drugs also taking into the economic aspects the benefit can be passed on to the patients for better efficacy and better compliance.

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CHAPTER

43 Recent Practice Changing Landmark Trials of Cardiology

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Abstract

Human medicine has always evolved as evident by the literature available. This change has come from scientific evidence accumulated from numerous clinical trials and studies. Cardiovascular diseases are one of the most important causes for morbidity and mortality. Most of the guidelines for management of the diseases come from the scientific data which gives us direction and insight into understanding of the disease and treatment. Hence, it becomes vital for the physicians to be updated with recently evolving scientific data in the form of clinical trials and studies. Here, we discuss briefly the recently published literature in the field of cardiology.

Introduction

Human medicine is a dynamic and ever-evolving field guided by new evidence derived from clinical studies. Cardiovascular disease is a major cause of morbidity and mortality in humans, hence it is crucial to explore this segment of medicine further to advance the aspects of diagnosis and management. Most of the clinical practice is dependent on evidence-based medicine. This evidence comes from the scientific data generated as a result of clinical trials, clinical studies, and experience of the scientific community. A clinical trial is a scientifically conducted investigation of a treatment or drug involving healthy people and patients. Clinical trials are needed to determine the correct dose of new drugs, to determine whether the drug will treat the disease effectively in humans, the safety of new drugs alone and in combination with other drugs, and to determine whether an intervention is better than the standard treatment. There are lots of trials being conducted every year and evidence-based guidelines also change, depending on the trial results. In this chapter, we discuss the recent scientific data on cardiology in the form of published landmark trials which are likely to have a significant impact on our clinical practice **(Table 1)**.

Heart Failure

Heart failure (HF) is an important cause of mortality and morbidity in patients with cardiac disease. Different treatment options exist ranging from drugs to various cardiac interventions. Sacubitril-valsartan has been studied in these patients and has shown good results. This drug was evaluated in acute decompensated HF patients.

PIONEER-HF (Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure) Trial[1]

Sacubitril–valsartan therapy is now widely used in chronic HF. In this trial, patients with HF with reduced ejection fraction who were admitted for acute decompensated HF were included after hemodynamic stabilization. The patients either received sacubitril–valsartan to a target dose of 200 mg (97 mg of sacubitril with 103 mg of valsartan) twice daily or enalapril to a target dose (10 mg)

TABLE 1 Summary of recently published clinical trials in cardiology

PIONEER-HF (Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure) trial	HFrEF patients getting hospitalized for acute decompensated HF, sacubitril–valsartan therapy causes reduction in the NT-proBNP than the enalapril therapy without an increase in worsening renal function, hyperkalemia, symptomatic hypotension, or angioedema
AUGUSTUS (Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation) trial	In patients with AF and a recent ACS or PCI on a P2Y12 inhibitor, addition of apixaban, without aspirin, resulted in lesser bleeding events, and hospitalizations without significant differences in the incidence of ischemic events than regimens that include a vitamin K antagonist, aspirin, or both
ISAR-REACT-5 (Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes) trial	In ACS patients undergoing invasive strategy, the incidence of death, MI, or stroke was significantly lower with prasugrel than ticagrelor, with no major difference in the incidence of major bleed
COLCOT (Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction) trial	Colchicine at a dose of 0.5 mg daily reduces the risk of ischemic cardiovascular events than placebo in patients with a recent MI
COMPLETE (Complete Revascularization with Multivessel PCI for Myocardial Infarction) trial	A complete revascularization strategy in STEMI but with multivessel coronary artery disease was seen to lower the risk of CV death or MI, or composite of CV death, MI or ischemia-driven revascularization
REDUCE-IT (Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia) trial	In metabolic syndrome with elevated triglyceride levels, the risk of ischemic events is found to be significantly lower among patients taking 2 gm of icosapent ethyl twice daily with statins as compared to statin therapy alone
CLEAR Harmony (Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol) trial	Addition of bempedoic acid to maximally tolerated statin therapy reduced the LDL cholesterol levels without an increase in adverse events
AFIRE (Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease) trial	In patients with AF and stable coronary artery disease, rivaroxaban monotherapy when compared to rivaroxaban and aspirin was seen to be similar in efficacy and superior for safety
THEMIS (Ticagrelor in Patients with Stable Coronary Disease and Diabetes) trial	In diabetic patients with stable CAD without prior ACS or stroke, ticagrelor plus aspirin was seen to have lower incidence of ischemic cardiovascular events but at a cost of higher major bleeding events than those who received placebo plus aspirin
TWILIGHT (Ticagrelor with or without Aspirin in High-Risk Patients after PCI) trial	Double blind trial. Conducted in high risk patients undergoing PCI, ticagrelor alone when compared to combination of ticagrelor and aspirin after 3 months of dual antiplatelet therapy was seen to have similar risk of death, MI, or stroke and a lower incidence of clinically important bleed
STOP DAPT-2(Effect of 1 month dual antiplatelet therapy(DAPT) followed by clopidogrel versus 12 month DAPT on CV and bleeding events in patients receiving PCI)	Multi-center, open label, randomized trial, tested a very short-term DAPT versus 12 DAPT, and found a lower rate of CV and bleeding events
DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) trial	Phase-3 placebo controlled trial. In HFrEF, dapagliflozin reduced the risk of worsening of HF or CV death irrespective of diabetic status
EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial	Type 2 diabetic patients who are at high risk for CV events were found to have reduced CV events and mortality when they received empagliflozin as compared with placebo
ISCHAEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial	Among patients with stable CAD and moderate to severe ischemia on stress testing, routine invasive therapy failed to reduce major adverse cardiac events compared with optimal medical therapy. Routine invasive therapy was associated with harm at 6 months (increase in periprocedural MIs) and associated with benefit at 4 years (reduction in spontaneous MI)
POET (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis) trial	Left sided infective endocarditis patients in stable condition had similar outcomes with a shift to oral antibiotics after 10 days of intravenous antibiotics as compared to continued intravenous antibiotics
PARTNER-3 (Transcatheter aortic valve replacement with a balloon expandable valve in low risk patients)	In severe aortic stenosis patients with low surgical risk, transcatheter aortic valve replacement with balloon expandable valve had lower risk of composite of death, stroke, or rehospitalization at the end of 1 year

twice daily. Patients on sacubitril-valsartan had a greater reduction in the N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels than the enalapril group from baseline till weeks 4 and 8. It was interesting to see that there was a decrease in the NT-proBNP levels as early as week 1. There was no significant difference noted in incidence of worsening renal function, angioedema, symptomatic hypotension, and hyperkalemia in the two groups.

Acute Coronary Syndrome

Acute coronary syndrome (ACS) comprises patients with angina and evidence of characteristic electrocardiographic changes and/or evidence of myocardial damage with biochemical markers. Patients may present with unstable angina, non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI). Its management comprises of antiplatelet drugs and evaluation of coronaries by coronary angiogram according to clinical presentation.

AUGUSTUS (Antithrombotic Therapy after ACS or PCI in Atrial Fibrillation) Trial[2]

Patients with atrial fibrillation (AF) with an ACS or who undergo percutaneous coronary intervention (PCI) require an appropriate antithrombotic regimen requiring anticoagulants in addition to the antiplatelets. This trial evaluated such patients who need to be on a P2Y12 inhibitor, and was randomized to either apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for a duration of 6 months. This trial concluded that patients with AF and ACS or post PCI who are planned for a P2Y12 inhibitor, apixaban, without aspirin, resulted in lesser bleeding events and hospitalizations, however, in the absence of significant differences in ischemic events as compared to the patients on vitamin K antagonist, aspirin, or both.

ISAR-REACT-5 (Ticagrelor or Prasugrel in Patients with ACSs) Trial[3]

In this randomized trial patients with ACS who were planned for invasive evaluation received either ticagrelor or prasugrel. The primary end-point was defined as composite of death, myocardial infarction (MI), or stroke at 12 months was seen in lesser patients on prasugrel as compared to ticagrelor (HR, 1.36; P=0.006). Bleeding event rates were similar in both the groups. Further, it was noted that the incidence of death, MI, or stroke was significantly lower in the patients receiving prasugrel than those with ticagrelor.

COLCOT (Efficacy and Safety of Low-Dose Colchicine after MI) Trial[4]

Colchicine is a mainstay therapy for hyperuricemia and is used frequently for management of pericarditis. This study tested effect of colchicine in patients with MI. Within 30 days, patients with MI were randomized to colchicines (0.5 mg once daily) or placebo. The composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization requiring revascularization was significantly lower in the colchicine group than the placebo (P=0.02). Thus, colchicine was seen to significantly lower the risk of ischemic cardiovascular events than placebo.

Revascularization in ACS

PCI of the culprit lesion in STEMI is shown to lower risk of cardiovascular morbidity and mortality.

COMPLETE (Complete Revascularization with Multivessel PCI for MI) Trial[5]

STEMI patients with multivessel coronary artery disease undergoing PCI of the culprit lesion were randomized to complete revascularization with PCI or no further revascularization. Further, these patients according to planned timing of non-culprit PCI (either during or after the index hospitalization) were randomized in groups. It was seen that at 3-year median follow-up, the composite of MI and CV death, or composite MI, CV death, and ischemia driven revascularization was lower in the complete revascularization group. This was irrespective of the timing of the complete revascularization.

Cardiovascular Drugs

Drugs for Dyslipidemias

REDUCE-IT (Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia) Trial[6]

In patients with known cardiovascular disease or who are at risk of CVD, this trial evaluated the effect of Icosapent ethyl (IPE) on cardiovascular events as compared to

placebo. Elevated triglyceride levels are an independent marker for ischemic events. IPE, a highly purified and stable eicosapentaenoic acid (EPA) when used as an adjunct to the diet in patients with triglyceride levels at least 500 mg/dL, lowers the triglyceride levels and in addition has been seen to have anti-inflammatory, plaque stabilizing, and also membrane stabilizing properties. Patients were started on 2 gm of IPE in addition to statins with fasting triglyceride level of 135–499 mg/dL and an LDL (low-density lipoprotein) cholesterol level of 41–100 mg/dL were randomized to receive 2 gm of IPE twice daily (total daily dose, 4 gm) or placebo. The primary outcome of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina was seen less in the drug group as compared to the placebo group (P<0.001). Additionally, the secondary outcome of cardiovascular death, nonfatal MI, or nonfatal stroke occurred in 11.2% in icosapent group and in 14.8% of patients in the placebo group (P<0.001). Hence, it was seen that IPE added with statins lowers the risk of ischemic events.

CLEAR Harmony (Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol) Trial[7]

Bempedoic acid is a prodrug, acts liver-specific, and lowers LDL cholesterol by inhibiting ATP citrate lyase, an enzyme which acts upstream of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A). This was a phase 3 randomized, double blind placebo controlled trial done in patients on highest tolerated doses of statins (alone or in combination with other drugs) with evidence of atherosclerotic cardiovascular disease, heterozygous familial hypercholesterolemia, or both. These patients were enrolled if LDL cholesterol level was at least 70 mg/dL and then were randomized to either bempedoic acid or placebo. There was reduction at 12 weeks in the LDL levels (19.2 mg/dL) translating to a change of 16.5% from baseline. The adverse events did not differ substantially between the two groups; however, more patients discontinued treatment due to adverse events in the bempedoic acid. The safety and efficacy was similar irrespective of the dose of statins used.

Antiplatelet Drugs

Antiplatelet drugs form the cornerstone of treatment in patients with coronary artery disease and patients undergoing percutaneous coronary interventions. Here, we describe the important trials evaluating the antiplatlet drugs in stable coronary artery disease, ACSs, and post PCI patients.

AFIRE (Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease) Trial[8]

In this trial, patients with AF undergoing PCI or coronary artery bypass grafting (CABG) more than a year back or who had evidence of insignificant coronary artery disease as documented by an angiogram were randomized to either rivaroxaban alone or a combination therapy with rivaroxaban plus a single antiplatelet agent. The primary (efficacy) end-point was a composite of MI, stroke, systemic embolism, unstable angina needing revascularization, or death from any cause. The primary end-point (safety) was major bleeding. It was decided to stop this trial early due to increased mortality noted in the combination therapy group. It was seen that rivaroxaban when given alone showed non-inferiority as compared to the combination therapy for the primary efficacy end-point. For the safety end-point, rivaroxaban alone was superior to combination therapy. Hence, to summarize rivaroxaban when given alone in patients with AF and stable CAD is non-inferior for efficacy and superior for safety when compared to the combination therapy of rivaroxban and aspirin.

THEMIS (Ticagrelor in Patients with Stable Coronary Disease and Diabetes) Trial[9]

Patients with diabetes and stable coronary artery disease have a higher risk of cardiovascular events as compared to non-diabetics. This trial tested whether addition of ticagrelor to aspirin in diabetics with a stable coronary artery disease with no previous history of MI or stroke, improves ischemic outcomes. Ticagrelor proved to reduce the incidence of ischemic events group (7.7% vs. 8.5%; P=0.04), but was associated with a higher bleeding events (2.2% vs. 1.0%; P<0.001). Further, it is to be noted that although the risk of intracranial bleed was higher (0.7% vs. 0.5%; P=0.005), but the incidence of fatal bleed was not different as compared to the placebo (0.2% vs. 0.1%; P=0.11). Hence, addition of ticagrelor to aspirin reduced the ischemic events but simultaneously increased major bleeding rates.

TWILIGHT (Ticagrelor with or without Aspirin in High-Risk Patients after PCI) Trial[10]

Post PCIs, after a period of dual antiplatelet therapy, most patients are preferrably shifted to a single antiplatelet drug. This dual antiplatelet therapy is given to reduce thrombotic risk in patients undergoing PCI, which is higher in case of certain clinical factors like diabetes or angiographic factors. Antiplatelet therapy is prescribed to maintain a balance between antithrombotic activity and risk of bleed. P2Y12 inhibitors alone have been evaluated in such patients in order to decrease the risk of bleed while maintaining safety after dual antiplatelet therapy. Here in this study, ticagrelor alone was compared to ticagrelor with aspirin after 3 months of dual antiplatelet (ticagrelor + aspirin) therapy for clinically important bleeding events or ischemic events in patients who were post PCI and had a higher risk of bleed. These patients were randomized to receive either aspirin or placebo after 3 months till 1 year. The bleeding events as defined by Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding was the primary outcome. The primary end-point was 4% in ticagrelor group versus 7.1% in ticagrelor plus aspirin group (P<0.001).

The incidence of death from any cause, nonfatal MI or nonfatal stroke, was 3.9% in both groups (P<0.001 for non-inferiority). Hence, ticagrelor monotherapy after 3 months of dual antiplatelet therapy was seen to reduce clinically relevant bleeding events without an increase in death, MI, or stroke.

STOPDAPT-2 (Effect of 1-Month Dual Antiplatelet Therapy Followed by Clopidogrel vs. 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI) Trial[11]

Current guidelines recommend a 12-month dual antiplatelet therapy for patients undergoing PCI. This trial evaluated a very short-term (1 month) dual antiplatlet therapy (DAPT) after PCI with a cobalt-chromium everolimus eluting (Co-Cr EES) stent in patients with high bleeding risk. Patients receiving 1-month DAPT followed by clopidogrel monotherapy were compared to 12 months of DAPT (aspirin and clopidogrel). The investigators found that very short duration of DAPT followed by clopidogrel monotherapy, compared with 12 months of DAPT, led to a significantly lower rate of a composite of cardiovascular and bleeding events, fulfilling the criteria for both non-inferiority and superiority. These findings suggest that a shorter duration of DAPT may provide benefits in patients undergoing Co-Cr EES, however, needs further testing in a larger trial involving other populations.

Diabetes and Cardiovascular Disease

DAPA-HF (Dapagliflozin in Patients with HF and Reduced Ejection Fraction) Trial[12]

Patients with diabetes mellitus type 2 have increased risk of cardiovascular disease and HF. The newer addition to diabetes treatment includes the inhibitors of sodium-glucose cotransporter 2 (SGLT2). These have been seen to reduce the rate of hospitalization for HF in diabetic patients. Whether SGLT2 inhibitors will reduce the risk of first hospitalization for HF with reduced ejection fraction irrespective of diabetic status is unknown and was studied in this trial. Patients with New York Heart Association (NYHA) class II, III, or IV HF and an ejection fraction ≤40% on recommended therapy were randomized to either dapagliflozin (10 mg once daily) or placebo. The primary outcome of composite of worsening HF (hospitalization or a visit needing an intravenous therapy for HF) was seen in lesser patients on dapagliflozin than in placebo group (16.3% vs. 21.2%, P<0.001). Death from cardiovascular causes were also less frequent in dapagliflozin group as compared to placebo (hazard ratio, 0.82; 95% CI, 0.69–0.98). These findings were similar in diabetics and non-diabetics. The frequency of adverse events also did not differ. Hence, it was concluded that in HF and a reduced ejection fraction, addition of dapagliflozin to guideline directed therapy reduced the risk of worsening HF or CV death, regardless of the presence or absence of diabetes.

EMPA-REG Outcome (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) Trial[13]

Empagliflozin, an inhibitor of sodium–glucose cotransporter 2, was studied in this trial and its effect on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk was evaluated. EMPA-REG outcome trial was done in patients with cardiovascular disease (10% had HF) and showed favorable outcome in terms of nonfatal MI, cardiovascular death, and nonfatal stroke. Further, a reduction in risk of hospitalization was seen, in addition to an improved renal

outcome. Among patients receiving empagliflozin, there was an increased rate of genital infection noted without an increase in other adverse events.

Trials for Stable Coronary Artery Disease

ISCHAEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) Trial[14]

Various studies have been done in the past comparing the different treatment strategies in patients with stable coronary artery disease. However, quantification of ischemia and relation to outcomes in such subset of patients has not been evaluated. In ISCHEMIA trial, these patients were tested with stress testing and a blinded computed tomographic evaluation of coronaries was done in those with moderate to severe ischemia. Patients having significant unprotected left main disease and non-significant CAD were excluded. Subsequently, these patients were randomized to two groups, one group underwent cardiac cathetrization and revascularization plus optimized medical therapy (OMT), and the other group being optimized medical therapy alone. It is worth noting that patients who failed on OMT underwent an invasive strategy. It was interesting to find that composite of CV death, MI, or hospitalization for unstable angina, HF, or resuscitated cardiac arrest was not different significantly in both the groups. Both the groups had lower incidence of death from any cause. Further, an improvement in symptoms was noted with invasive strategy more so in patients who had angina more frequently which was seen till 12 and 36 months. There are certain limitations which need to be seen, first being the power of the study which was reduced with lesser patients than was planned. Secondly, the effect of complete revascularization has not been reported as of now. Moreover, effect on left main disease, left ventricular dysfunction, ACS patients, and more symptomatic patients needs to be analyzed further.

Valvular Heart Disease

POET (Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis) Trial[15]

Infective endocarditis (IE) is managed with a prolonged course of intravenous antibiotics, the duration depends on the pathogen cultured. This trial evaluated the safety and efficacy of shift to oral antibiotics from intravenous antibiotics in stable patients with left sided IE caused by streptococcus, Enterococcus faecalis, Staphylococcus aureus, or coagulase-negative staphylococci. These patients who were stable and treated with intravenous antibiotics were randomized to continue intravenous treatment or to switch to oral antibiotic treatment. All patients received intravenous antibiotics for at least 10 days. If found stable, patients in the orally treated group were discharged and followed in outpatient department. There was no significant difference noticed in the primary outcome of all-cause mortality, embolism, unplanned cardiac surgery, or relapse of bacteremia with the primary pathogen [12.1% (I/V) vs. 9.0% (oral), P=0.40], till 6 months after completion of antiobiotic treatment. Hence, in stable patients of left sided IE, a shift to oral antibiotics was seen to be non-inferior than continued intravenous antibiotic therapy.

PARTNER-3 (Transcatheter Aortic Valve Replacement with a Balloon Expandable Valve in Low Risk Patients)[16]

Transcatheter aortic valve replacement (TAVR) is widely being done for high and intermediate surgical risk patients with severe aortic stenosis. In low surgical risk patients, the benefit of balloon expandable TAVR was evaluated in this randomized trial. One thousand patients were randomized to transfemoral TAVR or surgery. At the end of 1 year the primary outcome, a composite of death, stroke, or rehospitalization was less with TAVR as compared to surgery. However, this needs to be individualized after a heart team meeting as durability, and TAVR in younger age groups need further evaluation.

Conclusion

Cardiovascular science is a vital part of medicine and is being investigated aggressively. For physicians, being updated in this period of evidence-based medicine is important. In this chapter, we have summarized the recent key trials that were published and presented in the field of cardiology. Many of these studies will help guide clinical practice and guideline updates. Others have shown encouraging early data to guide further research development.

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CHAPTER

44

Iron Deficiency and Iron Deficiency Anemia in Chronic Heart Failure: A High Risk

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Abstract

Iron deficiency with or without anemia in chronic heart failure remains a very important issue and is associated with increase in morbidity and mortality. Various studies and trials have convincingly proved that management of deficiency of iron by intravenous iron therapy scores over oral iron therapy in improving the different parameters of exercise capacity, morbidity, and in decreasing the overall incidence of mortality. Thus, proper evaluation and management of iron deficiency in chronic heart failure needs utmost care and attention.

Introduction

Heart failure (HF) is one of the major public health problems, overall, about 2% of adult population suffers, the prevalence increases with rising age affecting 6–10% of people over age 65. Despite many advancement and advent of newer therapeutic approaches, prognosis of symptomatic HF remains poor. This sad scenario is compounded by the occurrence of anemia in general and iron deficiency anemia or only iron deficiency in particular. *Iron deficiency (ID)* is detected to be a frequent association with *chronic heart failure (CHF)* and is an important factor for reduced quality of life (QoL), diminished exercise ability and poor prognosis including recurrent hospitalization and mortality whether present with anemia or no anemia. Management with IV iron has been convincingly shown to improve the situation in different trials. Despite these facts, looking for ID in HF is not in the priority list of physicians leading to underdiagnosis and consequently undertreatment of deficiency of iron. Thus, as per evidence from many trials, ID needs to be recognized as high-risk factor in respect to consequences of CHF and evaluation of deficiency of iron requires to be included in the routine workup for CHF with proper management.

Prevalence of ID in CHF

Thirty-five to fifty percent of patients with HF found to suffer from ID and it remains the most significant cause of anemia in HF; however, ID without anemia is found to be associated with 46% of systolic HF.[1] An international cohort of 1,506 patients with CHF observed presence of ID to be closely associated with severity of HF with reduced ejection fraction assessed by New York Heart Association (NYHA) functional class or NT-pro BNP level.[1] Similar association of ID and severity of HF is also observed by Okonko et al.[2] and Jankowska et al.[3] Women found to have higher prevalence of ID in CHF.

However, the study done for prevalence of ID in HF with preserved ejection fraction (HFpEF) is comparatively much less but then similar rate of ID is reported in HFpEF compared to HF with reduced ejection fraction (HFrEF).[1,4] A small observational study showed the prevalence of 57% in HFpEF.

Etiology of Anemia and Iron Deficiency in Heart Failure

The development of anemia with HF can result from various etiologies such as a dilutional anemia, anemia of chronic disease, and blunted erythropoietin response with ID being the most significant cause.[5,6]

The causes of ID in CHF are multifactorial. In general, less dietary intake, disturbed absorption, and chronic blood loss cause ID. But besides these, increase in hepcidin level due to the inflammatory state induced by HF and liver congestion in CHF leads to diminished iron absorption and increased reticuloendothelial block of releasing iron for utilization resulting in ID and anemia.[7]

Definition of Iron Deficiency in HF

Iron deficiency is classified as absolute and functional and patients with CHF are prone to suffer to both forms. Absolute ID represents decline in total body iron store that is reduced or absent storage iron in bone marrow, liver, and spleen caused by improper dietary intake, disturbed gastrointestinal absorption, and prolonged blood loss whereas functional ID refers to impaired iron delivery to target cells despite normal or overly abundant iron stores due to chronic inflammation via increase in hepcidin production resulting in inhibition of iron exporter ferroportin leading to impaired iron absorption and utilization.

Diagnosis of ID in HF

Diagnosis of ID in CHF based on serum ferritin level warrants consideration of HF associated inflammatory state. The standard cut-off value of serum ferritin for diagnosis of ID in general is less than 30 mcg/L. But then this value does not apply in case of CHF as serum ferritin is an acute phase reactant and CHF underlies an inflammatory state.[6]

Presently based on landmark FAIR-HF study[8] and thereafter inclusion of the very criteria in 2012 ESC Guidelines on diagnosis and treatment of HF, serum ferritin level less than 100 mcg/L defines absolute ID, and serum ferritin level between 100–299/L combined with a transferrin saturation (TSAT) less than 20% defines functional ID.

Iron Deficiency and Cardiac Function

Iron deficiency leads to well-known derangement of erythropoiesis resulting in ID anemia affecting oxygen carrying capacity of blood with its effect on cardiac function. Besides this iron is incorporated in enzymes like cytochromes, peroxidases, and others subserving important and critical role in body metabolism including cellular immunity and so chronic deficiency of iron on its own leads to derangement of cellular energy mechanism including oxidative metabolism and immunity related activity resulting in impairment of functional and structural quality of myocardium culminating in LV dysfunction.

Clinical Outcome of ID in CHF

A number of studies have convincingly shown that ID impairs exercise capacity, causes poor QoL and leads to poor prognosis with recurrent hospitalization and enhanced mortality independent of anemia and left ventricular ejection fraction.

Okonko et al.[2] and Jankowska et al.[9] found that patients with CHF and ID suffers *poor exercise capacity* irrespective of hemoglobin level and severity of heart disease.

Iron deficiency independent of anemia has been shown to be accompanied by *suboptimal QoL* as measured by Minnesota Living with Heart Failure Questionnaire (MLHFQ), lower the TSAT lower is the QoL.[9,10] In a post-hoc analysis of CHF patients showed that patients with ID presented with poorer QoL compared with those having no ID.[4]

Several studies revealed that ID is an independent and strong predictor of poor prognosis in HF. In a large study of 1,506 CHF patients by Klip,[1] patients having ID showed remarkably *higher rates of mortality* at 6 months (8.7% vs. 3.6%) persisting throughout the study duration. Okonko et al.[2] in their study on 157 CHF patients found ID to be prognostically more ominous than anemia. In a big cohort of CHF patients, Jankowska et al.[3] observed that ID is a strong predictor of poor prognosis related to hospitalization and mortality with 3 years survival of 59% for patients suffering ID compared to 71% without having ID.

A cross-sectional study of 447 patients of HFpEF, iron deficient patients showed worse performance in the 6-minute walk test and poor QoL on MLHFQ compared to patients with normal iron status.[11]

Thus, *ID with or without anemia represents a high-risk factor* for worsening of symptoms of HF including poor QoL, diminished exercise ability, and increased hospitalization and mortality.

Treatment

Obvious clinical importance of ID and its high prevalence in CHF make restoration of iron status essential together with care of the cause of ID.

Use of oral iron is not favored because of its poor absorption due to CHF induced edema and congestion of gut mucosa together with high hepcidin level besides interaction with diet or drug, and because of need of much prolonged duration of treatment needed with oral iron to achieve the target. Clinical trial also does not support oral iron therapy. IRONOUT trial[12] using oral iron did not found betterment of exercise capacity over 16 weeks and also no change observed in iron biomarker. IRON-HF trial comparing oral iron versus IV iron showed clinically relevant difference in improvement of exercise capacity favoring IV iron; however, it lacks statistical power.

IV iron proves to be effective and its use is well supported by different clinical trials. It is cost effective as it saves expenditure by cutting down the given recurrent hospitalization in ID patients and by improving the survival.

FAIR-HF trial[8] comparing *ferric carboxy maltose* (FCM) versus placebo showed unexpected significant improvement in QoL, symptoms, and exercise capacity accessed by 6-minute walk distance test on IV iron arm in patients of CHF and ID with or without anemia. All patient's subgroup based on hemoglobin level, renal function, sex, and ejection fraction showed the improvement. NYHA functional class and global assessment of patient also showed betterment with IV FCM.

CONFIRM-HF trial[13] using FCM in symptomatic HF showed significant improvement in exercise capacity accessed by 6-miute walk distance at 24th week, also led to diminished risk of hospitalization for worsening HF at week 52.

Bolger et al.,[14] Tolle et al.,[15] Usmanov et al.,[16] and Ferric-HF trial[17] used *IV iron sucrose* supplementation in patients of CHF with ID and/or anemia and observed improvement in markers of iron status and also in exercise capacity, NYHA functional class, 6-minute walk distance and QoL.

Data relating to IV Iron treatment for ID in HFpEF is limited. Ongoing FAIR-HFpEF Study and PREFER-HF trial addressing the issue of benefit of IV iron treatment in patients with HFpEF and ID will resolve the query.

Nunes data[18] revealed that FCM therapy in 459 HF outpatient with ID resulted in increase in hemoglobin and TSAT and also found FCM to be well tolerated; moreover, higher doses of FCM (1,000 mg) showed a significant higher efficacy compared with lower dose (500 mg).

Thus, IV iron needs to be used for CHF with ID with or without anemia. However, comparative data for the different IV iron compounds are not available. But then FCM provides the advantage of high dose (500 mg) formulation and is well tolerated. The therapeutic target may be achieved with one or two injections only.

Guidelines for Treatment of ID in CHF Patients

2016 ESC guidelines for the diagnosis and treatment of acute and CHF[19] recommended to include serum ferritin and TSAT evaluation to screen ID for initial assessment of newly diagnosed HF (Class 1, Level C) and also recommends IV FCM for treatment of ID-Class IIA, Level A **(Table 1)**.

2017 ACC/AHA/HAS focused update of the 2013 ACCF/AHA guideline for management of HF[20] also recommends that in NYHA Class II to III patients with ID (Class II, Level B), IV iron might be reasonable to improve QoL and functional status **(Table 2)**.

Present Scenario in Clinical Workup/ Management for ID in CHF

PReP prospective registry[21] revealed that ID and anemia many a times remain unappreciated in CHF ambulatory patients by physicians despite its well-known high prevalence and clinical implication.

In a substudy of RAID-F registry,[22] it is observed that screening for ID in CHF and IV iron therapy for treating ID in CHF is much under practiced; oral iron found to preferred to be the first choice despite the fact that evidence favors use of IV iron.

TABLE 1 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure

Recommendations for the treatment of other comorbidities in patients with heart failure		
Recommendations	***Class***	***Level***
Iron deficiency		
I V FCM should be considered in symptomatic patients with HFrEF and I D (serum ferritin < 100 mcg/L, or ferritin between 100-299 mcg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	II a	A

TABLE 2 2017 ACC/AHA/HAS focused update of the 2013 ACCF/AHA guideline for management of HF

COR	*LOE*	*Recommendations*	*Comment/Rationale*
IIb	**B-R**	In patients with NYHA CLASS II and III HF and ID (ferritin <100 ng/L or 100-300 ng/L if transferrin saturation is <20%). IV iron replacement might be reasonable to improve functional status and QoL	NEW: New evidence consistent with therapeutic benefit.
III: No Benefit	**B-R**	In patients with HF and anemia, erythropoietin – stimulating agents should not be used to improve morbidity and mortality.	NEW: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.

Conclusion

Iron deficiency with or without anemia is one of the most common and important comorbidities of CHF and evidences reveal that ID is a high-risk factor for poor consequences of CHF in terms of increased morbidity and mortality. IV iron therapy proved to improve HF symptoms, QoL, 6-minute walk distance, New York Heart Association (NYHA) functional class, and results in better survival with decrease in recurrent hospitalization for worsening HF symptoms. Oral iron is not found to have comparable efficacy.

Thus, as per the evidences and so also as suggested by guidelines, screening for ID should be included in routine workup of all cases of HF and IV iron must be considered for its treatment.

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CHAPTER

45 Peripartum Cardiomyopathy

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Abstract

Peripartum cardiomyopathy is defined as symptomatic heart failure with reduced ejection fraction in last month of pregnancy and up to 5 months postpartum. Common risk factors include older maternal age, multiparity, and preeclampsia, Suggested etiopathogenesis includes nutritional deficiencies, viral myocarditis, and autoimmune process. Treatment in acute decompensated heart failure includes intravenous vasodilators, diuretics, digitalis. Data regarding use of vasopressors and bromocriptine is limited. Prognosis is variable. Between 50–60% of women completely recover normal heart size and function usually within 6 months of delivery. Patient with severe cardiac dysfunction should be considered for heart transplantation.

Introduction

Peripartum cardiomyopathy (PPCM) that affects women of childbearing age is a type of heart failure (HF) with reduced ejection fraction (systolic heart failure). Usually PPCM affects women during pregnancy or in early postpartum period.[1] In 1930, PPCM was recognized a distinct entity although it was first described as early as in the 18th century. Demakis et al. described the syndrome as "The peripartum cardiomyopathy" in 1971.[2]

The symptoms of PPCM are like the normal findings of late pregnancy. Thus, there is a delay in diagnosis usually. The severity and mortality vary from patient to patient. It is a relatively rare disease and the exact incidence in India is not documented, but a study from a tertiary care hospital from South India reports an incidence of 1 case per 1,374 live births.[3]

Definition

In women presenting with HFrEF, PPCM is a diagnosis of exclusion. It was earlier defined as symptomatic HF in the last month of pregnancy and up to 5 months postpartum.

Now, the 2010 Heart Failure Association of the European Society of Cardiology Working Group revised the definition of PPCM to "an idiopathic cardiomyopathy presenting with HF secondary to LV systolic dysfunction toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found." This diagnostic criterion indicates that EFis less than 45% and there may/may not be ventricular dilatation.[4] Outcomes can be complete recovery or rapid deterioration, persistent myocardial dysfunction, and HF leading to urgent mechanical circulatory support and cardiac transplantation.

Risk Factors

Many risk factors like African ancestry, older maternal age, hypertension, etc. have been associated with PPCM. The risk factors are summarized in **Box 1**.

Pathophysiology

The etiology of PPCM is multifactorial. Suggested etiopathogenesis of PPCM includes nutritional

BOX 1 Risk factors for peripartum cardiomyopathy

- African ancestry
- Pre-eclampsia and hypertension
- Multifetal pregnancies
- Multiparity
- Older maternal age
- Family history of cardiomyopathy
- Obesity
- Cocaine abuse, alcohol abuse
- Smoking
- Long duration of tocolytic therapy
- Selenium/zinc deficiency

deficiencies, viral myocarditis, and autoimmune process. Two vascular-hormonal models of pregnancy-associated cardiomyopathy were developed. These models suggested novel mechanisms for PPCM in humans. The 1st model—a STAT3 knockout mouse. In this model oxidative stress led to cleavage of the prolactin. This 16-kDa prolactin fragment was vasculo-toxic and pro-apoptotic, leading to vascular and myocardial dysfunction. Treatment with bromocriptine, a suppressor of prolactin secretion, had complete reversal of the condition in mice. Human prolactin has been more resistant to cleavage than prolactin in mice.

The 2nd model—cardiac-specific genetic deletion of proliferator-activated receptor gamma coactivator-1a (PGC-1a). This led to vasculo-toxicity by activation of prolactin fragment and decreased expression of proangiogenic vascular endothelial growth factor (VEGF). In this case there is only partial reversal with bromocriptine. For complete recovery addition of VEGF is required. In pre-eclampsia the levels of soluble Fms-like tyrosine kinase-1 (sFlt1), an antagonist of VEGF and placental growth factor are elevated markedly. Elevated sFlt1 levels also have been found in women with worse outcomes in PPCM.

Genetics

Observations suggest familial clustering of PPCM. Genetic contribution can be suggested by 6% co-occurrence with idiopathic dilated cardiomyopathy (DCM). A GWAS identified a single-nucleotide polymorphism near the *PTHLH* gene, which regulates vascular homeostasis. Rare pedigree evaluation suggests that both PPCM and DCM had likely pathogenic variants in genes, which were known to contribute to DCM-TTN and BAG3. But more than 90% subjects with TTN truncating variants do not develop DCM or PPCM suggesting that additional environmental genetic or epigenetic factors play a role. Incompletely penetrant genetic origin and role of additional factors is suggested by the fact that most women with PPCM do not have a family history of cardiomyopathy and it does not always recur with a subsequent pregnancy.

Clinical Features

The presentation of PPCM is indistinguishable from non-pregnant patients with systolic dysfunction or DCM. New/rapid onset of symptoms requires urgent evaluation. Most women are diagnosed typically in the 1st month postpartum. The symptoms are cough, fatigue, palpitations, orthopnea, chest pain, hemoptysis, weight gain, and unexplained abdominal pain. Signs of PPCM are enlarged heart, tachycardia, decreased SpO_2, elevated JVP, presence of S_3, and loud P_2. Mitral and Tricuspid regurgitation and pulmonary rales are noted. Worsening of peripheral edema, hepatomegaly and ascites may be seen. Arrhythmias are commonly found, which may lead to embolic phenomenon either peripheral or pulmonary. Moderate pericardial effusion may be seen. Findings of pre-eclampsia must be evaluated. High output cardiac failure has also been reported in some patients.

Diagnosis

Various cardiac diagnostic modality including imaging and biochemical investigations are used to identify PPCM. The investigations recommended and findings associated with PPCM are:

- *Chest X-ray:* Findings suggestive of PPCM are cardiomegaly. Also pulmonary venous congestion with interstitial/alveolar edema. Pleural effusion may be found. Chest X-ray should be avoided in pregnancy as findings are not specific and if needed an abdominal shield is used.
- *Electrocardiography:* Heart rate is usually normal. Sinus tachycardia, atrial fibrillation, other conduction abnormalities with nonspecific ST segment changes may be present.
- *Echocardiography:* This is the most important tool for evaluation and follow-up for women with PPCM.

Overall features of PPCM are like primary non-ischemic DCM. The findings on echocardiography are a decrease in myocardial systolic function, as manifested by reduction in left ventricular ejection fraction (LVEF) or fractional shortening. In women presenting late, left ventricular dilatation is frequently evident. Mild compensatory left ventricular hypertrophy can be seen. In early and immediate postpartum period a small pericardial effusion is found on echocardiography. Mitral insufficiency secondary to annular dilatation is seen when there is marked LV enlargement. Other reported findings are tricuspid/pulmonary regurgitation, left atrial/biatrial enlargement and intracardiac thrombus.

- *Endomyocardial biopsy:* The usual findings are features of myocarditis. Biopsies in patients with PPCM when performed earlier after symptom onset have the highest yield. Endomyocardial biopsy is not routinely recommended yet.
- *Viral and bacterial titer & cultures:* In selected cases antibody titer of virus like Coxasckie B should be considered. This approach is more useful for research than diagnosis.
- *Cardiac MRI (CMR):* Nowadays a highly studied and used entity at higher centers. CMR can characterize the myocardium and is used to measure global and myocardial contraction. Delayed gadolinium contrast enhancement can differentiate myocarditis from ischemia as a mechanism of myocyte necrosis. Myocarditis has a subepicardial nonvascular distribution with a nodular/band-like pattern while ischemia has a subendocardial or transmural vascular distribution. Chamber measurements can also be done. CMR can also be used as a guide for biopsy. It is a useful prognostic tool as well.[5]
- *Right heart catheterization:* Used for assessment of the filling pressure and cardiac output in patients with persistent HF, hemodynamic instability/evidence of an organ dysfunction. Enlargement of atria and ventricles will also be demonstrated.
- *Biochemical evaluation:* Creatine kinase and cardiac troponin evaluation is usually not significant in diagnosis. Brain natriuretic peptide (BNP) & N-terminal pro-BNP levels are elevated in PPCM patients.

Differential diagnosis of HF in pregnancy has been listed in **Box 2**.

BOX 2 Diffential diagnosis of heart failure in pregnancy

- Takotsubo cardiomyopathy
- Familial cardiomyopathy
- Pre-existing cardiomyopathy
- Recurrent peripartum cardiomyopathy
- Pre-eclampsia
- Hypertrophic cardiomyopathy
- Myocarditis consider
- Arrhythmogenic right ventricular cardiomyopathy
- Left ventricular noncompaction
- Valvular heart disease
- Congenital heart disease
- Tachycardia-arrhythmia mediated cardiomyopathy
- Hypertensive heart disease
- Ischemic heart disease
- Cardiomyopathy related to other systemic medical diseases and acute conditions
- Pulmonary embolism

Management

The most important concern for medical treatment in PPCM is fetal safety. To prevent thromboembolic complications in PPCM superimposed by the hypercoagulable state of pregnancy, anticoagulation is required especially in severely decreased LVEF during late pregnancy and 6–8 weeks postpartum. American Heart Association recommends anticoagulation when the EF is less than 30%,[6] while European Society of Cardiology when EF less than 35% as the threshold.[7] Warfarin is avoided during pregnancy. Low-molecular-weight heparin can be used. During lactation warfarin and low-molecular-weight heparin are safe. Novel anticoagulants are not studied widely in this context and not recommended as of now.

Experimental Treatment

Bromocriptine (dopamine agonist and inhibitor of release of prolactin) has been tried in PPCM based on the research that in mouse model PPCM is caused by the antiangiogenic and proapoptotic 16-kDa form of prolactin. Many studies have been done on this approach but still evidence is lacking. Implications on breast feeding also discourage its use. REBIRTH study—a randomized double-blind, placebo control (Randomized Evaluation of BromocriptineIn Myocardial Recovery Therapy) to investigate the effect of bromocriptine on myocardial

recovery and clinical outcome in PPCM with 200 women in the USA and Canada has been proposed by the IPAC group and is under evaluation. The 2018 ESC guidelines include a Class IIb recommendation for the use of bromocriptine.[8] Its use is also associated with thrombotic complications.

Treatment of Severe PPCM

In acute decompensated HF, intravenous vasodilators like nitroglycerin may be needed in during pregnancy. Inotrope Dobutamine has adverse effects and Levosimendan was not shown to improve outcomes in PPCM. Milrinone and Levosimendan showed comparable hemodynamic improvement.

Advanced therapies for cardiogenic shock during/shortly after pregnancy are mechanical circulatory support with intra-aortic balloon pump (IABP), percutaneous left ventricular assist device therapy, and extracorporeal membrane oxygenation (ECMO). These should be used early in women with hemodynamic instability in PPCM. Cardiac transplant has been shown to have higher chances of complications.

Labor and Delivery

A combined effort of cardio-obstetrics team is required to minimize maternal and fetal mortality. Timing and mode of delivery should be discussed with experts. To avoid prematurity and associated fetal complications stabilization of mother should be done. Early delivery is prompted in the setting of hemodynamic instability despite medical therapy. Vaginal delivery is recommended in stable patients except for obstetric cesarean section indications. Invasive hemodynamic optimization before delivery and strict monitoring is benefitting in unstable patients. After delivery relieving of caval compression, autotransfusion due to uterine contractions and fluid mobilization contribute to increase in preload. Thus, risk of fluid overload and pulmonary edema must be taken care of.

TABLE 1 Subsequent pregnancies in PPCM: counseling and management[1]

Subsequent pregnancy	*Recovered (LVEF ≥50%)*	*Nonrecovered (LVEF <50%)*
Preconception/First Visit	• Risk counseling • Follow-up planning • Clinical & EF reassessment of RAAS blocking agents for 3 months • Baseline Echo & BNP/NT-proBNP level	• Risk counseling also discussion of alternative ways to build a family • If not considering termination: • Close follow-up, • Stop RAAS blocking agents Switch to hydralazine or ISDN • Baseline Echo & BNP/NT-proBNP level
Maternal Risks	• Relapse in ~20% • Rare severe deterioration • Mortality unlikely • High rate of subsequent recovery	• Higher relapse • Deterioration of LV function in ~50% • Increased morbidity & mortality • Premature delivery & abortion
Medications	• Continue beta blocker • Diuretics & hydralazine/ISDN in case of clinical/LV functional deterioration	• Continue beta blocker • Hydralazine/ISDN for hemodynamic & symptomatic improvement • Digoxin considered • Consider anticoagulation when severe LV dysfunction
Labor and Delivery	• Multidisciplinary planning • Spontaneous vaginal delivery preferred • Monitoring for fluid overload in the first 48 hours after delivery, esp. in cases of recurrent LV dysfunction	• Multidisciplinary planning • Spontaneous vaginal delivery preferred • Early delivery when further reduction in LV function & hemodynamic deterioration • Hemodynamic monitoring for optimization prior to delivery & monitoring during & after delivery • Monitor for fluid overload
Follow-up	• Close monitoring of symptoms • Echocardiographic reassessment of LV function & BNP/NT-proBNP level at the end of the 1st & 2nd trimesters, 1 month before delivery, after delivery prior to discharge, 1 month postpartum & at any time if symptoms develop	

Prior to Hospital Discharge

Lactation: Earlier some studies and 2010 ESC advised against lactation in PPCM. But recent IPAC data showed that breastfeeding did not lead to adverse outcomes, persistent myocardial dysfunction, or inflammatory markers. This suggests that continued stimulation of prolactin secretion might not be harmful. Most HF medications can be given safely with breastfeeding **(Table 1)** and should not be a reason to advise women against lactation.

Contraception: Due to increased risk of thromboembolism, it is recommended to defer the use of estrogen-containing contraceptives. Subcutaneous progesterone-releasing implants/the Mirena IUDs are safe and effective choices. Second-line consideration can be given to injectable depot medroxyprogesterone. Tubal ligation and vasectomy are other options. In patients with persistent LV dysfunction, the risk of a subsequent pregnancy is more than any risk associated with contraception. Thus, contraception must be encouraged by both cardiologist and obstetrician.

Subsequent Pregnancies

The subsequent pregnancies and their management are the most important area of consideration in a patient treated for PPCM. This is elaborated in **Table 1**.

Conclusion

In all pregnant and postpartum women, the diagnosis of PPCM should be considered. Echocardiography gives an assessment of systolic dysfunction. Prompt treatment prevents adverse outcomes. Multidisciplinary team management with optimal HF management is rewarding. The optimal duration of medications after recovery is not yet known. Women considering subsequent pregnancy must be counseled and monitored. Long-term follow-up of patients of PPCM is essential.

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Section 4

Section Editor: **Viswanathan Mohan**

Diabetes Mellitus

CHAPTER

46 CVD in Diabetes: Pathophysiology and Clinical Impact

S Arulrhaj, Aarathy Kannan, Gurunadharao, Ankita Bajpai

Abstract

A close link exists between diabetes mellitus (DM) and cardiovascular disease (CVD), which is the most prevalent cause of morbidity and mortality in diabetic patients. Cardiovascular (CV) risk factors such as obesity, hypertension, and dyslipidemia are common in patients with DM, placing them at increased risk for cardiac events. In addition, many studies have found biological mechanisms associated with DM that independently increase the risk of CVD in diabetic patients. Therefore, targeting CV risk factors in patients with DM are critical to minimize the long-term CV complications of the disease. This paper summarizes the relationship between diabetes and CVD, examines possible mechanisms of disease progression, discusses current treatment recommendations, and outlines future research directions.

Introduction

Diabetes confers a two- to fourfold increased risk of coronary heart disease, stroke, and peripheral artery disease. The burden of cardiovascular disease related to diabetes has increased over the past two decades, and macrovascular events remain the leading cause of mortality. Insulin resistance is the major underlying factor for all the features of metabolic syndrome and is considered very crucial in the pathophysiology of vascular damage.[1]

The Pathophysiology of CVD in Diabetes

The two key metabolic abnormalities associated with type 2 diabetes mellitus (T2DM) are insulin-resistance and hyperglycemia .Whereas the two main pathophysiologic mechanisms in vascular wall that can lead to CV events are arterial stiffening and atherosclerosis.[2]

The patients with diabetes mellitus show both accelerated arterial stiffening as well as premature atherosclerotic changes.

Pro-Atherogenic Mechanisms Associated with Hyperglycemia (Flowchart 1)

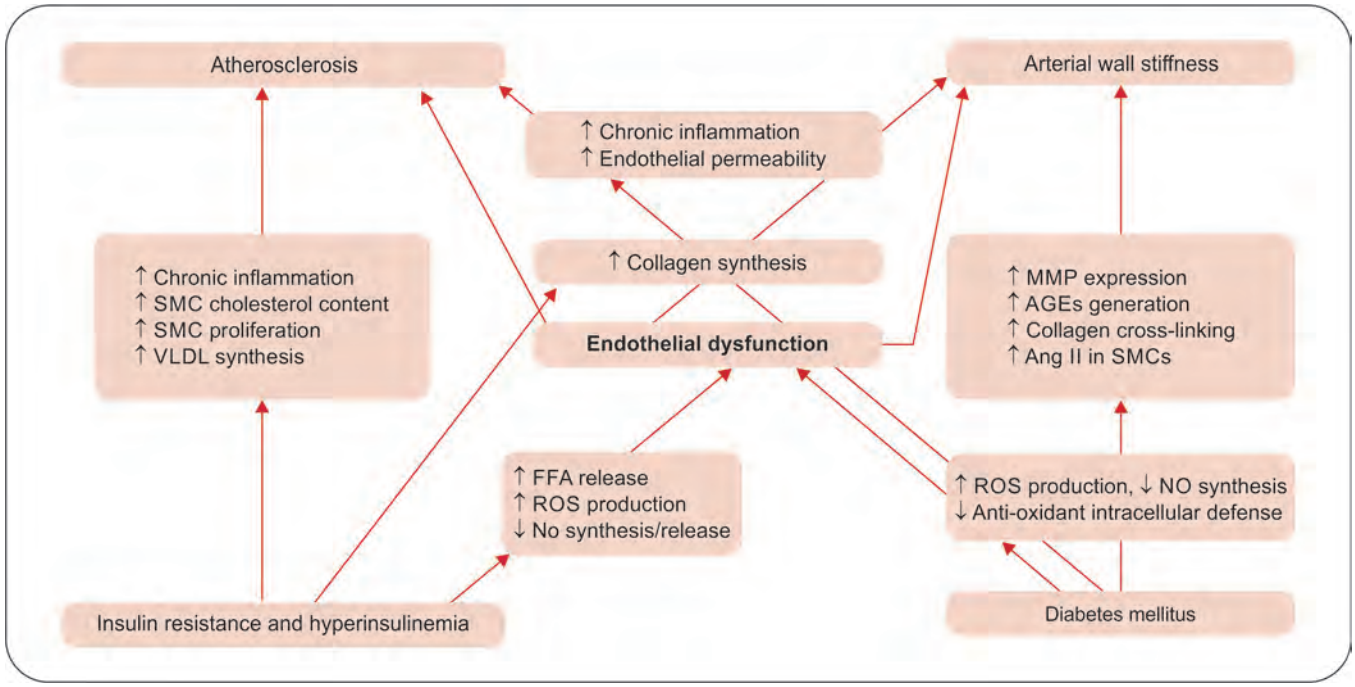
Different molecular mechanisms associated with hyperglycemia have been identified including:

- Increased glucose flux via polyol pathway
- Activation of protein kinase C (PKC)
- Formation of advanced glycation end products (AGE)
- Increased glucose flux via the hexosamine pathway, and activation of the 12/15-lipoxygenase (12/15-LO) pathway[3]
- *All these mechanisms finally result in increased superoxide formation*

Insulin Resistance (Flowchart 1)

Insulin receptors are seen in endothelial cells, macrophages, and vascular smooth muscle cells (SMCs). Insulin resistance has been shown to be due to decreased synthesis or release of NO and increased production of reactive oxygen species, as well as with an increased free fatty acids release from adipose tissue. The increased levels

Flowchart 1: Pathophysiologic mechanisms through which hyperglycemia and insulin resistance can affect the arterial wall



of free fatty acids in circulation may impair the endothelial function as well as induce a low-grade inflammatory reaction (through the activation of nuclear factor kB).[4]

Hyperinsulinemia augments the synthesis of hepatic very-low-density lipoproteins, increases cholesterol synthesis or transport in cultured arterial SMCs, stimulates the proliferation of arterial SMCs, increases collagen synthesis as well as stimulates multiple genes involved in inflammation.

Obesity and Insulin Resistance

Impaired nutrition contributes to hyperlipidemia as well as insulin resistance causing hyperglycemia. This leads to alterations in intracellular signaling and cellular metabolism that negatively impact cells.[5]

All these effects induce cellular events like:

- Modification of gene expression,
- Dyslipidemia and hyperglycemia,
- Activation of oxidative stress and inflammatory response,
- Endothelial dysfunction, and
- Ectopic lipid accumulation, which is favored by obesity and leads to metabolic deregulation.

In the cardiomyocyte, this damage can be through the following three actions:

- Alteration of insulin signaling,
- Increased substrate accessibility, and
- Inflexibility of metabolism changes.

Diabetes and Inflammation

Diabetes is a state of chronic and low-level inflammation. Insulin resistance may be preceded by some immune activation in diabetic and pre-diabetic states and may leads to increase in cardiovascular risk. Along with diabetes, obesity is also associated with increase in the levels of a number of adipokines. Diabetes accelerates the process of natural aging in arterial tree. The correlation between arterial stiffness and CV events or all-cause mortality can be explained by the hemodynamic effects of arterial stiffening. CIMT and Plaque Presence are the surrogate markers of atherosclerosis, plaque indicates an advanced atherosclerotic process **(Fig. 1)**.[6,7]

Endothelial Dysfunction

Healthy endothelium has the properties of vasodilation, anti-atherogenesis as well as anti-inflammatory. However,

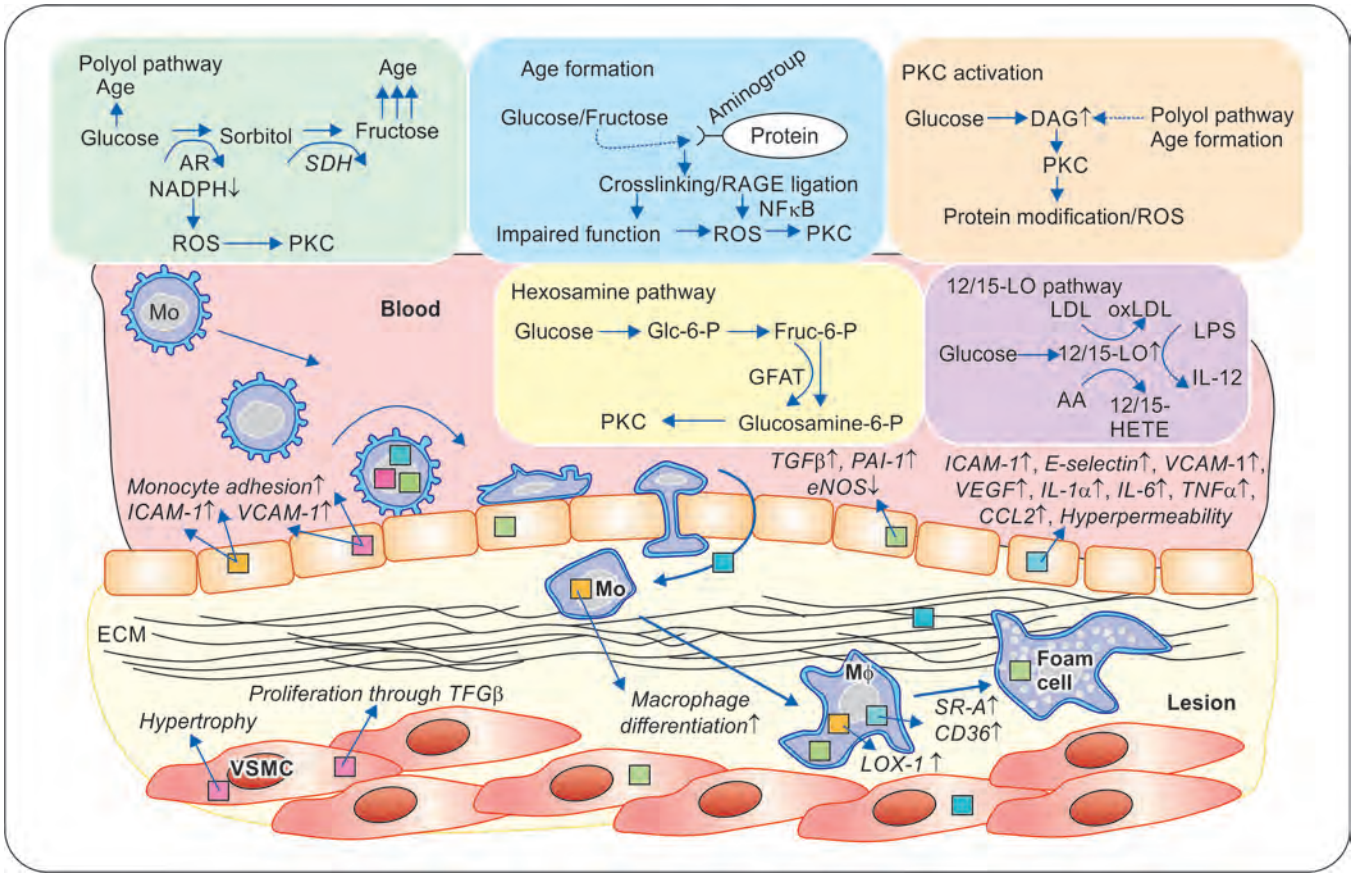


Fig. 1: Biochemistry and molecular cell biology of diabetic complications

a defective endothelium is associated with an accelerated process of atherosclerosis. Hence, both insulin deficiency as well as insulin resistance promote dyslipidemia along with increased oxidation, glycosylation, and triglyceride enrichment of lipoproteins, which further contributes to increase in atherogenicity and macrovascular disease in diabetes **(Fig. 2)**.[8]

Impaired Vascular Repair

Diabetes retards *the endothelial repair processes*, due to shortage of bone marrow (BM)-derived vascular regenerative cells like circulating progenitor cells (CPCs) as well as *endothelial progenitor cells (EPCs)*.[9] *EPCs released from the bone marrow* are involved in homeostasis of healthy as well as damaged endothelium and in physiologic as well as compensatory angiogenesis. Therefore, a reduction in their number as seen in diabetes is believed to promote the development and progression of cardiovascular disease.[10]

Hypercoagulability

Up to 80% of diabetics die of thrombotic events. In that 75% of these deaths are the result of a myocardial infarction, and the remainders are the result of cerebrovascular events and complications related to PVD.[11]

Epicardial Adipose Tissue (EAT)

EAT is an imaging biomarker (ECHO and CTA), and has gained attention due to its intimate location to the coronary vessels and the myocardium. Associated with prevalent subclinical atherosclerosis, ischemia, and future major adverse cardiac events, EAT is a transducer of the adverse effects of systemic inflammation and metabolic disorders on the heart, and thus represents an important target for therapeutic interventions.[12]

Clinical Presentations

See **Table 1**.

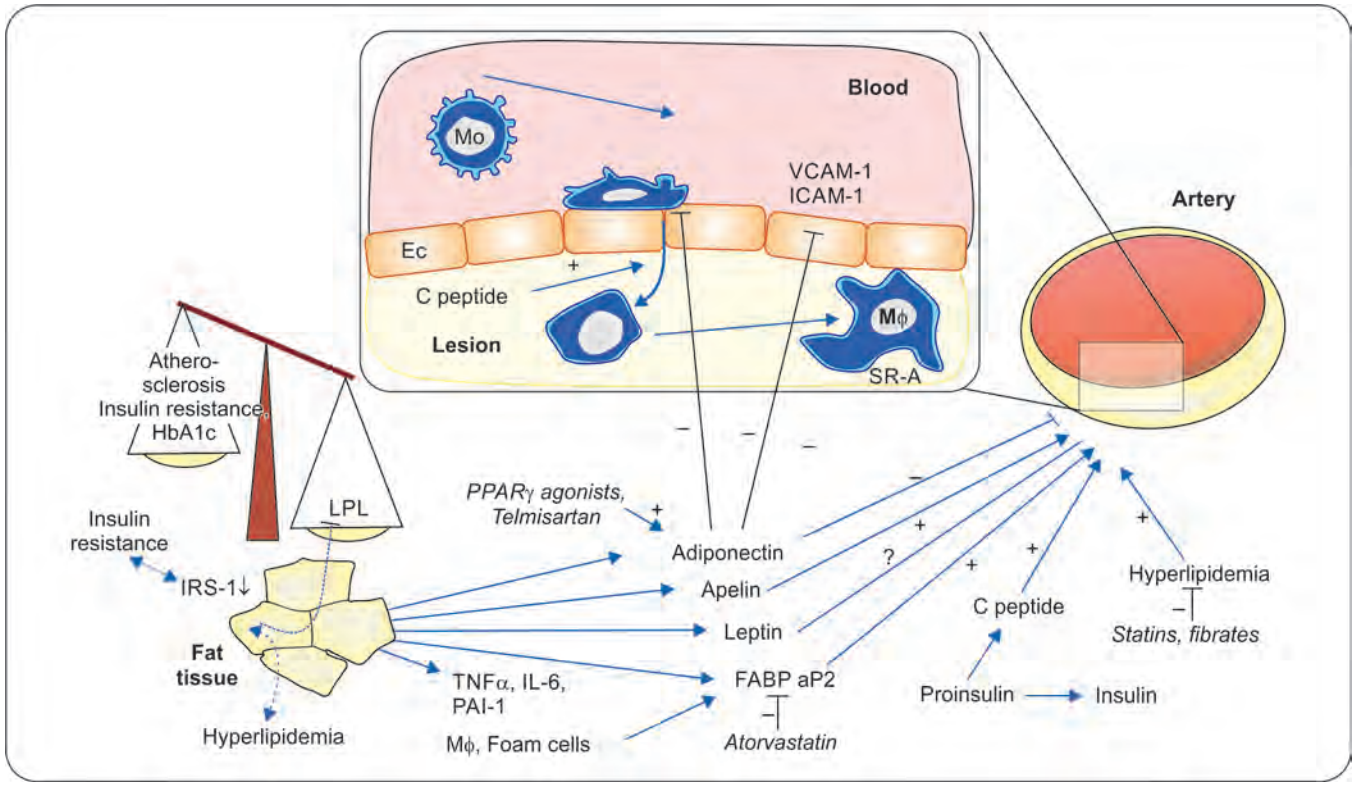


Fig. 2: Pro-atherogenic mechanisms of diabetes mellitus associated with insulin resistance

TABLE 1 Clinical presentations

Very high risk	• Patients with DM and established CVD or • Other target organ damage or • Three or more major risk factors or • Early onset T1DM of long duration >20 years
High risk	Patients with duration of DM >10 years without any organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with duration of DM <10 years, without any other risk factors

Macrovascular Disease

Characterized by fibrosis and arterial thickening, as well as vasomotor and endothelial dysfunction, can *increase risk of heart failure (HF)* in diabetes mellitus. Diabetic blood is more likely to be high in triglycerides. Hypertriglyceridemia in diabetes—insulin action regulates lipid flux **(Fig. 3)**.

Premature Atherosclerosis

Multiple mechanisms are associated with insulin resistance, which may promote atherosclerosis in type 2 diabetes **(Fig. 4)**:

- *Secretion of adipokines* from adipose tissue (apelin, adiponectin, or leptin),
- *Fatty acid binding protein (FABP)* aP2 secreted from adipocytes, foam cells or macrophages (Mφ),
- *C peptide as a decomposition product of proinsulin*, and
- *Diabetic hyperlipidemia. Lipoprotein lipase (LPL)* is inversely associated with insulin resistance, atherosclerosis, and non-enzymatically glycated hemoglobin (HbA1c).[13]

Cardiac Clinical Impact

Coronary Artery Disease

Diabetes mellitus is one of the major risk factors for the development of coronary artery disease and adversely

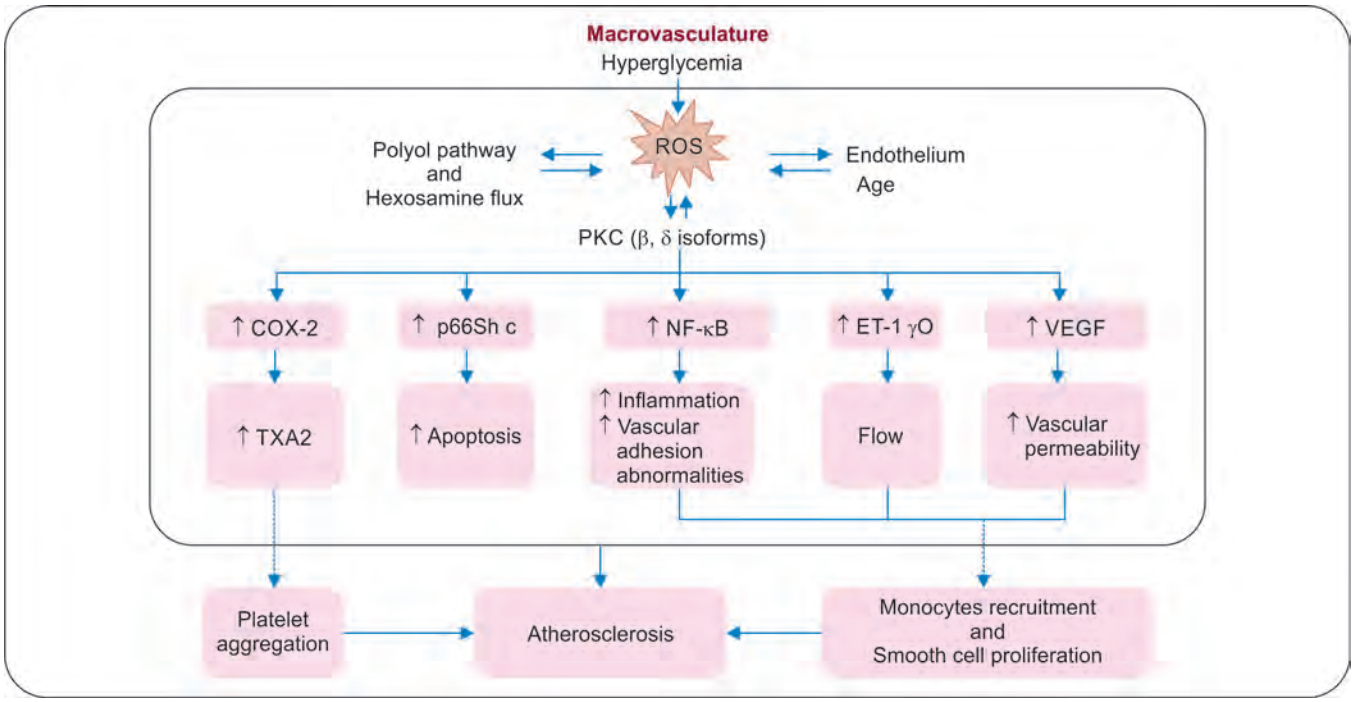


Fig. 3: Pathophysiology of macrovascular complication in diabetes

affects overall clinical outcomes. The absolute risk of death due to coronary artery disease is three to five times higher in patients with diabetes when compared to those without diabetes, regardless of their cholesterol concentration. Three-fourths of the diabetics have multivessel disease and the plaques involving multiple coronary segments. Coronary angiography of diabetic patients characterized as showing diffuse narrowing and multivessel disease. Pathologically in diabetics the plaques show larger necrotic cores, increased presence of inflammation as well as advanced coronary artery calcification. Diabetic patients show a less favorable clinical outcome after successful percutaneous coronary intervention, which will be manifested as higher incidence of restenosis of the artery or stent, a higher incidence of myocardial infarction or reinfarction, and a lower survival rate. After coronary artery bypass grafting, diabetic patients had twice the mortality when compared with those without diabetes.

Myocardial infarction: Diabetes is a prothrombotic and procoagulant state, which may be the reason for the higher incidence of myocardial infarction. The prevalence of diabetes in CAD is up to 40% in many countries.[14]

Silent CAD is far more common in patients with DM (10–20%) than those without DM (1–4%). *Diabetic neuropathy* is one of the key factors due to which there is an increased incidence of *silent ischemia* in diabetic patients. Risk for HF increases *5-fold in women* and *2.4-fold in men* in comparison with those without DM **(Fig. 5)**.

Hypertension

Hypertension is very common in patients with *T1DM* as well as *T2DM*, with prevalence rates of about 30% and 60%, respectively. Hypertension in diabetic patients is closely associated with the development of *diabetic nephropathy* (DN).

Diabetes can directly contribute to the development of *Diabetic cardiomyopathy* (CMP). Annual mortality rates up to 20%. Refer **Tables 2 and 3** for recent guidelines and management.

Heart Failure (HF)

So many observational studies have demonstrated an increased risk of HF of about 2–4 folds in diabetics compared with nondiabetics. Beyond the structural or functional changes due to diabetic cardiomyopathy, a

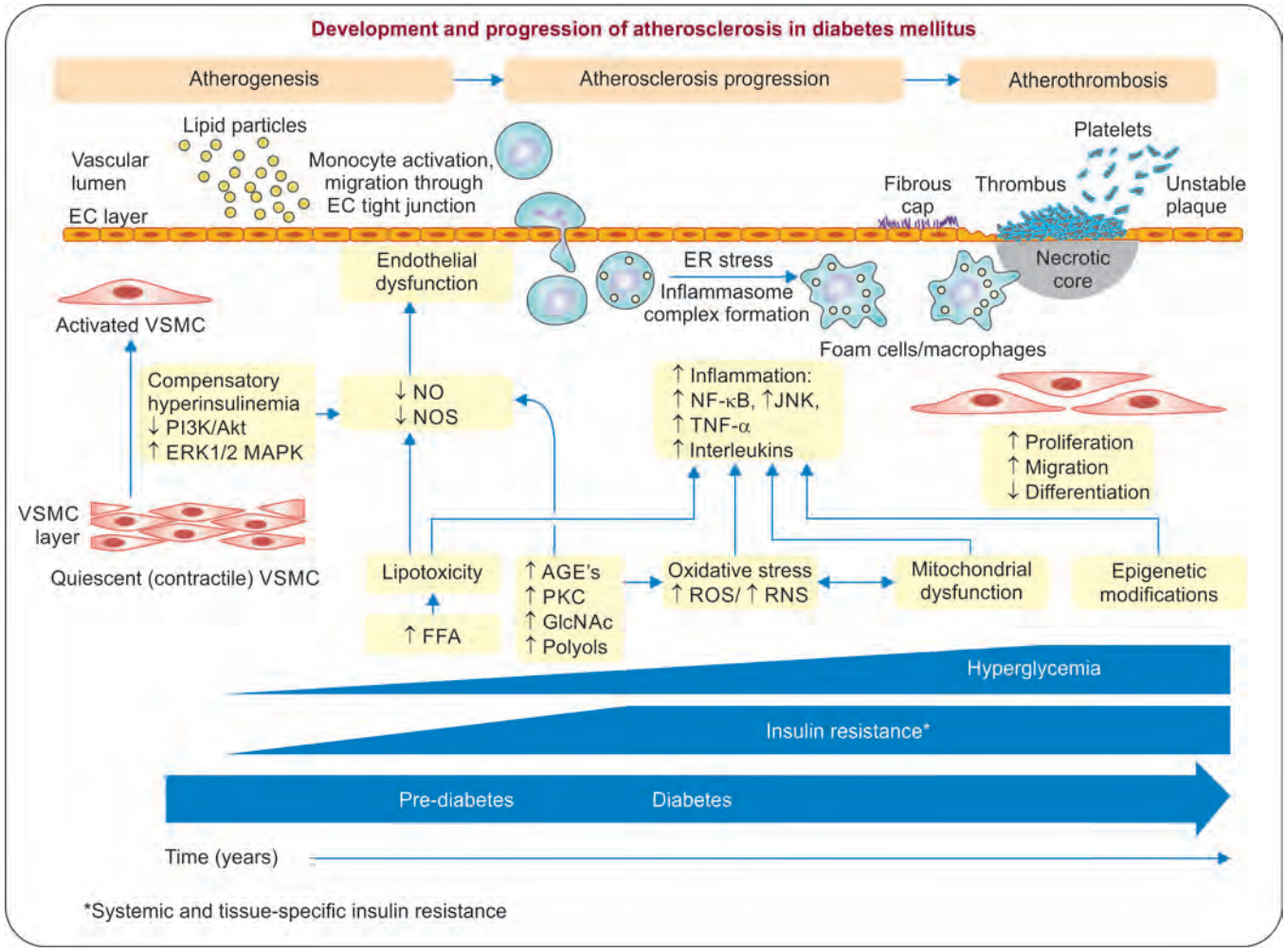


Fig. 4: Development and progression of atherosclerosis in diabetes

complex underlying, and interrelated pathophysiology exists. In spite of controlling hyperglycemia, the high prevalence of HF in T2DM persists **(Fig. 6)**. There is an increased the risk of developing HF both HF with reduced ejection fraction as well as HF with preserved ejection fraction.

A recent network analysis showed that biomarker profiles specific for HFrEF are related to cellular proliferation and metabolism, whereas those specific for HFpEF are related to inflammation and extracellular matrix reorganization. How these pathophysiological differences might translate into different outcomes in those with DM and HFpEF versus HFrEF remains unclear. Refer **Tables 2 and 3** for recent guidelines and management.

Diabetic Dyslipidemia

Low HDL, moderate to high LDL. *Dyslipidemia* is one of the factors by which *diabetes can promotes atherosclerosis and endothelial dysfunction*. Refer **Tables 2 and 3** for recent guidelines and management.

Cerebrovascular Disease

Diabetes is a major risk factor for the development of carotid atherosclerosis and stroke, both ischemic as well as hemorrhagic. Data from the Emerging Risk Factors Collaboration suggest that diabetes was associated with an increased risk of ischemic stroke for about 2.27 folds and that of hemorrhagic stroke for about 1.56 folds. Diabetes is already established as a risk factor for cognitive impairment, dementia, and Alzheimer disease **(Fig. 4)**.

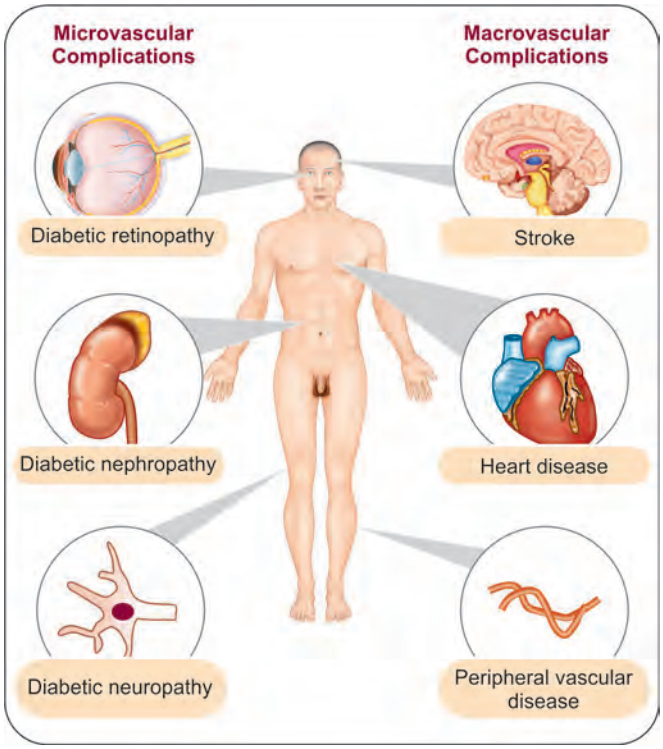


Fig. 5: Complications of diabetes

Diabetes is also associated with an *increased risk of lower limb ischemia for about twofolds*, and about 21% of diabetes patients have signs of peripheral artery disease (PAD). The *ABI* is the most widely used tool to diagnose PAD and its normal range is from 0.9 to 1.3. An ABI lower than 0.9 is commonly used to diagnose PAD both symptomatic and asymptomatic.

Diabetic Nephropathy

Efferent arteriolar hyalinosis is the major defect seen in DN. Nonspecific arteriosclerosis may be present, which is associated with more severe glomerular disease. "Matrix to Media ratio" is increased. Significant medial thickness may be associated with hypertension. Neovascularization is seen. Diabetic kidney disease includes glomerular hyperfiltration, progressive albuminuria, declining GFR, and, ultimately, ESRD.

ANS Dysfunction

Microcirculation is regulated by central as well as local regulatory mechanisms. Central regulation is through autonomic sympathetic and parasympathetic nerves.

TABLE 2 2019 ESC guidelines

Change in recommendations	
2013	***2019***
BP targets	
BP target <140/85 mm Hg for all	**Individualized BP targets are recommended** SBP to 130 mm Hg and, if well tolerated, <130 mm Hg, but not <120 mm Hg. In older people (>65 years) target SBP to a range of 130–139 mm Hg DBP to <80 mm Hg but not <70 mm Hg
Lipid targets	
In DM at high CV risk, an LDL-C target of <100 mg/dL In DM at very high CV risk, an LDL-C target of <70 mg/dL is recommended	In patients with T2DM at moderate CV risk, an LDL-C target of <100 mg/dL is recommended In patients with T2DM at high CV risk, an LDL-C target of <70 mg/dL is recommended In patients with T2DM at very high CV risk, an LDL-C target of <55 mg/dL is recommended
Antiplatelet therapy	
Aspirin for primary prevention is not recommended in DM at low CVD risk	Aspirin (75–100 mg/day) for primary prevention may be considered in patients with: DM at very high/high risk in the absence of clear contraindications
	Aspirin for primary prevention is not recommended in patients with DM at moderate CV risk
Glucose-lowering treatment	
Metformin should be considered as first-line therapy in patients with DM	Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk
Revascularization	
DES rather than BMS is recommended in DM	Same techniques are recommended in patients with or without DM

TABLE 3 New recommendations in the 2019 guidelines

CV risk assessment
Resting ECG is recommended in patients with DM with hypertension or suspected CVD
Prevention of CVD
Lifestyle intervention is recommended to delay/prevent conversion from pre-DM to T2DM
Glycaemic control
Use of self-monitoring of blood glucose should be considered to facilitate optimal glycemic control in T2DM
It is recommended to avoid hypoglycemia
BP management
Lifestyle changes are recommended in hypertension
RAAS blockers rather than beta-blockers/diuretics are recommended for BP control in pre-DM
Home BP self-monitoring should be considered in patients with DM
24-h ABPM should be considered for BP assessment, and adjustment of antihypertensive treatment
Dyslipidemia
In patients at very high risk, with persistent high LDL-C despite treatment with maximum tolerated statin dose in combination with ezetimibe, or in patients with intolerance to statins, a PCSK9 inhibitor is recommended
Statins may be considered in asymptomatic patients with T1DM aged >30 years
Statins are not recommended in women of childbearing potential
Antiplatelet and antithrombotic drugs
Prolongation of DAPT beyond 12 months should be considered for ≤3 years in patients with DM at very high risk who have tolerated DAPT without major bleeding complications
Glucose-lowering treatment
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events
Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death
Liraglutide, semaglutide, or dulaglutide are recommended in patients with T2DM and CVD, or very high/high CV risk, to reduce CV events
Liraglutide is recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce the risk of death
Saxagliptin is not recommended in patients with T2DM and a high risk of HF
Revascularization
Same revascularization techniques are recommended in patients with or without DM
Treatment of HF in DM
Device therapy with an ICD, CRT, or CRT-D is recommended
Sacubitril/valsartan instead of ACEIs is recommended in HFrEF and DM remaining symptomatic despite treatment with ACEIs, beta-blockers, and MRAs
CABG is recommended in HFrEF and DM, and two- or three-vessel CAD
Ivabradine should be considered in patients with HF and DM in sinus rhythm, and with a resting heart rate ≥70 b.p.m. if symptomatic despite full HF treatment
Aliskiren (direct renin inhibitor) in HFrEF and DM is not recommended
DM treatment to reduce HF risk
SGLT2 inhibitors are recommended to lower risk of HF hospitalization
Metformin should be considered in patients with DM and HF if eGFR >30 mL/min/1.73 m^2
GLP1-RAs and DPP4 inhibitors sitagliptin and linagliptin have a neutral effect on risk of HF and may be considered
Insulin treatment in HF may be considered
DPP4 inhibitor saxagliptin in HF is not recommended
Thiazolidinediones (pioglitazone and rosiglitazone) in HF are not recommended
Management of arrhythmias
Attempts to diagnose structural heart disease should be considered in patients with DM with frequent premature ventricular contractions
Hypoglycemia should be avoided as it can trigger arrhythmias
Diagnosis and management of PAD
Low-dose rivaroxaban 2.5 mg b.i.d. plus aspirin 100 mg o.d. may be used in patients with DM and symptomatic Lower Extremity Arterial Disease
Management of CKD
SGLT2 inhibitors are recommended to reduce progression of diabetic kidney disease

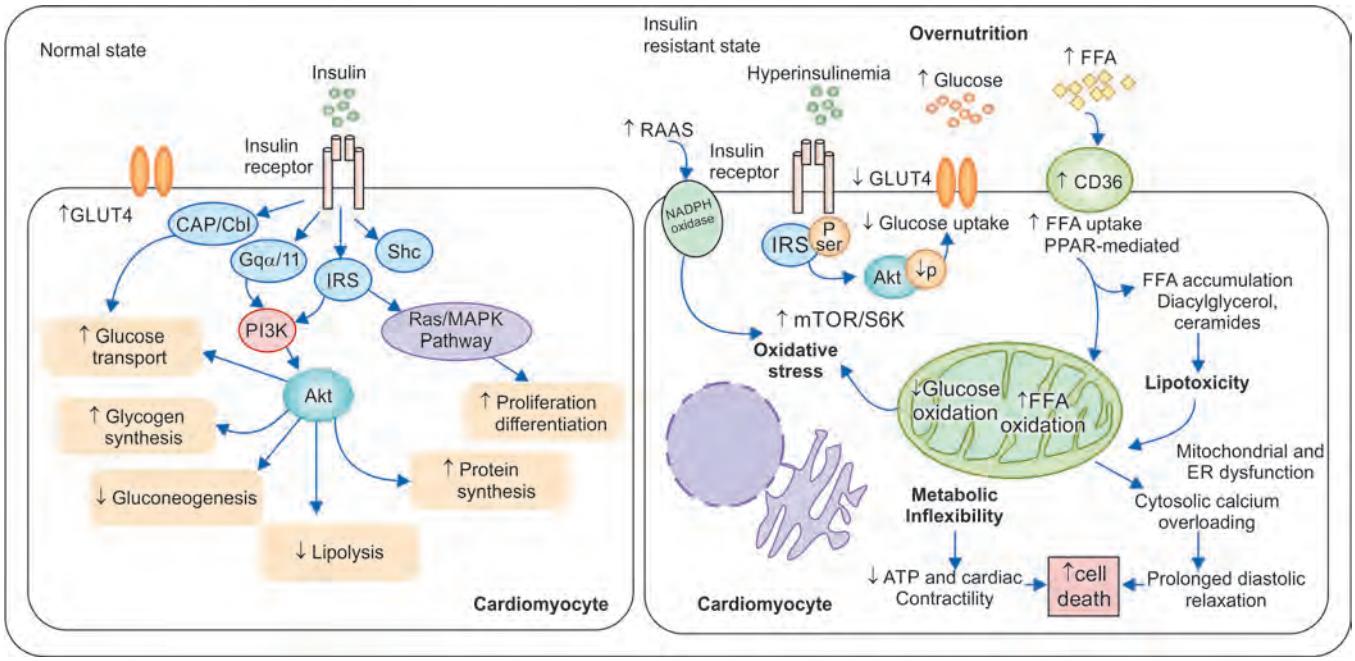


Fig. 6: Association between insulin resistance and the development of cardiovascular disease

Local regulation is by the substances produced by the endothelial cells. Diabetes contributes to defects in the autonomic nervous system, the endothelium, and local metabolism.[15]

Incidence of cardiovascular autonomic neuropathy (CAN) increases with age and inadequate glycemic control, which leads to a higher risk of developing both CAN and CVD in diabetes. It is very common in diabetes and is very well correlated with an increased 5-year mortality rate from CVD. The development and progression of CAN may be due to dysregulation of the autonomic nervous system (ANS) associated with increased sympathetic activity as well as elevated inflammatory markers.

Angiogenesis

There is a differential expression of *vascular endothelial growth factors (VEGF)* seen in diabetes, which leads to a paradoxical increase in angiogenesis in the retina and decrease in the peripheral limbs and myocardium.[16]

Conclusion

T2DM can be called as Coronary Equivalent. Hyperglycemia and Insulin Resistance are important components of metabolic syndrome and control of which will lead to a disease-free life. Main pathophysiology of DM includes Atherosclerosis and Arterial stiffness which in turn leads to various cardiac complications. Major macrovascular complications of DM are due to Lipid dependent & Endothelial Dysfunction whereas microvascular will be ANS dependent.

Strategies to prevent or delay the progression of diabetic microvascular complications mainly depends on:

- Elimination of hyperglycemia,
- Inhibition hyperglycemia induced vascular dysfunction,
- Neutralization of inflammation and oxidative stress, and
- Activation of tissue-specific protective factors.

Lifestyle management which includes Weight Reduction, Medical nutrition therapy, Physical activity, Tobacco cessation along with blood pressure control, Lipids regulation, Antiplatelet agents, and Glycemic control are recommended for Primary prevention of cardiovascular diseases in diabetic population. *Diabetic cardiovascular disease is an upcoming specialty in medicine which is rapidly growing in developed as well as developing nations.*

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CHAPTER

47 Development of Insulin: 99 Years and Counting

Sarita Bajaj

Abstract

The discovery of insulin earmarked the first effective treatment for diabetes. Till today insulin is an injectable agent. Modifications in the insulin peptide chain and genetic engineering have lead to the evolution of a variety of innovative insulins. Insulin analogues have several advantages over purified animal insulin. Research is ongoing for insulins which can be injected at a reduced frequency apart from non-injectable methods of administration. This chapter highlights all the major milestones and advances in the development of insulin over the last century.

Introduction

The word "Insulin" corresponds to the Latin word "Insula" meaning "island", so-called because of its formation in the island cells of the pancreas, the islets of Langerhans. Insulin was discovered in 1921 and is soon completing 100 year of its discovery. Insulin, over many decades, has enabled us to understand what we currently know of the disease called diabetes mellitus. With the discovery of insulin, it was for the first time that we got an effective treatment for diabetes; this also led to further research, gaining of knowledge in diabetes pathophysiology and management, in turn helping us to make advances in finding out other therapy options for treatment of this disease. Insulin is the first effective treatment available for diabetes and still retains its importance, despite the advent of other drug classes like sulfonylureas, biguanides, Thiazolidinediones, DPP-4i, SGLT-2i, GLP-1RA, etc. This is the journey of insulin in the past 99 years and what the future holds for it.

Diabetes—The Era before Insulin

Diabetes is not a new disease, the earliest account of its mention is found in Egyptian "Ebers Papyrus" written around 522 B.C., ancient Indian, and Chinese texts also mention this disease. The credit for naming this disease "diabetes" mostly goes to Greek physician "Demetrius of Apamea" (129–199 AD) or to "Aretaeus of Cappadocia (129–199 AD) from the word meaning "passing through."[1] Thomas Willis, a British doctor, was credited for coining the term "diabetes mellitus" in 1674, mellitus denoting the sweetness of the patient's urine. In 1776, in Liverpool, physician named Matthew Dobson discovered that "urine of diabetic patients is sweet because of the presence of sugar." In the latter part of 19th century, many scientists worked to explore the intricacies behind diabetes melltius—in 1869, Paul Langerhans, a German medical student, discovered groups of cells in the pancreas, unknown at that time and was later named as "Islets of Langerhans" once it was discovered that insulin is produced by these island of cells.[2]

Discovery of Insulin

In 1889, German researchers, Joseph von Mering and Oskar Minkowski while experimenting on dogs found out that if a dog's pancreas is removed it provokes severe symptoms of diabetes. Inferring from experiments that

pancreatic extracts can elevate the symptoms of diabetes, Minkowski tried injecting the powdered extracts of pancreas, but the toxicity of the extracts was too much to provide any suitable results. This understanding let to multiple attempts at treating diabetes. Many scholars tried using pancreatic extracts for treating diabetes like American pathologist, Lydia Maria Adams DeWitt (1906) and German physician George Ludwig Zuelzer (1908).[6]

Paulesco, a Romanian endocrinology experimenter, in 1916 reported that "the aqueous solution of pancreatic extracts leads to improvement in experimentally induced diabetes," but unfortunately he could not complete his experiments due to the ongoing World War I at that time.[6]

In 1920, Frederick Banting, a young Canadian orthopedic surgeon, got inspired by the works of other scientists in extracting insulin from pancreas and developed some of his own thoughts and theories. With his ideas, Banting approached John James Richard MacLeod, Professor and head of the department of physiology at University of Toronto. MacLeod gave him laboratory space, 10 dogs to do his experiments, a student assistant, Charles Best, and provided supervision and guidance. Banting started his experiments in May 1921, and by September they reported that removing pancreases in dogs leads to diabetes, which can be cured by giving intravenous injection of pancreatic extracts. Banting named this extract as "Isletin." In late 1921, Biochemist J. B. Collip, joined the group and was instrumental in purifying Isletin for human use. Considering the importance of these findings, MacLeod allowed human experimentation. On 11th January 1922, a young Canadian patient named Leonard Thompson became the first human being to receive an insulin injection. He was 14-years-old and dying when he received the first famous doses, but without much impact. He developed "sterile abscess" at the site of injection, there was no effect on ketosis and only a mild lowering of glucose levels is seen. Banting, Best, and Collip further purified the pancreatic extracts, and second series of injections were given on 23rd January 1922. This time the results were promising with normalization of glycemia, glycosuria, and Ketosis. Blood glucose levels dropped from 520 mg/dL to 120 mg/dL.[3-6]

This was hailed as a landmark discovery, resulting in the 1923 Nobel Prize for MacLeod & Banting. The prize also led to a controversy as Best and Collip were excluded. Banting at that time strongly criticized the Nobel Prize committee and decided to share his prize money with Best, in turn MacLeod also decided to share his with Collip. By 1923, the extraction process had been improved, and insulin was commercially available in North America and Europe.[5,6]

Insulin Era

Immediately after discovery, insulin was primarily sourced from animals; particularly bovine and porcine insulin. This was possible because all mammalian insulins are structurally similar, that is, composed of 51 amino acids in two linked polypeptide chains (A and B). In 1955, Fredrick Sanger showed "the sequence of all amino acids in the insulin molecule," a great feet since it was for the first time that a complete protein had been sequenced, this resulted in Nobel Prize for Sanger in 1959. The two commonly used animal insulins were bovine and porcine. Porcine insulin is very similar to human insulin, differing only in single amino acid difference in polypeptide chain. Bovine insulin is most similar to feline insulin.[5] Animal insulin became the first to be available insulin to treat diabetes.[6] The disadvantages were insulin reactions, antibody formation, allergies, and sacrificing a large number of animals for extracting the insulin from their pancreas.[7,8]

In the 1980s, biosynthetic insulins were produced, with human DNA using biotechnology and were made available commercially. **Figure 1** depicts the timelines in the development of insulin.

Recombinant DNA Technology and Human Insulin

The recombinant DNA (rDNA) technique was the advancement we all were waiting for and this ensured a uniform and continuous supply of insulin for the days to come. This technique involves inserting the human insulin gene and the promoter gene in the plasmids of either "*Escherichia coli* or yeast (*Saccharomyces cerevisiae*)." The genes for insulin A and B chains are isolated and then inserted as separate entity in the plasmid of two different *E. coli* cultures. The *E. coli* cells are than incubated and allowed to grow in a medium containing lactose, which induces the synthesis of chain A & B separately. The insulin chains so obtained can be isolated, purified, and joined together to give human insulin. This breakthrough provided the first opportunity to "mass-produce 'human' insulin using gene technology resulting in recombinant insulins."[9]

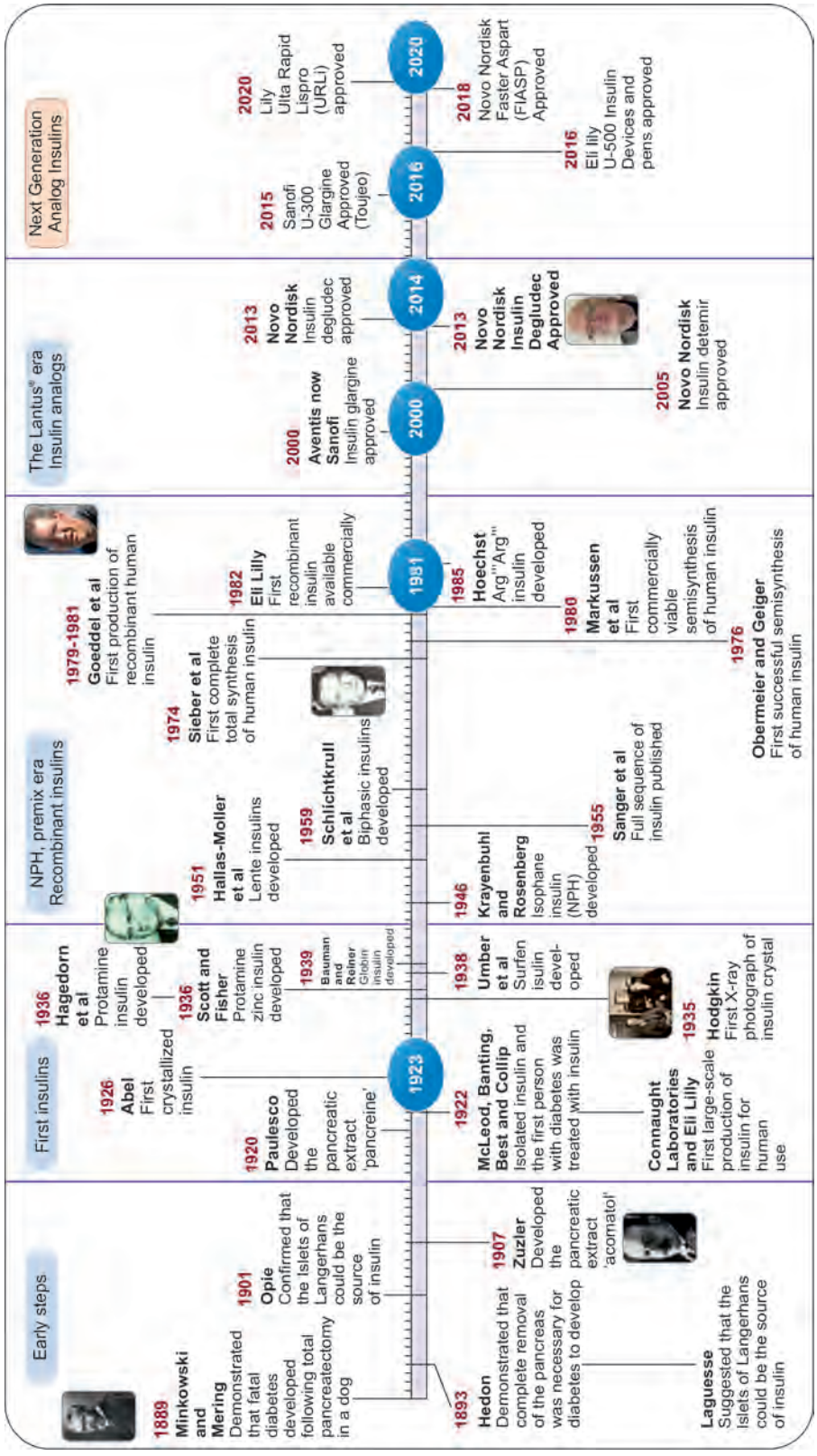

Fig. 1: Timelines in insulin development

Types of Human Insulin

Human insulin is available in three forms:

- Normal regular insulin which is short acting.
- Insulin which is crystalized using fish protein Protamine, named as "Isophane or NPH (Neutral Protamine Hagedorn)."
- Mixed insulin or premix insulin, where NPH insulin is present as suspension with regular insulin.

Short acting (regular) insulin starts to act about 30 minutes after injecting, and the peak action is reached between 2 and 3 hours of dosing. The duration is up to 10 hours. Intermediate acting insulin or NPH takes about 2–4 hours for onset of action with peak action happening at about 4–10 hours. The total duration of action can be up to 18 hours.

The main principle employed to enhance the time of action of insulin is to use protamine, which crystalizes the insulin and makes it insoluble, along with that zinc is employed to stabilize the insulin hexamers in solution. This protaminated insulin dissolves slowly, along with slow dissipation of zinc after subcutaneous injection destabilizes the hexamers resulting in slow release of insulin monomers, which readily gets absorbed.[10]

Premix insulins are suspensions of short acting soluble insulin and insoluble protaminated long acting insulin. Due to this nature before ever dose "insulin vial should be rolled or repeatedly turned upside down," this ensures the uniformity of dosing of each component whole injecting. The premix insulins are formulated generally in ratio of either 30:70 or 50:50, but other variations are also available.[10]

Human recombinant insulins have some advantages over highly purified animal insulins, namely:

- Lower immunogenicity shown by lower titers of circulating antibodies to insulin;
- Few reactions at injection site;
- Better and more rapid absorption in circulation; and
- Low breakdown at the site of injection itself.

Insulin Analogues

Insulin analogs are formed by altering the amino acid sequence such that the receptor activity is preserved while providing other benefits. Genetic engineering is employed to modify or change the amino acids of the peptide chains resulting in changed absorption, distribution, metabolism, and excretion (ADME) characteristics.[10]

These modifications are done to have better pharmacokinetic profile of the insulins in terms of their duration of action and metabolism. These are done to have two types of insulin analogs. One which are fast acting, faster than the regular human insulin and also those which provide a better basal coverage with long duration if action and no peak effect, better than what can be achieved by NPH insulin.

Basal Insulins

Glargine: First long acting basal insulin analogue which was formulated by adding two arginine residues to the C-terminus of the B-chain and the substitution of glycine for asparagine at position A21. These changes made it possible for glargine to be soluble at acidic pH (resulting in a clear insulin in the vial) and the solubility decreases once the pH becomes neutral or basic. This when injected in slightly basic environment of subcutaneous tissue forms micro-precipitates at the injection site. These micro precipitates take time to dissolve, and hence we get long duration of action.

Detemir: With insulin detemir, the threonine residue at position B30 was deleted and a myristic acid (fatty acid) side chain was added to the lysine residue at position B29. These modifications enable insulin detemir to bind reversibly to albumin with high affinity once injected. These modifications results in slow release of insulin from albumin binding thereby delaying both absorption and breakdown. This prolongs the duration of action but in few instances twice daily dosing is needed. The fatty acid side-chain not only enhances self-association of monomers in the subcutaneous depot, but also provides the added benefit of reduced glycemic variability.[11]

Glargine U-300: An advanced formulation of glargine insulin. The glargine insulin polypeptide chain is unchanged in Glargine U300, only the concentration of glargine is changed to 300 units/mL. This increased concentration leads to the formation of more compact depots in the subcutaneous tissue once injected. This more compact depots decrease the surface area and dissolution rates, further leading to an increased subcutaneous half-life. The result is a better flatter insulin profile in circulation when compared to glargine U100. This concentrated formulation results in a good half-life of 18–19 hours with action up to 36 hours.[12] **Table 1** gives action profile of basal insulins.

TABLE 1 Action profile of basal insulins[11-14]

Basal insulin	*Onset (h)*	*Peak (h)*	*Duration (h)*	*Frequency of administration*
NPH Insulin	1.5	4.0–10	10–16 hours	Twice daily
Insulin degludec	1–2	Peak less	>42 hours	Once daily
Glargine U300	6	Peak less	Up to 36 hours	Once Daily
Insulin glargine	2–4	No peak	Up to 24 hours	Once daily
Insulin detemir	2	No peak	14–21 hours	Once daily

Degludec: In insulin degludec, the threonine residue at position B30 is deleted and the ε-amino group of LysB29 is acylated with a 16-carbon fatty acid side-chain via a g-L-glutamic acid linker. In solution degludec is present in the form of stable dihexamers due to the presence of phenol. Once injected, phenol rapidly dissipates from the subcutaneous tissue and these dihexamers link up end to end to form large chains of multihexamer. These multihexamer chains increase the size and prevent the absorption of insulin, which can happen only when these mutihexamers are converted to monomers. The process happens gradually with the removal of zinc from one end of these chains.

Rapid-Acting Insulin Analogs

"Rapid-acting insulin analogs" are designed to provide rapid onset of action which also terminate early in comparison to regular human insulin. Currently, three such insulins are available commercially: insulin aspart, insulin lispro, and insulin glulisine.[13]

Rapid acting insulin analogs are administered with the meals or shortly before starting the meal, as they are rapid absorbed in systemic circulation from subcutaneous tissue. The peak action is reached in 1–2 hours of administration and it takes around 4–6 hours for their action to wean off completely. Rapid acting insulin analog therapy is directed to have a good postprandial glycemic control.

Rapid-acting insulins also found their use in insulin pumps, also known as "continuous subcutaneous insulin infusion (CSII) devices." In CSII therapy, insulin is administered as a continuous infusion in the subcutaneous tissue. This continuous supply of rapid acting insulin works to provide both bolus and basal coverage as well as correctional doses.

TABLE 2 Action profile of rapid acting insulins[13-15]

Rapid Insulin	*Onset (min)*	*Peak (h)*	*Duration (h)*
Regular insulin	30	1.5–3.5	7–8
Insulin aspart	10–20	1–3	3–5
Insulin lispro	15	2.4	2–5
Insulin glulisine	20	1	Not available
Faster aspart	5–10	1–2	3–5
Ultra-rapid lispro	5	1–3	3–5

Insulin lispro: Modifications done in insulin peptide chain include the reversal of amino acids at positions B28 (proline) and B29 (lysine). This makes it similar to the sequence seen in "insulin-like growth factor 1 (IGF-1)." This change makes the absorption faster with a definite advantage over regular human insulin.[14]

Insulin aspart: Modification to peptide chain includes replacing proline at B28 with another amino acid, that is, aspartic acid. This structural alteration results in increased monomer fraction.[14]

Insulin glulisine: Insulin glulisine is formed by "replacing glutamic acid for lysine at B29 and replacing asparagine with lysine at B3." This has resulted in addition of extra charge to the peptide chain resulting in somewhat lower isoelectric point in comparison to regular human insulin; this enhances solubility of insulin glulisine at normal body pH.[14] **Table 2** delineates action profile of rapid acting insulins. **Figure 2** shows action profile of different insulins.

Inhaled (Technosphere) Insulin (AFREZZA)

Technosphere insulin (Afrezza) was FDA approved in 2014. Its pulmonary absorption leads to a more rapid

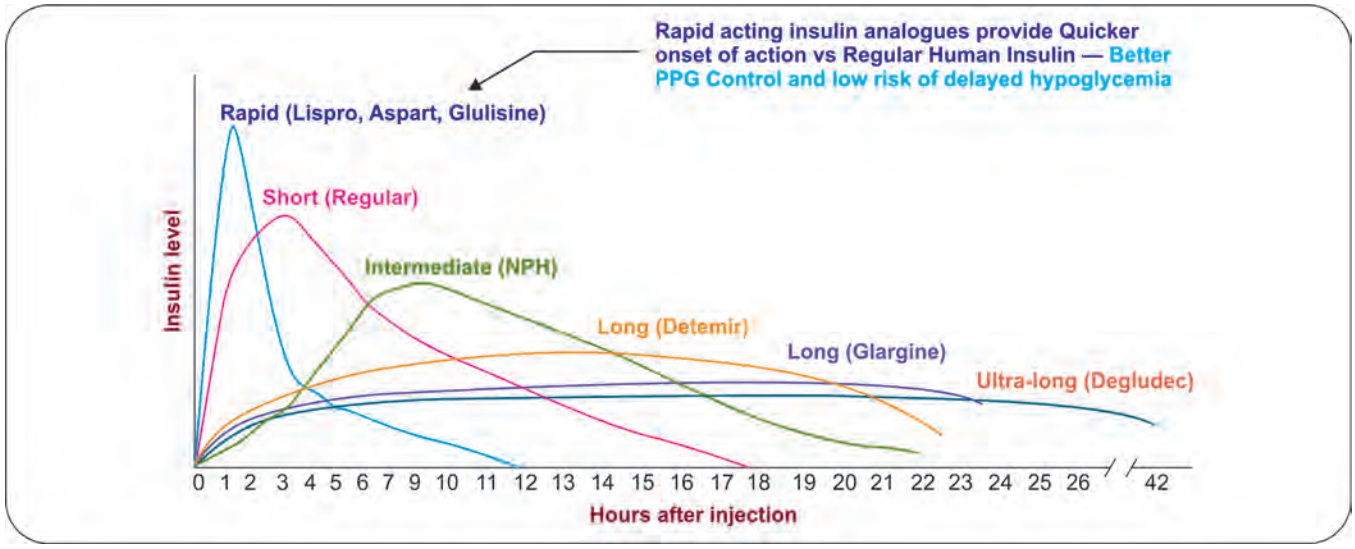

Fig. 2: Time action profile of different insulin (schematic)

absorption than currently available, subcutaneously administered rapid-acting insulin preparations but due to many side effects not preferred.[14]

Ultrafast Acting Insulin

Further development aimed at mimicking the natural physiological insulin release had resulted into the development of ultra-rapid acting insulins. Many approaches were used to make insulin act faster than available bolus insulin. Such as by increase of local blood flow, inhalation of a rapidly absorbed insulin, intradermal application or spreading the insulin into a wider area in the SC tissue (either mechanically or enzymatically), or adding excipients that promote monomerization of insulin molecules.[15,16]

Finally, after incremental research faster-acting insulin aspart was developed. Insulin Faster Aspart is a new formulation containing insulin aspart and two additional excipients (nicotinamide and arginine). Nicotinamide, commonly known as Vitamin B3, acts as an absorption enhancer in the subcutaneous tissue while arginine provides stability to insulin hexamers while in storage.[14] Its onset of action is about 6 minutes earlier, the peak is 7 minutes earlier, and it gives 74% greater action during the first 30 minutes compared to traditional aspart.[15]

Another ultra-rapid acting insulin, currently in development is Insulin Ultra-Rapid Lispro (URLi). URLi is insulin lispro with added excepients—Treprostinil & Citrate. Treprostinil increases absorption by causing local vasodilation in sub-cutaneous tissue without any systemic exposure, while citrate increases vascular permeability at injection site. The onset of action is 11 minutes faster than insulin lispro.[16]

Premix Insulin

The pharmacokinetic and pharmacodynamic limitations of the premixed human insulin formulations have been largely overcome with the introduction of premixed insulin analogues containing a rapid-acting insulin analogue for postprandial glycemic control and an intermediate-acting insulin analogue that controls basal glycemic levels. Unlike premixed human insulin formulations, premixed insulin analogues can be administered within 15 minutes of a meal, a convenience for patients with irregular meal schedules that may increase adherence to treatment.

It consists of premix human insulin or premix insulin analogue in ratio of 30:70 and 50:50. Rapid/short-acting component (30% or 50%) covers mealtime glucose excursions, while intermediate/long-acting insulin (70% or 50%) augments background insulin levels. In clinical terms this gives the added benefit of controlling both fasting (FPG), prandial (PPG), and thereby also leading to better HbA1c, all with one injection only.[17]

There is evidence that premix may be used as an option is situations like primary care. The INITIATE study showed that addition of premix insulin to oral antidiabetic drugs

(OADs) was more effective, than adding basal insulin for treatment of type 2 diabetes.[18]

- Rapid-acting insulin, Lispro, is combined with insoluble lispro protamine suspension in a 50:50 and 75:25 (75% protaminated lispro suspension and 25% insulin lispro) ratio.
- Insulin aspart combinations also are available as 70:30 mixtures (70% insoluble protamine aspart and 30% soluble insulin aspart).

Insulin Degludec Aspart Co-Formulation (IDegAsp)

IDegAsp is a co-formulation of two soluble insulins, consisting "70% of insulin degludec and 30% of insulin aspart." It consists of insulin degludec, a long-acting insulin, and insulin aspart, a rapid-acting insulin both of which function as independently acting blood-glucose-lowering agents.[19]

This co-formulation is made possible because insulin degludec, due to its unique properties, can be combined in a soluble solution with a mealtime insulin analogue without having any effect on the pharmacokinetics and pharmacodynamics of each other.[18] Because of these unique and unprecedented formulation, it is termed as a co-formulation.[19]

Analog versus Human Insulin: Are there any Advantages?

There has been a great deal of advancement in insulins over last 99 years but how this has translated into better clinical outcomes has be debated quite a number of times. In current clinical practice, though the adoption of analogue insulins has increased but a large number of patients are still using the good old human insulins. In terms of achieving the glycemic targets and lowering of HbA1c, both analogue and human insulin are many times considered similar. The difference lies in better safety with the newer analogue insulin preparations. Two aspects where the analogue insulins clearly win are:[20,21]

- Type 1 diabetic patients where the basic requirement of 24 hours of insulin coverage can be best fulfilled by using basal and bolus analog insulins in combination.
- Patients who suffer from night time or overnight hypoglycemia in type 2 diabetes. It is helpful to prescribe a rapid-acting insulin analogue before dinner if the hypoglycemia occurs early in the night or a basal analogue insulin if it occurs toward morning.

Analog insulins provide better outcomes and increases convenience over human insulins. Advantages of using analogue insulins can be summarized as:

- Better mimicking of normal physiological insulin release
- Less rate and chances of hypoglycemia
- Better flexibility in timings of dosing
- Better response at lower dose
- Less immunogenicity

The Future of Insulin

Current innovations going on in insulin development, holds a good promise for the future. A great amount of research is going on to modify the pharmacokinetics and pharmacodynamics of insulins for the better.[22,23]

Insulin icodec: A once weekly insulin, this will significantly reduce the burden of injections involved with insulin therapy. Icodec has recently finished phase 2 clinical trials with promising results.[22]

Oral insulin (ORMD-0801): An oral insulin under development from Oramed has good results in a recently released results of a pilot study with good reduction of hepatic fats.[22]

Insulin Ultra-Rapid Lispro (URLi): An ultra-rapid insulin from Lilly, it is formulated by adding Treprostinil and Citrate as excipients to insulin lispro. This given it an onset of action 11 minutes faster than the conventional insulin lispro. URLi is recently been approved in the European Union as an ultrafast acting insulin.[22]

BioChaperone lispro insulin: Again a modification of insulin lispro, this is another ultrafast acting insulin, currently in phase 3 trials. To make this faster, citrate is added along with a novel excipient with a modified oligosaccharide chain, BC222.[22]

Cone snail insulin: Another ultrafast acting insulin under development, where the insulin molecule remains in monomer state. It is being derived from the poison of certain cone snails.[22]

Other than the above mentioned, there is a good research going on to modify the action of action of insulin. One such example is the ongoing development of Smart Insulin—"Glucose responsive insulin (GRI)." This next

generation under development insulin will work on the principle of demand and supply. If the blood glucose is more, more of insulin will get activated and show its effect, while if the blood sugar goes down, activated insulin supply will be cut off.[22,23]

Conclusion

Even after 99 years of its discovery and use, insulin is still going strong. Different insulin formulations have been tried over a period of time, some are found to be quite good compared to their predecessor, others fared not so well. Some major milestones in the journey of insulin therapy include—development of NPH insulin, move from animal to human recombinant insulin, and the advent of analog insulin. Innovation is still on and what we can see in the future is a once weekly insulin or even an insulin which is glucose controlled. The future holds a lot of promise for insulin therapy. In terms of effective therapy for diabetes, insulin is sitting on the pedestal as a winner amongst all available options and will remain so for a long time to come.

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CHAPTER

48 What Is in Store for Future Insulin Research?

Ajay Kumar

Abstract

Insulin is the natural therapy for diabetes and its long journey had gone through various modifications and advancements so as to suit the physiological needs and enhance the adherence among patients. The time tested, most potent drug, Insulin is still a life saving agent and documented to improve quality of life of millions of diabetics. Once weekly basal insulin, Icodec, has promising results and is expected to bring a paradigm change in the management of diabetes. The future of insulin is bright as we discuss here about the newest insulins and various delivery devices and techniques that are in research pipeline.

Introduction

Ever since, Banting and Best's novel discovery in 1921, Insulin remains the indispensable treatment in diabetes as it primarily regulates carbohydrate and fat metabolism.[1] It's the centenary celebration, this year since insulin has been described as a polypeptide hormone from the islets of Langerhans in the pancreas and yet the quest for the perfect physiological insulin remains. The increase in burden of diabetes and drawbacks in injectable insulins are leading researchers to pursue novel approaches in more effective insulin production, application and delivery. Accordingly, numerous drug candidates are being developed, evaluated and now progressing through the clinic. The development of a once-weekly basal insulin therapy that remained a dream for ages is now ready for Phase 3 trials.

Expanding Horizons with Weekly Basal Insulin—Icodec

The pursuit of the quest to develop weekly insulin remains challenging. In order to improve patient convenience and adherence without increasing hypo/hyperglycemia, a new longer acting once weekly novel insulin named icodec has been developed. It has completed three phase 2 clinical trials in March 2020 and is planned to initiate phase 3a program by the year end.

Molecular and Biological Properties of Insulin Icodec

Insulin icodec [icosaGreek numerical prefix representing 20; dec-derived from degludec] is an insulin analogue with a terminal elimination half-life of ~196 hours with a single subcutaneous injection. This insulin molecule was modified to achieve an albumin-bound circulating inactive depot which acts just as human insulin (HI) but is more slowly cleared. Strong but reversible albumin binding is ensured with the addition of C20 fatty diacid side chain at B29K via a hydrophilic linker. Three amino acid substitutions (A14E, B16H, and B25H) ensure reduced enzymatic degradation of icodec and contribute to attenuating insulin receptor (IR) binding and clearance, further prolonging the half-life **(Fig. 1)**.

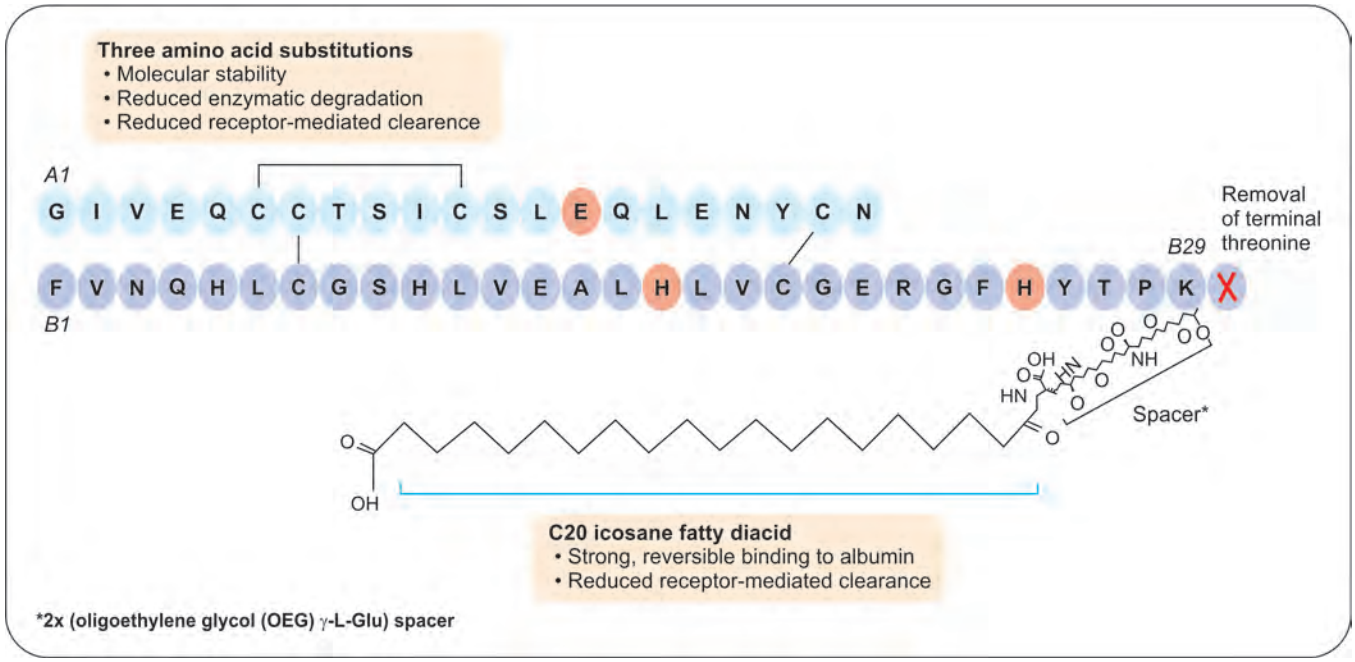


Fig 1: Key modifications in insulin icodec

The affinity of icodec for the IGF-1 receptor was found to be proportionately lower than its binding to the IR resulting to relatively low IR affinity but full activity, allowing a gradual effect over an extended time period. A steady state is achieved that provides the full therapeutic effect after three to four once-weekly injections. Icodec, in functional assays elicited metabolic effects (like glucose uptake and lipogenesis in fat cells, and stimulation of glycogen synthesis in liver cells) like HI.

Formulation and Dosing

Icodec is formulated into a concentrated concentration as 700 units per mL (700 U/mL) to ensure that the injection dose and volume is not increased. Comparable to insulin NPH and degludec, it is also coformulated with standard pharmaceutical excipients: Zinc functions as a stabilizing agent, while phenol and m-cresol are preservatives.

Phase 1 Data: PK/PD Properties Support Once-Weekly Dosing with a Good Safety and Tolerability Profile[2]

Fifty patients with T2D enrolled for phase I trial to evaluate the PK/PD parameters and safety of insulin icodec at three escalating fixed doses over a 5-week period **(Fig. 2)**. The median Tmax was 16 hours and the geometric mean T1/2 was 196 hours, with no systematic differences between dose levels. As depicted in **Figure 3**, there was relatively even distribution of glucose-lowering effect over the 7 days, irrespective of dose. The maximum effect was achieved at days 2 and 3 after administration. By day 7, the level was close to the maximum. Adverse event rates were not dose dependent. During the trial, no serious AEs or serious hypoglycemic episodes recorded.

Phase 2 Data: Insulin Icodec Provides Similar Efficacy and Safety to Once Daily Glargine[3]

This pivotal phase 2, 26-week treat-to-target trial with a randomized, double-blinded, double-dummy design evaluated the efficacy and safety of once-weekly icodec versus once-daily insulin glargine U100 (IGlar U100) in 247 insulin-naïve patients with T2D inadequately controlled (A1C 7.0–9.5%) with metformin ± DPP-4i. At end of trial period, estimated mean A1C were 6.69% and 6.87% for icodec and IGlar U100, respectively (mean change from baseline: –1.33% for icodec and –1.15% for IGlar) **(Fig. 4)**. So, no statistically significant treatment difference for change in A1c from baseline to week 26 (–0.18%, 95% CI, –0.38; 0.02) noted. Total dose of insulin glargine was

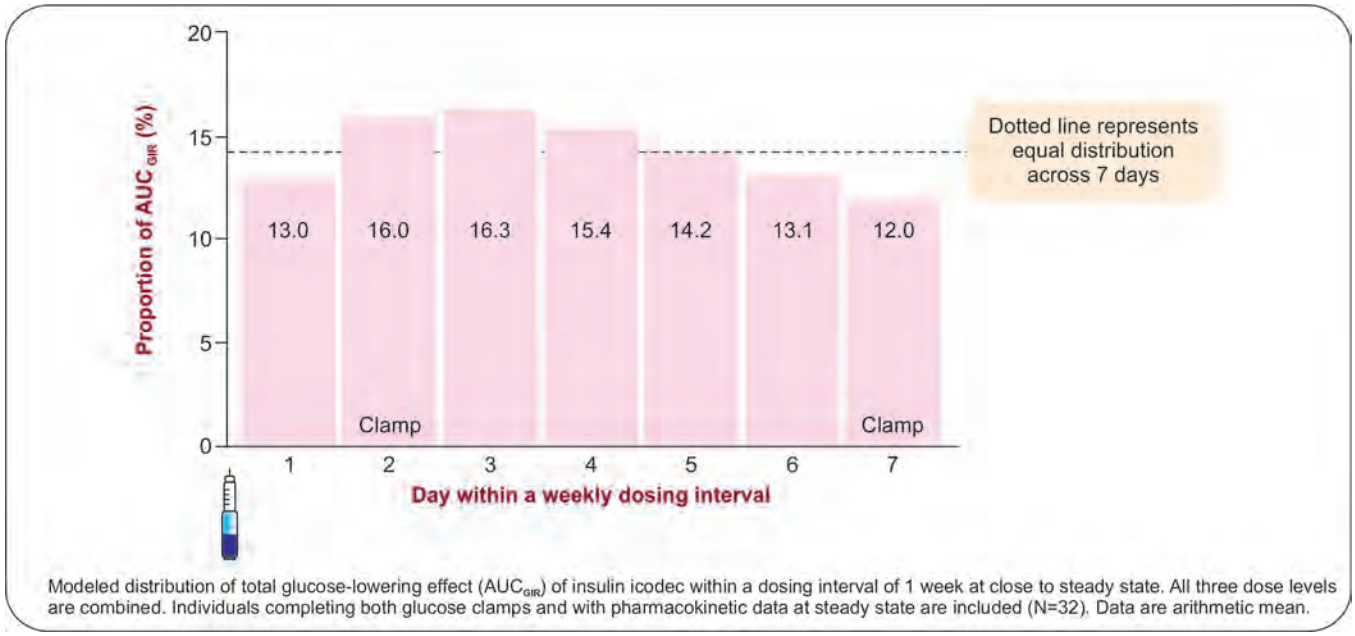


Fig. 2: Modeled glucose-lowering effect of insulin icodec
AUC, area under the curve; GIR, glucose infusion rate

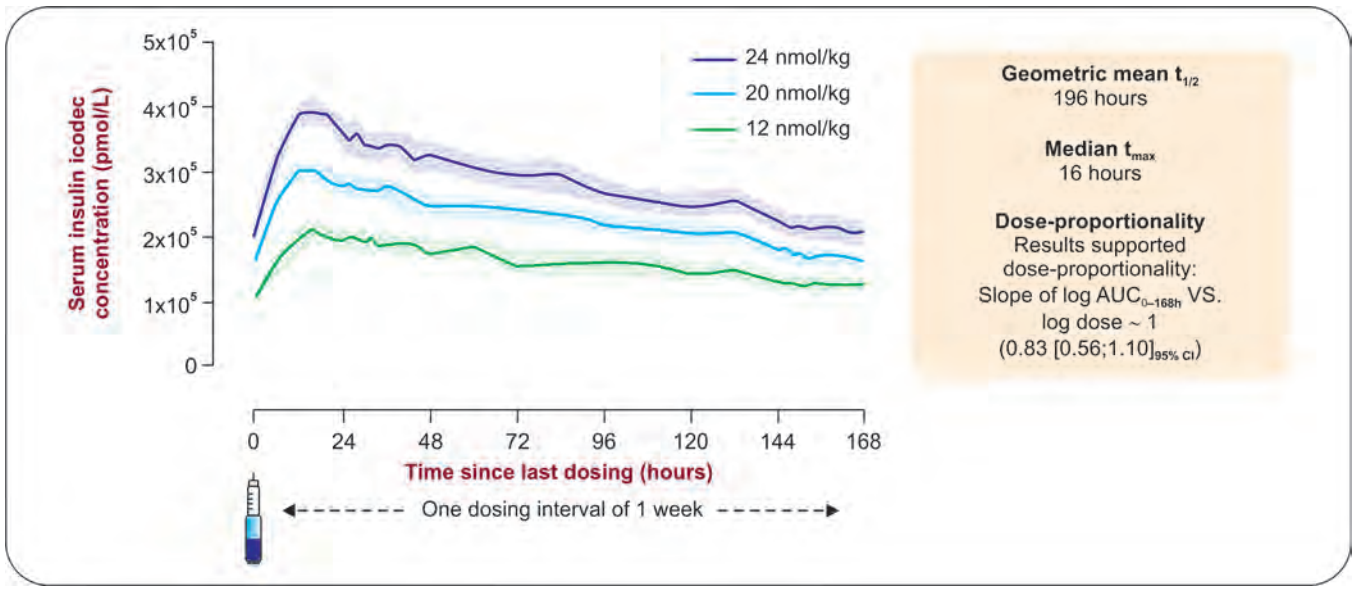


Fig. 3: Pharmacokinetic profiles of multiple dosing of insulin icodec in T2D individuals

significantly higher than the dose of insulin icodec in order to achieve similar effect. No new safety issues were identified. Observed rates of level 2 & 3 hypoglycemia were low (60.55 and 52.36 events per 100 patient years of exposure for icodec and IGlar U100, respectively). There was no increase in the rate of level 2 or 3 hypoglycemia compared with insulin glargine ($p = 0.85$).

To summarize, after promising results from Phase 1 & 2 clinical trials, a comprehensive phase 3 program will be conducted for icodec. Fewer injections, more convenience

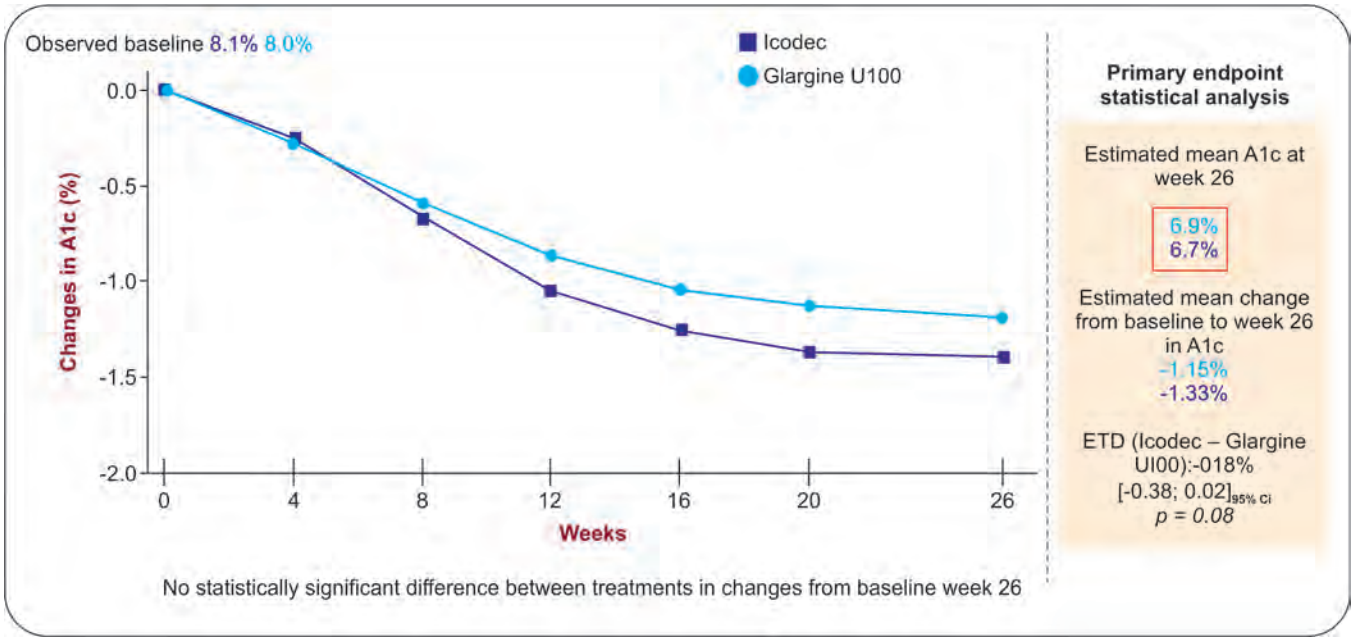


Fig. 4: HbA1c changes over time

and simplicity with insulin icodec, will overcome clinical inertia and more patients will accept initiation and continuation on insulin therapy more readily.

Newer Dimensions in Insulin Research

Newer Ultra Rapid Acting Insulins

Normally insulin glargine cannot be combined with insulin lispro as the pH required to combine them both is not viable. To overcome this challenge, a polyanionic amphiphilic polymer, BioChaperone (BC147) has been devised. With the help of this, glargine can be solubilized at neutral pH enabling it to be combined in a stable formulation with insulin lispro. A combination of 25% of insulin lispro and 75% of insulin glargine known as BioChaperone Lispro or BCLIS has demonstrated a higher significant reduction in postprandial pharmacokinetic exposure leading to significant decrease in both 1 hour and 2 hours PPG levels when compared to Insulin Lispro.[4,5] BCLIS elicited a superior earlier PPG control both against LisproMix and to Insulin Glargine, and Insulin Lispro administered separately. BCLIS also demonstrated lower hypoglycemic episodes when compared to Insulin LisproMix.[4]

Insulin is always present in the hexameric state. This state is required to help stabilize the insulin outside the human body. Once insulin is injected, it is broken down into monomers, which then act in the body. It is essentially this which hinders the insulin to act fast enough to mimic the human physiology. In the most recent developments, an Ultra-Fast-Absorbing-insulin-Lispro (UFAL) has been developed. Insulin when presents as monomers cause aggregation into amyloid fibrils. A unique acrylamide carrier/dopant copolymer excipient has been developed which helps prevent the aggregation of insulin monomers. Insulin being in the monomeric form takes a lot lesser time for absorption once inside the body.[6] Preclinical studies have already shown the molecule to be stable for a period of 25 hours in stressed conditions along with a peak action of 9 minutes. Such exciting trials make the molecule more promising in creating a breakthrough in the future treatment of diabetes.[6]

Inhaled Insulin

Technosphere technology has enabled the development of pulmonary routes of insulin drug delivery and presently, rDNA originated inhaled HIs are being reviewed by the FDA for approval.[7] Pre-metered unit doses of insulin in

breath activated inhaler devices dissipates into liquid form once exposed to the neutral pH of the alveolar epithelium. Gastrointestinal peptidases that break down insulin in the GI tract are absent in pulmonary route, hence these insulin delivery bypasses the first-pass metabolism system.[8]

Oral Insulin

Oral route supposed to mimic physiological secretion to the portal vein will definitely improve convenience and compliance. Nanoparticle-based approach improved the bioavailability by protecting insulin from proteolytic enzymes and harsh gastrointestinal environment. Anionic natural polymer blocks the release of insulin into the stomach to prevent its degradation. There occurs cellular uptake of nanoparticles or paracellular transport across tight junctions, which enhance paracellular insulin absorption.[9-11] An oral insulin formulation (ORMD-0801) elicited clinically significant reductions in HbA1c in poorly controlled T2DM (mean HbA1c levels >8%) patients on standard therapies, without increasing hypoglycemia rates or weight. Preliminary observations from a trial on oral insulin [ORMD-0801] suggested a palliative effect of on non-alcoholic steatohepatitis in T2DM patients by reducing in liver fat content and chronic hepatitis.[12,13]

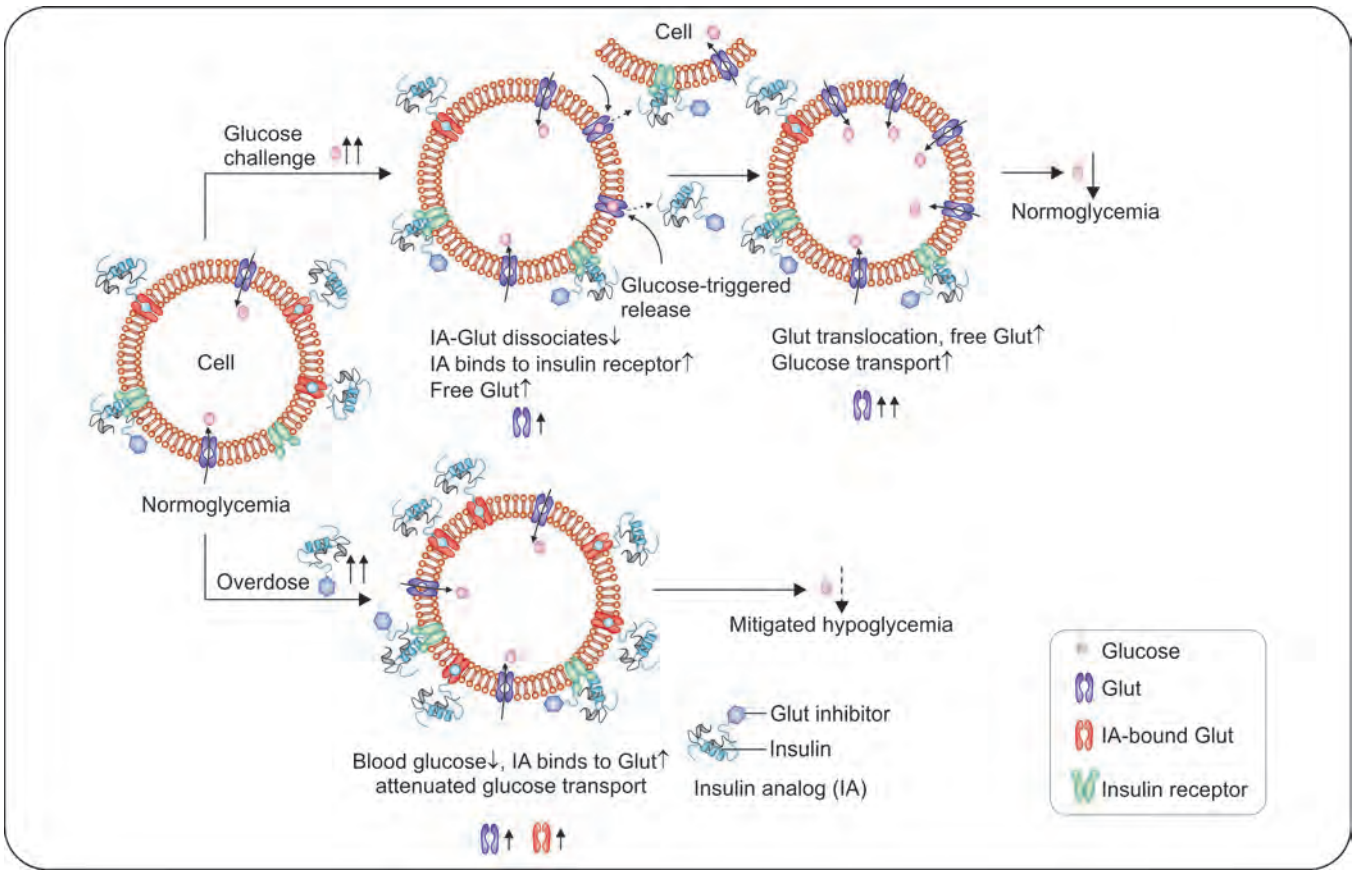


Fig. 5: Schematic of regulating the glucose-transport activity with insulin analog (IA; in this study, i-insulin serves as a model analog). Insulin analog can bind to Glut in a glucose-responsive manner. Upon injection and in normoglycemia, insulin analog achieves a regular blood glucose clearance rate, and an insulin analog–Glut complex reservoir is formed. Upon a glucose challenge, increased blood glucose levels result in the release of insulin analog from the insulin analog–Glut complex, which subsequently binds to IR to trigger the translocation of Gluts to cell membranes. With dissociation of insulin analog, glucose-inaccessible insulin analog-bound Glut becomes free Glut, enhancing excess blood glucose clearance. Upon an excess insulin analog injection (i.e., overdose), the formation of the insulin analog–Glut complex attenuates the glucose transport activity of Glut, therefore mitigating hypoglycemia risk[14]

Recently, researchers have also explored the use of liposomes, biliosomes, and proliposomes for insulin delivery, which will encapsulate the insulin using the appropriate phospholipid/cholesterol ratio and prevent degradation and enhance bioavailability of oral insulins.

Glucose-responsive "Smart" Insulins

A form of smart insulin, named as *i*-insulin, which comprises an insulin analogue attached to a glucose transporter [Glut] inhibitor is developed by bioengineers at the University of California. Endogenous Glut associated delivery reservoir of insulin that is capable of modulating glucose metabolism in a blood glucose-dependent manner could be achieved by Insulin facilitated Glut inhibitor conjugate-a long-acting insulin analogue.

Plasma and tissue glucose levels modulate its binding affinity to Glut. The in situ—generated insulin analogue—Glut complex will dissociate in states of hyperglycemia and will release insulin analogue and glucose-accessible Glut to restore normal blood glucose levels in **Figure 5**. In situations of hyperinsulinemia, glucose uptake will be reduced due to enhanced binding of insulin analogue to Glut that will suppress the glucose transport activity of Glut.[14] Thus, it prevents over-uptake of glucose into cells when there is dip in blood glucose level. When an extra dose of *i*-insulin was administered in diabetic mice, the modified insulin kept blood glucose levels within the normal range longer and protected them from hypoglycemia.[15]

Transdermal Patch

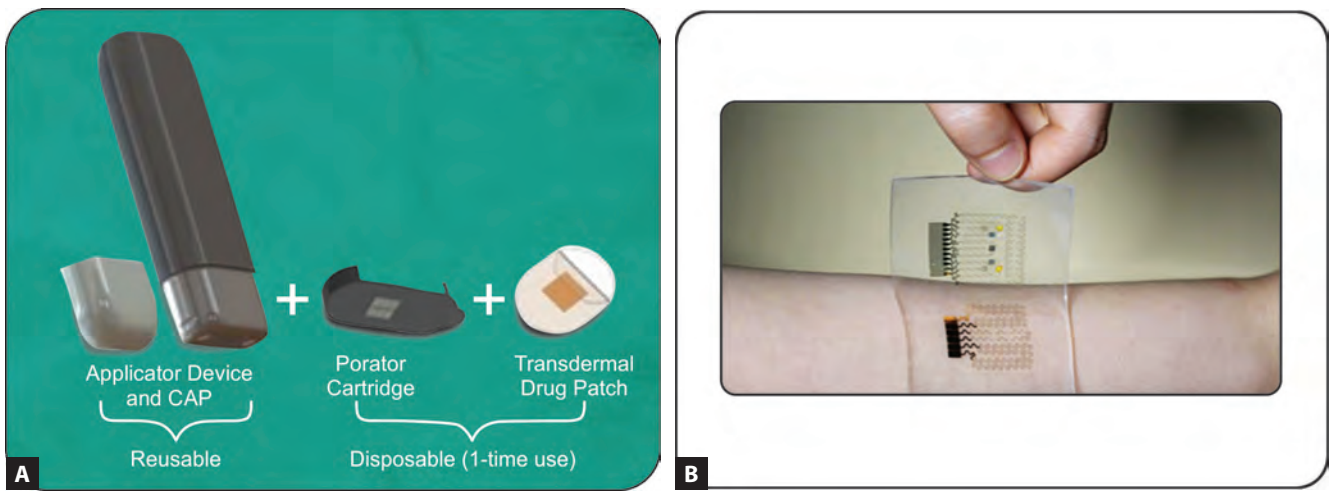
With the advent of techniques like iontophoresis, sonophoresis, or phonophoresis, transdermal administration is considered to be an encouraging approach for insulin delivery in near future **(Figs. 6A and B)**.[16,17]

Stem Cell Therapy

Stem cell therapy that aims to ameliorate insulin resistance, improve pancreatic islet β cells regeneration and protect pancreatic islets from apoptosis is looked upon as cure for diabetes. Programmed stem cells (especially, Mesenchymal Stem Cells or MSCs) differentiating into insulin-producing cells (IPCs), evolves as an alternative to islet cell transplant as it also promises to create an optimal environment by secretion of paracrine factors.[18-24]

Bioresponsive Insulin Delivery System

An artificial beta cell with a glucose-sensitive hydrogel membrane that traps glucose-oxidase enzymes in a hydrogel polymer is integrated in this system. This membrane reduces the pH of the membrane and increases the permeability of the hydrogel membrane to insulin. Thus, the system works to accelerate the release of insulin with increasing levels of glucose to ensure feedback-controlled delivery of insulin.[9,25] The development of closed-loop systems for real-time glucose sensing and controlled insulin release will aim at achieving near-physiological precision in glucose control.[26,27]



Figs. 6A and B: Transdermal application of insulin

Conclusion

Insulin therapy because of being injectable and risk of hypoglycemia is delayed inordinately even though it is considered as cornerstone of managing diabetes. It has been recommended by every guideline based upon data from several landmark trials. Once-a-week icodec may result in a major paradigm shift in patients' acceptance of insulin. Promising results have been reported from phase 2 trial demonstrating similar efficacy and hypoglycemia risk with icodec versus once daily glargine. However, search for ultimate therapy for managing hyperglycemia remains among the spectrum of new concepts of insulins and delivery systems that remains further down the road to see the light of clinical reality.

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CHAPTER

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Blood Pressure Variability in Diabetes: Its Role in Development of Diabetes Complications

KK Pareek, Girish Mathur, GD Ramchandani, Ashutosh Chaturvedi

Abstract

Recently, blood pressure variability (BPV) has gained focus owing to its role in predicting cardiovascular (CV) outcomes. Additionally, alterations in BPV contribute to the progression of end organ damage and trigger vascular events in hypertensive patients. Therefore, amelioration of BPV is considered a potentially important target and different classes of drugs are used to achieve the desired blood pressure (BP) goal. Based on several studies and clinical trials, treatments with CCB such as amlodipine have been found to be most effective in the management of BPV in hypertensive patients with diabetes. Growing evidence substantiates the role of amlodipine in significant reduction of BPV, thus, lowering the risk of diabetes-related complications. This review sheds light on the importance of BPV reduction and the effectiveness of amlodipine in preventing cardiovascular morbidity and mortality in hypertensive patients with diabetes. Reduced arterial compliance in patients with diabetes mellitus has been shown in several studies, but it has not been significantly associated with either atherosclerosis or vessel wall thickness. BP variability is still poorly explored in diabetic patients. The aim of this study was to compare BP variability and arterial compliance in patients with type 2 diabetes mellitus and controls matched for sex, age, and weight.

Introduction

The coexistence of diabetes and hypertension is greatly linked to the causation of several entities, viz., cardiovascular events, microvascular complications, retinopathy, nephropathy, and increased contribution to all-cause mortality.[1] Blood pressure variability (BPV) is now considered as an important risk factor responsible for various complications occurring in hypertensive and diabetic patients. Although physiological blood pressure (BP) variations are commonly seen in most individuals, but when these variations exceed the acceptable range, they acquire pathological significance. Normal circadian BP rhythm is retained during the initial phase of development of hypertension but variability tends to increase when the target organ damage alters the regulatory mechanism of B.P. These findings become of greater importance in case of diabetic patients who are already at a significantly higher risk of development of cardiovascular (CV) events as compared with non-diabetic individuals.

Type 2 diabetes (T2D) patients usually have autonomic dysregulation of cardiovascular functions which increases BPV. In several studies it has been seen that intensification directed at multiple risk factors which are responsible for development of complications in T2D patients, have beneficial effects in respect of macro and microvascular complications.

Blood Pressure Variability

BPV, in very simple terms, can be defined as the variations in BP over time. B.P fluctuations are initiated by a complex interplay between multiple cardiovascular control mechanisms or during change between day to day

life, behavior and triggered by changed environmental situations.[2] These variations increase in patients who are having disordered cardiovascular control mechanisms.[3] Typical examples of routine fluctuations are like BP rise after physical activity or psychological stress and BP reduction when person is in sleep or relaxation.[2] Research has shown that increased BPV values are a strong predictor of CV mortality and morbidity.[4]

In addition to diabetes and hypertension, many studies have shown that like glucose variability visit-to-visit BPV is a great risk factor for macro- and microvascular complications in T2DM patients.

BP measurements undergo automatic variations due to multiple reasons. Short-term variations (within 24 hours) may be due to day-night changes. Likewise long-term variations can be due to differences between days, months, and seasons. Also, systolic BP increases with age and diastolic BP also exhibits an age-related biphasic change;[5] management of such patients with antihypertensive therapy might help to obtain normal BP control with optimal CV protection. This may be valuable in understanding the basic concepts of BPV.

Types of BPV

BPV can be classified into the following four different types:

- Short-term (24-hour BPV)
- Very short-term
- Mid-term
- Long-term

These four types are depicted in **Figure 1**.

Short-term or 24-hour BPV

Twenty-four-hour BPV is due to many factors, like physical activity, emotional stimuli, and sleep. Day and night changes can be under the influence of signals initiated by the brain. BPV can also be because of mechanical forces generated by ventilation and due to humoral and local vasomotor phenomena. Night time BP (sleep) is on an average 10–20% lower as compared to daytime (waking hours). However, in hypertensive patients, the 24-hour BPV patterns may remain different. Some show >20% or <10% decrease in BP at night, and some may even show a rise in night time BP as compared with day time BP values.

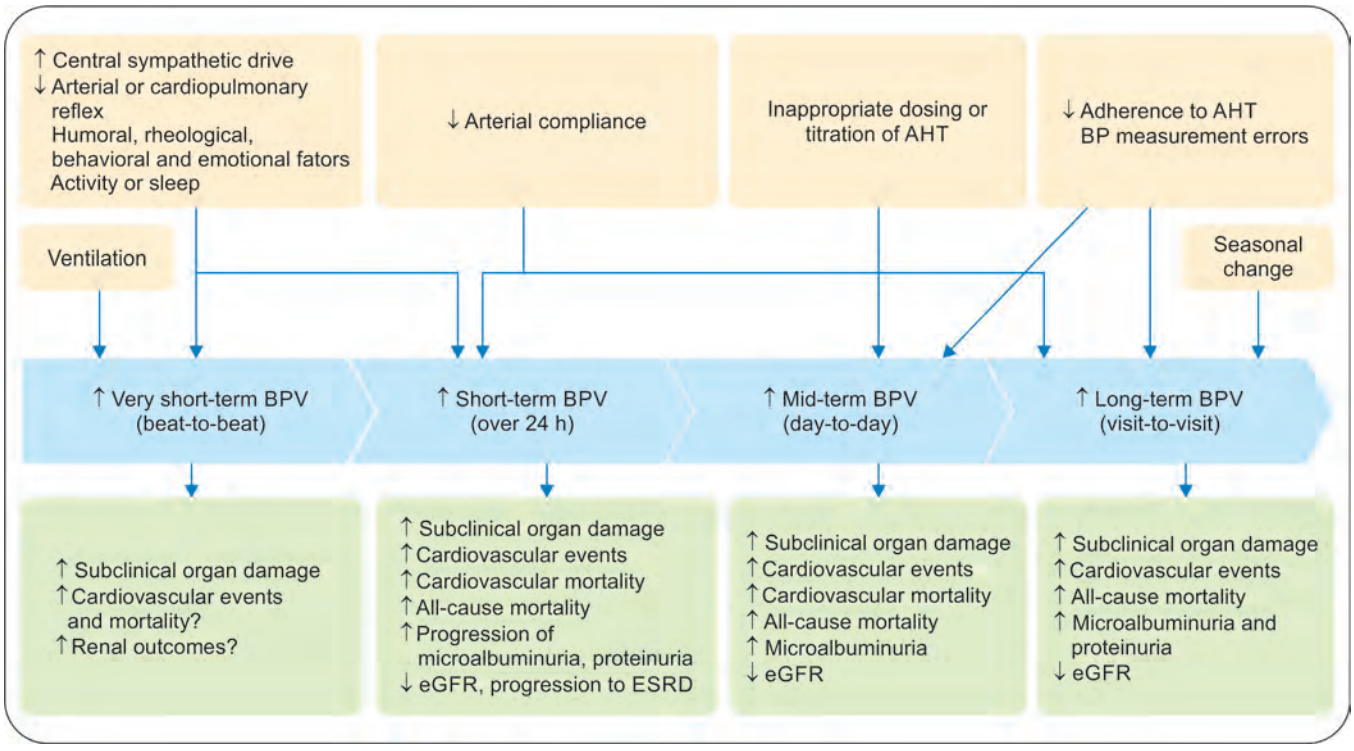

Fig. 1: Various types of BPV, their determinants, and prognostic relevance for cardiovascular and renal outcomes

TABLE 1 Salient features of morning BP surge or morning hypertension

Morning hypertension (surge) *Early morning BP ≥ 135/85 mm Hg (HBP/ABP)*	
Patterns of morning HT	***Clinical outcomes***
• Extension of nocturnal HT	• ↑ Cardiovascular risk
• ↑ BP variability over 24-hr	• ↑ Occurrence of events
• Morning surge (rapid BP rise)	• Target organ damage
Factors influencing morning hypertension	
• Physiological BP surge	• ↑ Sympathetic, neuroendocrine activities
• Associated conditions	• Stress, OSA, drinking, cold, old age
• Inadequate 24-hr control	• Loss of drug efficacy at night/over 24-hr

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Depending on their SBP values patients can be categorized as *extreme dippers* (night-day BP ratio ≤ 0.8), *dippers* (0.8 < ratio ≤ 0.9), *nondippers* (0.9 < ratio ≤ 1.0), and *reverse dippers* or risers (ratio > 1.0).

Reverse dippers have worse outcomes as compared to dippers, and the reasons for this rise in BP at night may be because of:

- Nocturnal autonomic dysfunction
- Disturbed baroreflex sensitivity
- Sleep apnea
- Abnormal sodium handling
- Nocturnal volume overload

Table 1 outlines the salient features of morning BP surge or morning hypertension.

Mid-term or Day-to-day BPV

Day-to-day variations in BP can be defined as mid-term BP variations. These mostly occur because of inappropriate, non-titration, and poor adherence of patients to antihypertensive therapy. Many a times errors in BP measurement by the clinicians can also lead to such variations. Other factors which can influence *mid-term* BPV are:

- Advanced age
- Increased arterial stiffness
- Female gender
- Excessive alcohol intake
- Cigarette smoking
- History of peripheral artery disease, cardiovascular disease, diabetes mellitus, and diabetic nephropathy

Long-term BPV

Long-term BPVs are seasonal variations, day-to-day variations, and also visit-to-visit (VVV) variations. Behavioral characteristics play an important role in the development of long-term BPV as seen by the clear-cut differences seen in ambulatory BP (ABP) values measured during weekdays and weekends. Insufficient antihypertensive treatment due to non compliance of BP treatment or improper dosing/titration of medications by the physician might also influence long-term BPV. In VVV BPVs, the errors in BP measurement play an important role. Also BP variations between summer and winter indicate the influence of temperature and day light hours due to changes in seasons. Multiethnic Study of Atherosclerosis (MESA) has showed that arterial stiffness can also be the cause for long-term BPV.

Very Short-Term BPV

It can be defined as beat-to-beat variability.

Mechanism of BPV

The association of BPV and all-cause mortality in patients suffering from diabetes (where this is not "dampened" by BP lowering medication) may be because of increased arterial stiffness. So, BPV may be a marker of age-related changes in arterial morphology resulting in arterial stiffness. Thus, an association between BPV and all-cause mortality in patients with diabetes but (not on BP lowering drugs) may be because of accelerated vascular aging. An increased BPV in persons with diabetes is a sign of *autonomic dysfunction*, in the form of *impaired baroreflex sensitivity*. Cardiovascular autonomic neuropathy is an important complication of diabetes, and increases mortality risk in patients where it is present. Longer duration of diabetes and evidence of target organ damage can be considered its predictors. The beat-to-beat BP changes occur due to interaction between several CV regulatory systems, such as the baroreceptor reflex, renin-angiotensin system, vascular myogenic response, and release of nitric oxide from the endothelium. But definitive evidence is lacking for the exact underlying mechanism.

Oxidative Stress

Oxidative stress itself is an independent predictor of increased LV mass and correlates with abnormal glucose and BPV. In short-term diabetic patients having optimal

metabolic control but impaired GV and BPV risk are associated with endothelial and cardiovascular damage. Not only HbA1c, high SBP, and high DBP but also glucose and BPV are significant in the clinical management of patients suffering from T2DM and hypertension.

Arterial Compliance

Many studies have shown that in T2DM patients, that hyperglycemia may affect the compliance of the vascular system, which results in large BP fluctuations. This indicates the need to control glycemic status, high BPV and reduced arterial compliance of patients to prevent increase end-organ damage.

Figure 2 outlines the mechanisms of BPV in patients with diabetes.

Methods of BPV Measurement

Various methods for BPV measurements are available:

- Continuous beat-to-beat BP recordings
- Repeated office BP measurement (OBPM)
- 24-hour ambulatory BP monitoring (ABPM)
- Home BP monitoring (HBPM) for long periods[6]

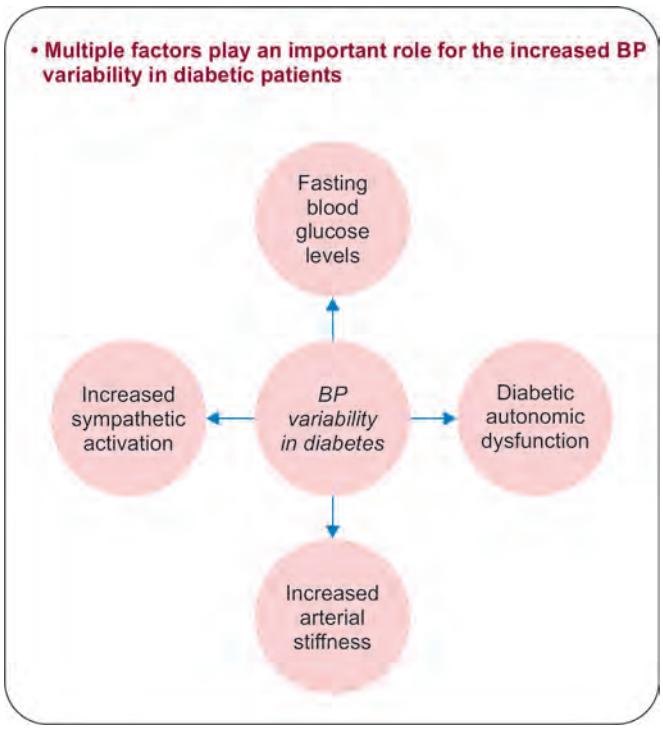

Fig. 2: Mechanisms of BP variability in patients with diabetes

The key index of short-term BPV is standard deviation (SD) of 24-hour average ABP measurements. Since night time decrease in BP interferes with accurate BPV measurements, it has been suggested that 24-hour SD can be a useful guide for the correct assessment of BPV. Day-to-day BPV can be assessed by ABPM for over 48 hours, which may not be a convenient modality for most of the patients. The alternative to ABPM assessment of BPV is use of HBPM that can gather data over many days. The availability of day-to-day BPV may be useful to our physicians in streamlining the management much earlier.[6] Visit-to-visit BPV can be assessed by ABPM or OBPM. However, OBPM is not a correct modality to assess VVV BPV since it might not reflect the BP burden during the patient's normal activities and also requires multiple visits to the physician's office. As ABPM cannot be measured frequently, it may not be a good modality to measure VVV BPV. On the other hand, HBPM looks to be an ideal tool for the assessment of VVV BPV under fairly constant conditions without the "*white coat effect*".[6]

But it is also true that ambulatory BP monitoring not only provides information regarding BP level, but also indicates changes in BP. As BPV is a multifaceted phenomenon which includes short-term as well as long-term components, the same can be estimated by the SD of the BP values over a defined period of the day or the night-to-day BP ratio, respectively. In T2DM patients, dysregulation of the autonomic control of cardiovascular functions can increase BPV.

Night Time BPV

For night time BPV in diabetic patients, it has been shown that ABP measurement is much better modality as compared to clinic BP measurement as it can also confirm the role of abnormal circadian BP variations in predicting future CV events. The SDs of sleep SBP and DBP were independent predictors for CVD risk but the SD of awake BP was not. These finding are in consonance with a study of isolated systolic hypertension which showed that increased night time SBP variability was an independent risk factor for development of stroke.

In a study in diabetic population, neither an abnormal dipping pattern nor the morning BP surge was a predictor of CVD events, whereas the night time BPV appeared to be a strong predictor of CVD risk, independent of ABP level, and other traditional risk factors. These results

indicate that in addition to ABP measurement, evaluation of night time BPV, which can suggest early change of diabetic autonomic neuropathy, may be important for the prediction of cardiovascular events in future.

BPV—Causal or Casual?

Visit-to-visit variability of BP is associated with risk of developing stroke and CAD, independently of mean BP in office visits. It is possible that this association may be causal and that BPV may be an important and significant factor especially in presence of higher autonomic imbalance[2] as it occurs in diabetes patients. This is supported by many studies that visit-visit BPV is not only an independent predictor of macrovascular and microvascular complications in patients with T2D patients, but all-cause mortality.

The observational study—"Retrospective Epidemiological Study to Investigate Outcome and Mortality with Glucose Lowering treatment in Primary Care setting" (ROSE) on 9,855 diabetic patients included the main analysis of associations between BPV and all cause mortality. It indicated that although BPV may result in little improvements in mortality prediction, but may not translate into clinical usefulness for risk prediction above and beyond that of other routinely measured predictors of BP. It was found that mean BP level is better predictor of CVD and all-cause mortality than BPV.

Recent studies have shown that BPV persisting across several clinic visits (i.e., long-term BPV) is associated with the risk of stroke,[3,4] CAD and all-cause mortality.[5] Short-term BPV measured over 24 hours by ambulatory BP monitoring is also associated with increased CVD events[6,7] but many studies have shown that within-visit BPV is associated with metabolic syndrome score,[8] target organ damage (left ventricular hypertrophy and albuminuria),[9] and the risk of stroke,[3,4] but not with overall CV events or all-cause mortality.[10,11]

Clinical Significance of BPV in Diabetes

- In a study of 8,811 patients with T2D in the ADVANCE trial it was concluded that VVV of SBP was significantly associated with the incidence of major micro- and macro-vascular events and all-cause mortality.[11]
- A retrospective cohort study which evaluated the effect of VVV of SBP on CVD and all cause mortality among 124,105 Chinese patients with T2DM identified a positive linear relationship between the VVV of SBP and the first incidence of CVD and all-cause mortality over a median follow-up time of 39.5 months.[12] Further, the patients with SD of SBP <5 mm Hg had the lowest risk of CVD and all-cause mortality, and those with SD of SBP ≥10 mm Hg had significantly higher risk.
- Study conducted on 2,161 T2D patients over 5.5 years, VVV BPV significantly predicted all-cause mortality, irrespective of mean BP values.[13]
- Ushigome et al. evaluated in 858 Japanese patients with T2D for 14 consecutive days the relationship between day-to-day variability and to macro albuminuria by HBPM. After adjusting for several factors, the analysis showed that CoVs of morning SBP and DBP as well as those of evening SBP were independently linked with the algorithm of urinary albumin excretion (UAE), so coefficient of variations of HBPM can be a novel factor which correlates with macro albuminuria after accounting for known risk factors in patients with T2D.

Table 2 depicts some of the salient studies of BPV in diabetes.

TABLE 2 Evidence indicating the effect of BPV on various parameters in diabetes patients

Study	*Population characteristics (n)*	*BPV index*	*Outcome*
Kilpatrick et al. (2010)[14]	T1DM patients (1,441)	Visit-to-visit BPV	High risk of nephropathy
Ozawa et al. (2009)[15]	Hypertensive diabetic patients (72)	Night time Systolic blood pressure variability	Increased risk of coronary heart disease
Ushigome et al. (2011)[16]	Patients with T2D (858)	Day-to-day BPV	Increased risk of macro albuminuria
Hsieh et al. (2012)[13]	Patients with T2DM (2,161)	Visit-to-visit SBPV and DBPV	High risk of all-cause mortality

Within-Visit BPV is Associated with Prediabetes and Diabetes

This study included 17,795 individuals aged 40–74 years who underwent health check-ups in Japan and completed two BP measurements. Associations between within-visit BPV and risks for cardiovascular events were investigated.

It was concluded that high within-visit BPV is significantly associated with the prevalence of prediabetes and diabetes, independent of mean SBP, in a large general population. Therefore, it was considered that blood sugar parameters should be monitored in patients with high-BPV as BPV can be assessed in a single visit and may prove to be a useful modality to diagnose patients at greater risk of impaired glycemic control.

BPV Management: Protection Provided by Antihypertensive Drugs

BPV is known to decrease with decrease in BP induced by antihypertensive management. But effect of different antihypertensive classes compared to one another is yet not known. Long acting dihydropyridine calcium channel blocker are undoubtedly the most promising drugs in the management of BPV. Many clinical studies have consistently found the advantage of these drugs in reducing ambulatory, home, and clinic BPV.[17] In fact, the smoothness index (an index that includes information on the homogeneity of antihypertensive drug effects over 24 hours) correlates with both a reduction in 24 hour BPV and the regression of organ damage in hypertension[18] with the use of long acting antihypertensive drugs. Apart from the use of specific drugs, drugs which cause iatrogenic increase in BPV (like the use of short acting antihypertensive treatment) should be avoided.

A study on hypertensive patients with diabetic nephropathy has shown that treatment with ARBs or ACE inhibitors could improve ambulatory short-term BPV. After 12 weeks of treatment 24-hours, daytime, and night-time short-term BPV were significantly decreased.[19] Evidence is also available that some classes of oral anti-diabetic drugs, that is, thiazolidinediones, may not only have a beneficial effect on 24-hour BP levels but also improve day-night BP profile in diabetic subjects.[20]

Conclusion

The concept of BPV has been there for last many years but did not get the attention and importance in routine clinical day-to-day practice. BPV has been identified as a risk factor for various hypertension-related complications, more so in diabetes patients. SD is the easiest way to calculate BPV. Mobile app can be helpful to the clinicians to calculate SD immediately. Various modalities such as ABPM, HBPM, and OBPM can be used to measure BPV depending on the availability and feasibility. The treatment of any patient of BPV and also of diabetes should be individualized accordingly. It has been shown to be beneficial if we adhere to the night time dose regimen of antihypertensive drugs. Based on several evidences the association between BPV and various complications like CV events, all-cause mortality, diabetic and renal complications, etc., it may be useful to include BPV in the diagnostic pool of hypertension management and there is a need for further research for determining the affect of BPV on CV complications and target organ damage in a patient of T2DM and hypertension.

Subjects with higher night time than day time BPV had a higher risk of death. However, reverse dippers on antihypertensive drugs were older and usually had a history of diabetes mellitus or previous CV events.

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CHAPTER

50 Insulin Resistance and Ectopic Fat—A Complex Interrelationship

NK Soni, VB Jindal

Abstract

Ectopic fat is defined by excess adipose tissue in locations not classically associated with adipose tissue storage or contains only small amounts of fat, such as the liver, skeletal muscle, heart, and pancreas. Ectopic fat can interfere with cellular functions and hence organ functions and is associated with insulin resistance. Adipose tissue consists of adipocytes and the vascular fraction that contains blood vessels. Adipose tissue has the unique capacity to store large amounts of energy in the form of triglycerides. For a long time, it has been presumed that energy storage was the only function of adipose tissue. However, adipose tissue acts as an endocrine organ by secreting various hormones and cytokines known as adipokines. These adipokines have effects on glucose and lipid metabolism and energy homeostasis. It now appears that adipose tissue dysfunction plays a role in developing insulin resistance. Adipose tissue dysfunction is characterized by large adipocytes and secretion of adipokines with a proinflammatory profile. The aim of this article is to discuss the pathophysiology of ectopic fat and its effect on insulin resistance. We will elaborate on the effect of ectopic fat deposition on the cellular level as well as on the various organ level involved in the pathogenesis of insulin-resistant. Genetic, environmental, and behavioral factors are involved in excess energy intake and decreased physical activity leading to ectopic fat deposition. Physiologic versus pathologic fat accumulation also plays an important role in its dysfunction. Human adipocytes can grow up to ~20 fold in diameter and several thousand-fold in volume. Too large adipocytes will release stress signals in response to hypoxia when vascularization is inadequate for the expanded adipose tissue and endoplasmic reticulum stress which is induced by hypoxia or nutrient excess. Consequences of ectopic fat accumulation depends upon the specific organ although cellular mechanisms remain same but Visceral fat accumulation is linked to higher level of insulin resistance. We have also discussed the issue in reference to diagnosis and its prevention with diet and lifestyle intervention.

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial disease with complex interplay of genetic, environmental, and lifestyle factors contributing to insulin resistance and impaired insulin secretion, which leads to a state of chronic hyperglycemia and its attendant complications.[1] A dramatic rise in the number of people with obesity has been witnessed in the last few decades, with doubling of individuals with body mass index (BMI) >30 kg/m^2 in the last 30 years. Obesity predisposes to the development of insulin resistance, T2DM, metabolic syndrome, cardiovascular disease, and cancer. Interestingly people with metabolic syndrome present a fivefold higher risk of developing T2DM. It is expected that incidence of diabetes will double by 2025, and in 2030 diabetes will be the seventh cause of death in the world.[2-7]

Insulin resistance is an excellent predictor for the clinical onset of T2DM and precedes occurrence of the

disease by many years. Typically in obesity, the level of circulating triglycerides and free fatty acids (FFAs) at some stage begins to exceed the metabolic capacity of adipose tissue, leading to excessive accumulation of fat in other organs, including liver, pancreas, and skeletal muscles. This results in serious metabolic and clinical consequences as increased lipid accumulation inhibits insulin-mediated glucose uptake and thereby reduces insulin sensitivity of the organs.[8]

Dysfunction of Adipose Tissue

In obese subjects that develop insulin resistance, adipose tissue dysfunction plays a major role. Adipose tissue dysfunction is characterized by large adipocytes formation and secretion of adipokines with a proinflammatory profile ultimately leading to ectopic fat deposition.[9] Ectopic fat is defined as storage of TG in tissues other than adipose tissue, that normally contain only small amounts of fat, such as the liver, skeletal muscle, heart, and pancreas. Ectopic fat can interfere with cellular functions, and hence organ function and is associated with insulin resistance.

Mechanism of Ectopic Fat-induced Organ Dysfunction

The consequences of ectopic fat accumulation depend on the specific organ involved. Firstly, it has to be noted that lipids can be dispersed intercellularly or accumulate intracellularly. Deposition of lipids in intercellular space might impair organ function via paracrine effects of the released adipokines. However, it is the intracellular lipid accumulation that is associated with decreased insulin sensitivity **(Fig. 1)**.

It appears that it is not the FFAs themselves, but metabolites like long-chain acyl-CoA (LC-CoA), diacylglycerol (DAG), and ceramides, which are deleterious for the cell. These fatty acid metabolites induce a sustained activation of serine/threonine kinases such as protein kinase C (PKC) isoforms, IKB-kinase-β, and Jun N-terminal kinase, which phosphorylate insulin-receptor substrates (IRS) on serine residues.[10] The subsequent defects in insulin signaling lead to a decrease in cellular function that depends on the cell type.

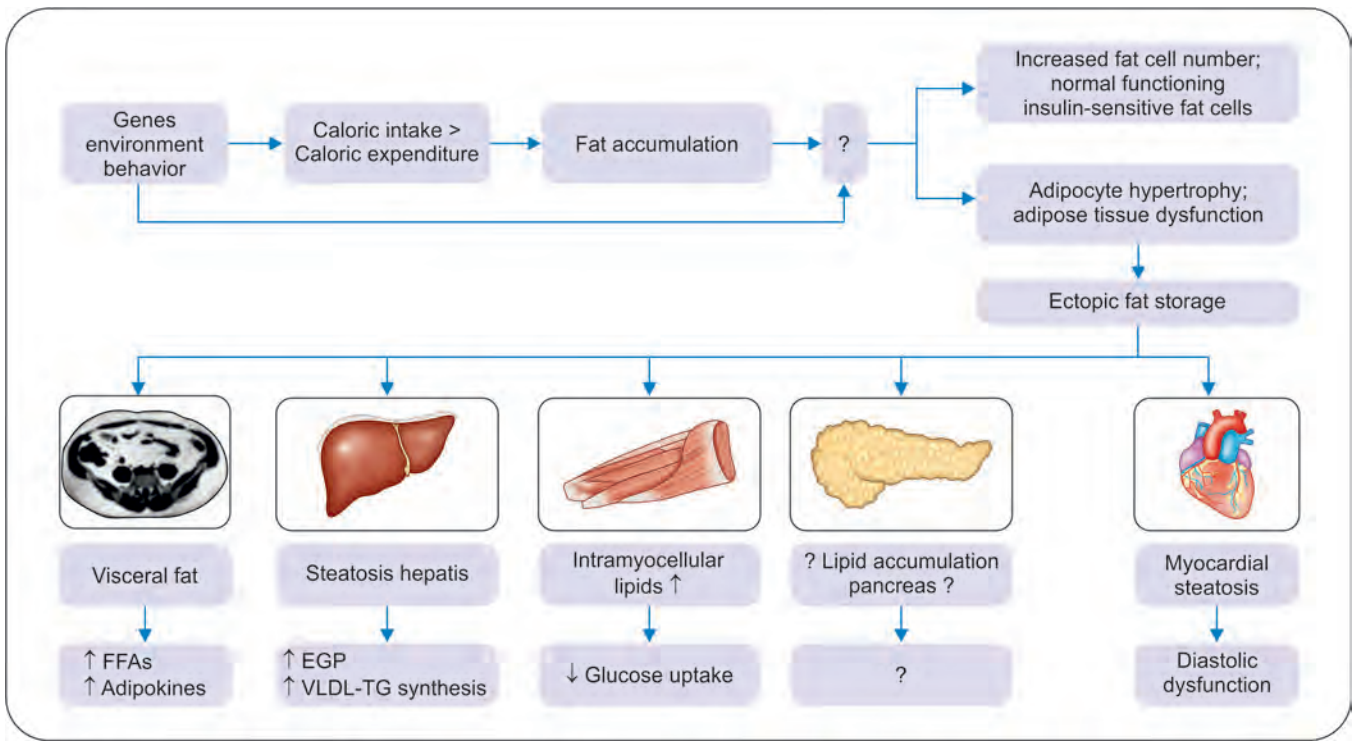

Fig. 1: Pathophysiology of ectopic fat deposition

FFAs are taken up by the skeletal muscle cell mainly by protein-mediated membrane transport, fatty acid transport protein (FATP), along with passive diffusional uptake. After uptake in muscle metabolites of these fatty acids induce a sustained activation of serine/threonine kinases leading to phosphorylation of insulin-receptor substrate (IRS1) on serine residues.[10] Serine-phosphorylated forms of IRS1 cannot associate with and activate phosphatidyl-inositol3-kinase (PI3K), resulting in a decreased glucose transporter 4 (GLUT4) regulated glucose transport over the cell membrane.

The mechanism behind hepatic TG accumulation and the development of hepatic insulin resistance are much similar to that described for skeletal muscle.[10-12]

Fatty Liver a Cause or Consequence of Hepatic Insulin Resistance?

Accumulation of TG in hepatocytes reflects an imbalance between hepatic TG synthesis and its utilization. Utilization includes mitochondrial beta-oxidation, production of ketone bodies, and secretion of TG in very-low-density lipoprotein (VLDL) particles.

Histologically, the fatty liver can be classified as *micro-* or *macrovesicular*.[13] Causes of microvesicular steatosis, such as fatty liver during pregnancy, Reye's syndrome, and certain drugs and toxins, are thought to share a common mechanistic feature—impairment of mitochondrial beta-oxidation.[13] Microvesicular steatosis is often accompanied by severe hepatic dysfunction. The causes of macrovesicular steatosis include alcohol, non-alcoholic fatty liver disease (NAFLD) associated with features of insulin resistance, total parenteral nutrition, protein-calorie malnutrition, and jejunoileal bypass. NAFLD is a term describing a large spectrum of conditions ranging from fat alone to fat plus inflammation, fat plus ballooning degeneration, and non-alcoholic steatohepatitis (NASH).[14]

Endogenous or Exogenous Factors that Affect Ectopic Fat, Liver and Muscle IR

Gender differences have been linked to ectopic fat accumulation and IR[15] and these could partly be related to differences in body fat distribution in men and in women. Generally, women have a higher percentage of subcutaneous adipose tissue (SAT) as compared to BMI-matched men, who generally have more visceral adipose tissue (VAT). The expandability of SAT also could be a critical factor in the development of insulin resistance.[16,17]

Lipids may be predominantly stored in SAT before marked VAT expansion occurs. VAT has been linked to higher levels of inflammatory markers, insulin resistance, and other cardiometabolic complications.[18,19] Moreover, in general women accumulate more adipose tissue in the gluteal-femoral regions as compared to the abdominal fat deposition. Abdominal obesity is associated with an increased risk of developing T2DM and cardiovascular diseases.[20]

Furthermore, although not completely elucidated, the metabolic differences between men and women are, also partly, a consequence of differences in hormonal status. Estrogen has been shown to reduce intrahepatocellular lipid (IHCL) accumulation and IR in both sexes. Until menopause, women have a lower risk for developing fatty liver, whereas postmenopausal women have a similar risk compared to age-matched males.

Age also seems to be a very relevant factor in the etiology and pathophysiology of IR, and seems to be positively related to ectopic fat accumulation.[21]

Imaging and Measurement of Ectopic Fat

Magnetic resonance imaging (MRI) examination which allows noninvasive assessment of lipid infiltration in various organs may become an ideal tool or gold standard imaging technique that can help to quantify and illustrate the effects of obesity. MRI will allow early detection of reversible metabolic changes as well as their further monitoring. It is believed that in the future, the method could also be used as a biomarker for indicating the development of prediabetes insulin resistance.

Effect of Macronutrients on Ectopic Fat in Distinct IR Phenotypes

There has been a debate on different dietary approaches in the prevention of T2DM and tackling insulin resistance. One of the approaches is the Mediterranean diet, rich in olive oil, which may provide cardiovascular benefits. Secondly, diets low in fat and high in complex carbohydrates with increased fiber content along with lifestyle interventions may decrease the cumulative incidence of diabetes by more than 50% over next 3–6 years.[22-26]

Available evidence clearly indicates that there is great potential to optimize the effectiveness of dietary interventions on glucose homeostasis by, for example, targeting liver- and muscle-IR phenotypes. A first step toward the development of more personalized nutrition could be to investigate the role of tissue specific IR and related ectopic fat content in the effectiveness of dietary interventions, in particular when studying the effect of manipulation of the macronutrient composition of the diet.

Conclusion

Ectopic fat accumulation in insulin-sensitive tissues is associated with insulin resistance independent of overall obesity. However, our understanding of the causes and mechanisms underlying fat accumulation in skeletal muscle and the liver are limited. Identifying why some individuals store fat in insulin-sensitive tissues, but others do not, may be of great importance for the development of new insulin-sensitizing agents and for optimal use of current therapies.

Diet and exercise are powerful tools in improving both ectopic fat deposition and the function of the organ in which the ectopic fat is deposited. Diet and lifestyle intervention, therefore, deserve more attention, both as preventive measure for obesity and T2DM as well as for the treatment of insulin resistance and T2DM.

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CHAPTER

51 Acute Metabolic Complications in Diabetes Mellitus

Anuj Maheshwari, Nisha Maheshwari

Abstract

Acute increase in plasma glucose causes acute metabolic complications leading higher occurrence of morbidity and mortality in patients with diabetes. This can easily be prevented by early identification and aggressive treatment. Insulin insufficiency is coupled with rise in level of counter regulatory hormones which is usually precipitated by prolonged fasting, dehydration, pregnancy, physical stress, infection apart from missing exogenous insulin dose, and very high insulin resistance. Poor carbohydrate utilization prepares the ground of deriving energy from alternative fuel resources causing ketosis, acidosis and dehydration which is further aggravated by osmotic diuresis along with hyperglycemia and superadded electrolyte loss. Best strategy for prevention is early detection and identification of precipitating factors so they can be treated before causing acute metabolic diseases. Youngsters especially type 1 diabetes are more prone for diabetic ketoacidosis. Contrary to this, elderly individuals, especially with newly detected diabetes have higher risk for hyperglycemic hyperosmotic state, mostly in females. Raising awareness at community level is significant intervention for prevention. Treatment should be targeted to correct dehydration by restoring extracellular and intracellular fluid volume together with treating electrolytes imbalances, hyperglycemia, and acidosis.

Introduction

Diabetes mellitus (DM) is a chronic endocrine disorder, which occurs of pancreatic insufficiency to make insulin or to impaired action or both causing hyperglycemia. Acute rise in plasma glucose may lead to acute metabolic complications like diabetic ketoacidosis (DKA), hyperglycemic hyperosmolar nonketotic coma (HHNKC), lactic acidosis (LA), and hypoglycemia. These complications lead to increased mortality and morbidity, which can only be prevented by early identification and aggressive management.[1]

Pathogenesis

Underlying pathology includes raised blood sugar, metabolic acidosis, electrolyte abnormalities, hyper ketosis and water deficit for all acute metabolic complications except hypoglycemia. Mostly it is because of relative insulin insufficiency together with excess of counter regulatory hormones like glucagon, catecholamines, cortisol, and growth hormone.[2] Relative insulin insufficiency not only caused by β-cells failure but also due to abrupt deprivation caused by missing exogenous insulin and high resistance to insulin. Various precipitating factors, like prolonged fasting, dehydration, physical stress, infection, play a significant role in presence of excess of counterproductive hormones.[3,4] Poor carbohydrates utilization is further worsened by synthesis of ketones causing acidosis and dehydration. Dehydration increases further by osmotic diuresis due to glycosuria and excretion of neutralized ketoacids by kidney. In addition there is an increased load of amino acid influx from muscles for metabolism together with saturation of hepatic functioning with gluconeogenic precursors thereby leading to higher

pyruvate and lactate synthesis. Unavailability of insulin begins utilization of amino acids and triglycerides as energy source. Unregulated lipolysis gives rise to increased levels of glycerol and free fatty acids.[5,6] In state of insulin deficiency, glucagon in excess converts free fatty acids to ketones and produces glycerol and alanine while causing gluconeogenesis in liver. The culprit ketoacids that result in metabolic acidosis are acetoacetic acid and beta-hydroxybutyric acid. Acetoacetic acid converts to acetone, which is difficult to clear by respiration when accumulated. Uncontrolled hyperglycemia causes marked osmotic diuresis along with superadded loss of electrolytes under effect of ketones.[7] Despite being actually in deficit, potassium levels are initially seen normal due to shift of potassium extracellularly with regards to acidosis. However, these levels further decline with insulin treatment and thus periodic K^+ check is needed to avoid hypokalemia.[8]

Including poor compliance of insulin treatment, infection, infarction, ischemia, intoxication with alcohol or drug abuse are five important stressors to increase secretion of stress hormones, glucagon, cortisol, and adrenaline causing hyperglycemia, which may end up with DKA in invariably in type 1 DM but sometimes in type 2 DM with insulin resistance along with erratic medication and poor diet plan.[8] On the other hand the pathogenesis of hyperglycemic hyperosmolar state (HHS) differs from that of DKA as it occurs with more severe dehydration due to osmotic diuresis without significant ketosis/ketonemia.[2,9] A higher concentration of circulating hepatic insulin may keep it free from ketosis. Patients presenting with HHNKC have lower level of free fatty acids, cortisol, growth hormone, and glucagon than patients with DKA. Patients with HHNKC may have mild metabolic acidosis due to compromised kidney functions and dehydration **(Fig. 1)**.[9]

Reactive oxygen species (ROS) play an important role in synthesis of advanced glycation end products (AGEs), increased activity of protein kinase C (PKC), stimulation of hexosamine pathway together with higher contribution from the polyol pathway actually underlies the whole pathobiological process.[10] LA is an elevation of lactic acid beyond 5.0 mEq/L with acidosis (pH <7.3). Ketones are absent or very low. It accounts for 1.2% of all hospitalizations with diabetes in decade of 2001–2010 and is showing consistently rising trend from earlier data 0.6% in 1989–1991. Similar rising trend from 0.3% to 1% is noticed among non-diabetics. Hypoglycemia has also been identified as an underlying cause among 5.4% of total hospitalization with diabetes during 2001–2010. Severe hypoglycemia are increasing among patients aiming lower glycosylated hemoglobin (A1c) without enough prior education and support.[11] Hypoglycemia caused

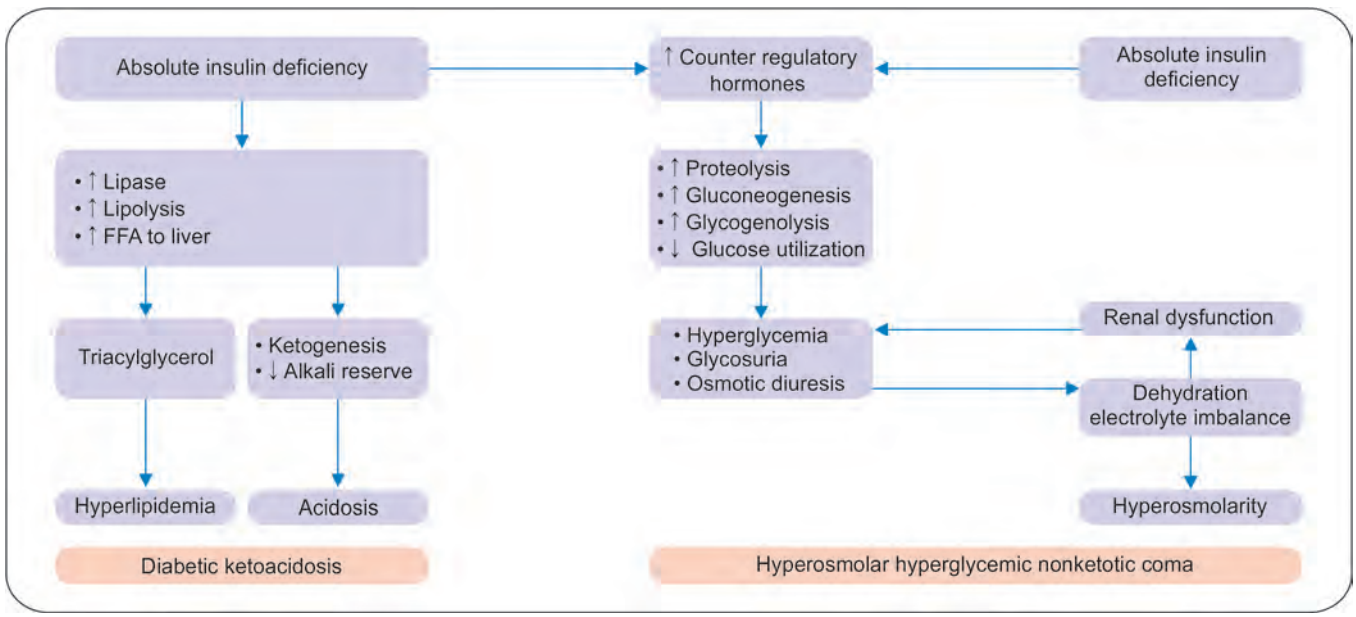

Fig. 1: Mechanism for the development of acute complications in diabetes

by sulfonylureas is more prolonged and hazardous in comparison to that caused by insulin.[10]

Predictors and Precipitating Factors

DKA occurs more commonly in younger age with established type 1 DM. Younger age can be taken as risk factor as children below 2 years of age have three times more risk than older kids.[12] It increases with age in females but not in males. It is commoner in ethnic minorities.[13] Apart from this lower socioeconomic status including low income and poor educational status and lower level of awareness of family members play an important role in causation of DKA.[12] Family history of diabetes, particularly the presence of a first degree relative of type 1 DM plays a protective role. Medications like steroids, antipsychotics like clozapine or olanzapine, diazoxide, cocaine, and lithium can precipitate DKA especially in newly diagnosed patients with diabetes. Missing dose of insulin, pump failure, or treatment error like inadequate insulin therapy during acute illness, infection, myocardial infarction, or surgery may also lead to DKA.[10,14] Ketoacidosis with normal or near normal plasma glucose level may occur during fasting, pregnancy, very young or partially treated patients, which is called Euglycemic Ketoacidosis.[15] It is also reported in modern days patients being treated with newer molecules like SGLT-2 inhibitors.[16]

Contrary to DKA, elderly individuals, especially with newly detected diabetes have higher risk for HHS with female preponderance. Most of HHNKC episodes are precipitated by an infection followed by cerebrovascular accident, alcohol abuse, pancreatitis, myocardial infarction, trauma, and medications affecting carbohydrate metabolism like steroids, thiazides, and sympathomimetic agents like dobutamine and terbutaline.[10,17]

LA is a medical emergency most commonly results from oxygen deprivation in the body's tissues, impaired liver function, respiratory failure, or cardiovascular disease. Other conditions poor oxygenation like hypoxemia, shock, sepsis, carbon monoxide poisoning, and some medications like phenformin and metformin, especially when they are used in patients with renal failure. Alcohol abuse also commonly causes LA in diabetic patients.[18]

Modifiable predictors of severe hypoglycemia include intensive insulin treatment with the intention of low HbA1c using higher dose of insulin. Patients keeping HbA1c levels below 7.0% (<53 mmol/mol), especially in patients with age of 75 years or more, with serum creatinine level more than 2.0 mg/dL or having cognitive impairment or dementia had shown higher occurrence of overtreatment translating into hypoglycemia.[13]

Prevention and Treatment

Best strategy for prevention of DKA is early detection of type 1 DM before the occurrence of DKA. Removal of precipitating factors after identifying them well should be the next. Raising awareness at community level is significant intervention for prevention. Treatment should be targeted to correct dehydration by restoring extracellular and intracellular fluid volume together with treating electrolytes imbalances, hyperglycemia, and acidosis. If there is no cardiac compromise, isotonic saline should be infused at a rate of 15–20 mL/kg/h, which must not be less than 1–1.5 L at least in the 1st hour. After that fluid replacement should be given on the basis of hemodynamic status, serum electrolyte levels, and urinary output. For hyperglycemia correction insulin treatment should be given in initial bolus dose of regular insulin intravenously at the rate of 0.1 units per kg followed by the infusion of 0.1 units/kg/h. A prospective randomized study has shown that a bolus dose of insulin can be avoided if hourly insulin infusion is given at the rate of 0.14 units/kg body weight.[2] As per ADA recommendations criteria for resolution of DKA is blood glucose less than 200 mg/dL with any two of the three including

- Bicarbonate ≥15
- pH >7.3
- Anion gap ≤12.

Patients with HHNKC should be hospitalized and treated in similar way with goals of correcting volume deficits, reducing plasma hyperosmolality to normal. Hyperglycemia will be corrected with insulin while providing intravenous rehydration to resolve HHNKC promptly. After doing early fluid replacement with 1 liter of normal saline in first hour, fluids should be given intravenously as per patient's hemodynamic and electrolyte status maintaining hourly infusion between 250 and 500 mL/h. Patients with normal or high corrected sodium can be shifted to half normal saline after 1 hour. Dextrose of 5% or 10% to be added after plasma glucose level approaches 250 mg/dL. Total body potassium deficit should be replaced after urine output is adequate. Between 20–30 mmol (20–30 mEq) potassium in each

liter of intravenous fluid should be added, when serum potassium level touches less than 5.2 mmol/L and patient start passes urine. As insulin therapy causes intracellular shift of potassium, it is recommended that insulin should not be started if the serum potassium is less than 3 mmol/L (<3 mEq/L) if it is needed, so that it may not worsen hypokalemia. Routine replacement of phosphate is not advisable. Insulin should be started only after correction of hypokalemia at the same dose as in DKA. If plasma glucose does not go down by 50–75 mg/dL/h from the initial value in the first hour, insulin infusion should be increased every hour till it touches 250–300 mg/dL and is to adjusted with dextrose to maintain this level until HHS is resolved.[9] Insulin infusion can usually be stopped once patient starts taking orally but intravenous fluids can be continued a bit longer if intake is not adequate. Normal osmolality and regaining normal mental status are the signs of recovery.

LA can easily be prevented if we can stop cardiovascular disease or sepsis in patients with diabetes maintaining optimum glucose control and augmentation of other risk factors. Most effective treatment for LA is to stop lactic acid synthesis improving tissue oxygenation. Treatment of underlying conditions like shock or myocardial infarction by restoring fluid volume, cardiac function, treatment of sepsis, and hyperglycemia are the mainstays of treatment.[19]

Risk of hypoglycemia can be reduced by using technological advances, which improve insulin delivery may it be insulin pump, sensor technology in glucose monitoring and using designer insulin analogues with intensified teaching and improving compliance. The goal of treatment of hypoglycemia is to immediately increase the blood glucose approximately ~55–70 mg/dL, which can easily be achieved with glucose tablets, sweetened fluids in patients who are not lost their consciousness and intravenous dextrose or glucagon injection in unconscious patients.[11,20]

Conclusion

Despite increasing awareness, technological advancements, development of designer insulins, and clear cut guidelines, acute metabolic complications are on the rise in last two decades. DKA is not only remained a complication of type 1 DM. With the advent of SGLT-2 inhibitors now we can see it in patients with less than 200 mg/dL plasma glucose level as euglycemic ketoacidosis. Apart from this pump failure, missing the dose of insulin knowingly or unknowingly, infections, acute illness, inadequate insulin treatment, or other treatment errors have caused not only higher occurrence of DKA but also HHNKC. LA has emerged as more frequent acute complication than earlier due to higher use of biguanides like metformin in patients with renal failure. Rising alcohol abuse has also posed a challenge of LA among people having diabetes. Intention of maintaining lowest possible HbA1c has caused an increase in hypoglycemia. Increasing use of self-monitoring of blood glucose (SMBG) devices and sensor technology has made it possible to detect and document hypoglycemia at every level. Undoubtedly it adds up the protection of patient when we can easily know overnight and early morning hypoglycemia but obviously it is affecting statistics of hypoglycemia. Sensible use of advanced technology in newer medications, insulin analogues, delivery devices, and sensors can reduce overall acute complications in diabetes. Increasing awareness among patients and their relatives is the most important step to begin with.

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CHAPTER

52 Environmental Endocrine Disruptors and Diabetes: Novel Insights from Nallampatti

Krishnan Swaminathan

Abstract

There has been a huge explosion of diabetes over the last decade, especially in lower and middle income countries. While traditional risk factors like diet, lifestyle, urbanization, fast food culture, and less physical activity are extremely important risk factors, we believe that these factors alone do not explain the huge increase in diabetes in India. Our work in Nallampatti showcases the effects of endocrine disruptors, especially pesticides and heavy metals in the prevalence of diabetes and atherosclerosis. While in no way this study is confirmatory of the association, our work does highlight important unexplored aspects of diabetes pathophysiology in India that needs further large scale studies.

Introduction

South Asia, particularly India, home to around 18% of the world's population, is currently in the midst of an epidemiological transition from infectious and nutritional illness to non-communicable diseases (NCDs), especially cardiovascular disease, predominantly driven by a cluster of "traditional risk factors" like diabetes, prediabetes, obesity, diet & lifestyle, hypertension, hyperlipidemia, and atherosclerosis. Individually, each of the above risk factor has huge health care, economical, and societal implications. Collectively, this "Axis of evil" is a disaster in the making for India and a "ticking time bomb" that will wreak the nation's health.

Diabetes is a "vascular disease" and not a metabolic disorder alone. India leads the world in the numbers of patients with diabetes and has the infamous tag of being referred to as the "Diabetes Capital of the world." Currently, it would not be an exaggeration to practically define diabetes as a state of premature cardiovascular death associated with chronic hyperglycemia and in the absence of effective treatment to control glucose levels, will lead to blindness, kidney failure, and foot amputation. In fact, there is good evidence for terming diabetes as a "coronary risk equivalent." Studies have shown that diabetic patients without a previous heart attack have the same high risk of getting a heart attack as someone without diabetes who already had a previous heart attack.[1] Poorly controlled diabetes is a major risk factor for end stage kidney disease (ESRD) needing dialysis and renal transplants in India. More than 1 lakh patients enter the renal replacement therapy annually in India, but due to extremely scarce resources, only 10% of this population receives renal replacement therapy.[2-4] Poorly controlled diabetes is a leading cause of foot amputations in India. Foot ulcerations occur in 25% of patients with diabetes and approximately 15% of such foot ulcerations result in amputations.[5] With this background, we are now witnessing a huge explosion in diabetes epidemic that can have potentially catastrophic consequences for the health care of our nation. One hospital admission with a diabetes-related complication will drain the family of all their resources, especially from the, lower socioeconomic backgrounds, as 70% of Indian urban and rural households visit only private sector providers over public services.[6]

Prediabetes is the prelude to diabetes. Colloquially, this is termed as "borderline diabetes." Intuitively, one would underestimate prediabetes, as this is not yet full-blown diabetes. However, even many physicians are unaware that prediabetes is also associated with the same set of comorbidities like heart attacks and strokes, very similar to diabetes.[7] Indians also have one of the highest conversion rates from prediabetes to diabetes. Data from follow-up of patients over 10 years from the Chennai Urban Study (CURES Study) indicates a conversion rate of prediabetes to diabetes in the order of 60%.[8] Taken together based on the above discussions, Indians have one of the highest incidence rates for diabetes with rapid conversion from prediabetes to diabetes. The pressing need of the hour is to slow down and reverse this epidemic in our population.

The concern for all health-care professionals and policymakers is the fact that the transition in both the risk factors and diabetes prevalence in India has occurred over a relatively short period of time.[9] To compound this, India is a "Nation within a Nation," where many states have populations close to that of countries in Europe! Therefore, there will be huge regional variations in diseases and risk factors that will have a bearing on how scanty resources can be utilized to optimize health care. Our concern is primarily centered toward rural Indian population where the triple burden of lack of awareness, health care costs, and poor health care facilities add significantly to morbidity and mortality from non-communicable diseases. The progression of this NCD epidemic, especially in rural areas, is characterized by a multitude of factors including rapid urbanization, reversal of socioeconomic gradients, fast food culture, less intake of fruits and vegetables, tobacco and alcohol use/abuse, less access to health care in the poorer socioeconomic strata of the society, and much more.[10] Efforts to understand the pathophysiology of this transition have been traditionally focused on the above factors. However, there is growing body of evidence for the role of non-traditional risk factors, especially pesticides and heavy metals in fertilizers, in the development of diabetes, prediabetes, hypertension, atherosclerosis, and cardiovascular disease.[11-32] Our aim was to adopt and explore the burden of NCDs in a traditional rural farming village in our area, do a longitudinal follow-up, and assess the role of both traditional as well as non-traditional risk factors like pesticide and heavy metal use in this population.

Material and Methods

KMCH: Nallampatti Non-communicable Disease-I (KMCH-NNCD-I) Study

Nallampatti is a typical farming village in Tamil Nadu, South India (Latitude: 11°21'2.39" N; Longitude: 77°32'4.79" E) **(Fig. 1)** with a population of around 3,000. This study, named the "Nallampatti non-communicable disease study-I—2015 (NNCD-I, 2015)," was conducted on every Sunday during a period of 4 weeks (15 March–05 April, 2015). Advertisements were given through pamphlets, word of mouth, and through administrative heads like the Panchayat President. The study design and protocol were approved by KMCH Ethics Committee, Kovai Medical Center and Hospital Limited, Coimbatore (Approval No. EC/AP/02/2015, dated 16 Feb, 2015), and informed written consent was obtained from all participants prior to participation and followed the principles of Declaration of Helsinki.

A total of 865 participants were screened with a questionnaire, bloods including HbA1c, non-fasting lipid profile, creatinine, carotid intima thickness (CIMT) using carotid ultrasound transported to the venue along with urine for heavy metals and serum pesticides. Methodology for all the above along with definitions for diabetes and prediabetes have been published.[33-35] All subjects native to the village aged more than 20 years were invited for the study. Urine heavy metals and serum pesticides were stored at -80°C and transported to IIT Madras for analysis by ICP-MS and GC-MS, respectively.

Results

The topline results from our study showed a diabetes prevalence of 16.2%, prediabetes of 42%, hypertension 39%, hypercholesterolemia in 33%, and atherosclerosis in 10.3%. This was much higher than the ICMR-INDIAB prevalence **(Table 1)**, even though comparing both studies may be analogous to comparing apples and oranges! Allowing for the methodological variations and confounding factors, the double-digit prevalence of diabetes was very consistent with our clinical experience and other studies done by our study group in rural Madurai & Theni districts of Tamil Nadu.

On multiple logistic regression analysis, diabetes in our rural population was surprisingly not associated with traditional risk factors except for age **(Table 2)**. Generally,

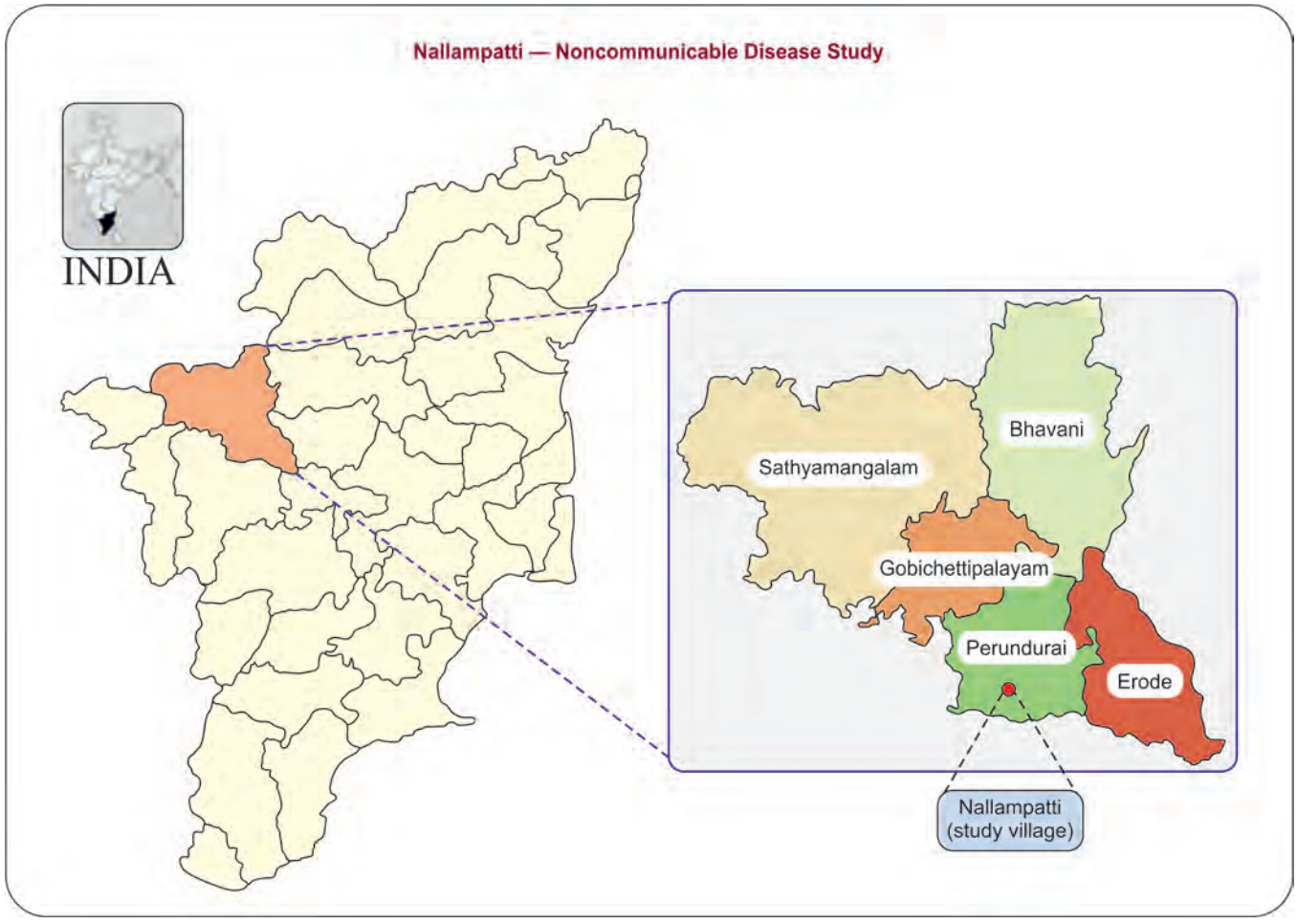

Fig. 1: Geographic location of the study village (Nallampatti)[33]

TABLE 1 Differences in prevalence of NCDs between ICMR-INDIAB study and our study: Are we seriously underestimating the risk?[33]

Factors	***ICMR-INDIAB study***		***KMCH-NNCD study***	
	Definitions	***Tamil Nadu (Rural)***	***Definitions***	***Tamil Nadu (Rural—Nallampatti)***
N		2,480		865
Known diabetes (%)	IFG + IGT[1]	4.1	HbA1c ≥ 6.5	9.1
Newly detected diabetes (%)		3.8		7.1
Ratio of KD:NDD		1:0.9		1:0.78
Total diabetes (%)		7.8		16.2
Prediabetes (%)	IFG or IGT or both[1]	7.1	HbA1c 5.7–6.4	42

Contd...

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Factors	ICMR-INDIAB study		KMCH-NNCD study	
	Definitions	Tamil Nadu (Rural)	Definitions	Tamil Nadu (Rural—Nallampatti)
Hypertension (%)	SBP ≥ 140 and/or DBP ≥ 90[2]	26.2	SBP ≥ 140 and/or DBP ≥ 90	39
Hypercholesterolemia (%)	≥ 200 mg/dL (≥ 5.2 mmol/L)[3]	16	≥ 200 mg/dL (≥ 5.2 mmol/L)	33.4
Hypertriglyceridemia (%)	≥ 150 mg/dL (1.7 mmol/L)[3]	29.6	≥ 150 mg/dL (1.7 mmol/L)	43.5
L-HDL (%)	< 40 for men (1.04 mmol/L)/ < 50 for women (1.3 mmol/L)[3]	67.6	< 40 for men (1.04 mmol/L)/ < 50 for women (1.3 mmol/L)	58.2
H-LDL (%)	≥ 130 mg/dL (≥ 3.4 mmol/L)[3]	13.2	≥ 130 mg/dL (≥ 3.4 mmol/L)	24.1
Generalized obesity (%)	BMI ≥ 25 kg/m^2[4]	22.1	BMI ≥ 25 kg/m^2	31.6
Cystatin C (%)	NA	NA	≥ 1 mg/L	28.4
CIMT	NA	NA	≥ 1.0 mm	10.3

CIMT, Carotid Intima Media Thickness; DBP, diastolic blood pressure; HDL, high density lipoprotein; KD, known diabetes; KMCH-NNCD, Kovai Medical Center Hospital-Nallampatti Non communicable disease study; LDL, low density lipoprotein; NDD, newly detected diabetes; SBP, systolic blood pressure.

TABLE 2 Multiple logistic regression with diabetes as dependent variable: non association of traditional risk factors with diabetes

	KMCH-NNCD study	
	Odds ratio (95% CI)	p-Value
Age	19.9 (8.55–46.5)	<0.0001
Male sex	1.13 (0.63–2.01)	0.672
Smoking (daily smokers)	0.71 (0.15–3.47)	0.676
Alcohol (daily drinkers)	1.92 (0.389–9.504)	0.422
Generalized obesity	1,295 (545–2356)	0.996
Hypertension	1.50 (0.98–2.30)	0.060
High LDL-cholesterol	0.83 (0.51–1.35)	0.449

one would intuitively expect diabetes to be associated with other traditional risk factors like smoking, obesity, hypertension, and hypercholesterolemia. The absence of such an association in our study raised a hypothesis generating question as to whether there may be non-traditional risk factors involved in the huge burden of NCDs in rural areas, especially in farming populations.

Urine Heavy Metals and Diabetes

Fertilizers are a big source of heavy metals especially arsenic. Arsenic has been implicated in diabetes by various mechanisms including beta cell toxicity and interference with insulin signaling. Increased level of these urinary metals, especially arsenic and zinc, were noted among the diabetic subjects in comparison with non-diabetic subjects **(Table 3)**. On correlation and regression analyses of the urinary metals with cardiometabolic risk factors (HbA1c, systolic and diastolic blood pressure, BMI, total cholesterol, CIMT-left, CIMT-right, and cystatin-c), only HbA1c, and CIMT showed significant correlation with the metals.

Pesticides and Diabetes

We noticed a significant positive correlation between all the organophosphate residue levels and HbA1c **(Table 4)** indicating the role of insecticides in glucose homeostasis. Based on detection of insecticide residue level, the population was categorized as "detected below limits of detection (LOD)" and "detected above LOD." On multivariate regression analysis between these two groups,[36] significant odds ratio was obtained for monocrotophos, methyl parathion, malathion, chlorpyrifos, and profenofos for prediabetes, while for diabetes, all the above except profenofos showed significant association.

TABLE 3 Odds ratio (95% CI) of diabetes associated with quartile of urinary metals[35]

	Model	Odds ratio (95% CI)				P_{trend}
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Cd	Unadjusted	1.00	1.25 (0.72–2.17)	1.07 (0.61–1.87)	1.60 (0.91–2.79)	0.142
	Adjusted*	1.00	0.99 (0.54–1.84)	0.92 (0.49–1.72)	1.46 (0.79–2.75)	0.352
As	Unadjusted	1.00	2.05 (1.14–3.71)	2.44 (1.35–4.42)	2.94 (1.63–5.30)	0.001
	Adjusted*	1.00	1.87 (0.98–3.57)	2.44 (1.27–4.69)	2.68 (1.40–3.80)	0.005
Pb	Unadjusted	1.00	1.34 (0.75, 2.38)	2.09 (1.22, 3.60)	1.90 (1.10, 3.31)	0.091
	Adjusted*	1.00	1.35 (0.56, 3.25)	2.46 (1.10, 5.50)	2.70 (1.16, 6.32)	0.134
Cr	Unadjusted	1.00	1.04 (0.58–1.89)	1.69 (0.96–2.97)	2.15 (1.22–3.77)	0.034
	Adjusted*	1.00	1.05 (0.58–2.02)	1.87 (0.99–3.51)	2.40 (1.26–4.56)	0.012
Al	Unadjusted	1.00	0.79 (0.43–1.46)	1.93 (1.11–3.35)	1.80 (1.02–3.16)	0.019
	Adjusted*	1.00	0.86 (0.44–1.67)	2.03 (1.10–3.74)	2.19 (1.16–4.12)	0.025
Zn	Unadjusted	1.00	2.15 (1.14–4.04)	3.54 (1.87–6.71)	4.12 (2.23–7.60)	<0.001
	Adjusted*	1.00	2.10 (1.10–4.38)	3.93 (1.96–7.87)	3.32 (1.70–6.49)	<0.001
Cu	Unadjusted	1.00	1.51 (0.85, 2.67)	1.98 (1.13, 3.46)	2.16 (1.25, 3.74)	0.048
	Adjusted*	1.00	1.32 (0.57, 3.09)	1.66 (0.76, 3.67)	2.27 (1.02, 5.02)	0.272
Ni	Unadjusted	1.00	0.85 (0.48–1.51)	1.34 (0.76–2.33)	1.47 (0.85–2.54)	0.187
	Adjusted*	1.00	0.75 (0.40–1.41)	1.12 (0.61–2.08)	1.36 (0.74–2.57)	0.256

TABLE 4 Association of serum pesticides and diabetes[36]

	Total no. of samples above LOD (%)	Samples above LOD		Samples below LOD		Odds ratio (95% CI)
		No. of diabetes	Percentage of diabetes	No. of diabetes	Percentage of diabetes	
Dichlorvos	274 (38%)	25	9.1	116	19.6	0.41 (0.26–0.65)
Acephate	339 (47%)	62	18.3	79	15	0.66 (0.42–1.01)
Monocrotophos	563 (78%)	125	18.4	16	8.7	2.36* (1.37–4.09)
Phorate	312 (41%)	58	18.5	83	15	1.29 (0.90–1.87)
Dimethoate	469 (65%)	88	15.6	53	17.7	0.860 (0.59–1.25)
Methyl parathion	491 (68%)	112	19.1	29	10.4	1.25*** (1.18–1.52)
Malathion	548 (76%)	135	20.4	6	2.9	1.47** (1.18–2.55)
Chlorpyrifos	527 (73%)	124	19.7	17	7.2	1.18*** (1.07–1.42)
Quinalphos	259 (36%)	45	12.8	96	18.7	0.64 (0.43–0.93)
Profenofos	296 (41%)	45	15.2	96	16.8	0.88 (0.60–1.30)

LOD, limits of detection
Adjusted: For confounding factors (Age, sex, hypertension, cholesterol)
*p<0.05, **p<0.01, ***p<0.001

Conclusion

The work that depicted in this chapter highlights the burden of diabetes, prediabetes, and atherosclerosis in 865 subjects more than 20 years of age in a rural farming population. It also explores the role of non-traditional risk factors like heavy metals in fertilizers and pesticides on the health of the studied population.

In summary, we showed significant associations between heavy metals in urine and pesticides with prevalent diabetes in Nallampatti village. All subjects had heavy metal analysis done in their urine samples, which was then categorized into four increasing quartiles, quartile 1 the least and quartile 4 the most. Increasing urinary levels of arsenic and zinc was associated with diabetes in this study, even after adjustment for multiple confounding factors. The results of this study raise vital research questions on link between metals, especially arsenic used in fertilizers and diabetes & vascular disease.

All of our subjects had serum pesticides measured by GC-MS and the levels were categorized into above and below LOD. Monocrotophos, Methyl parathion, and Chlorpyrifos particularly showed a significant association with diabetes after adjustment for multiple confounding factors. We conclude by hypothesizing that pesticides seem to be an attractive non-traditional "diabetogenic link" for the society at large due to ubiquitous and unscrupulous use of pesticides in the everyday fruits and vegetables we consume, apart from being a risk factor for farmers spraying pesticides without personal protective equipment (PPE).

Doctors and scientists have predominantly focused on traditional risk factors in the etiology of diabetes and vascular disease. Our work is an attempt to focus on the role of non-traditional risk factors, especially agrochemicals in the development of diabetes and atherosclerosis. We envisage progress in the future in the following areas: more focus on occupational safety, especially use of PPEs by farmers, promotion of safer regulatory policies governing the use of pesticides and fertilizers by Governmental agencies, for example, ICAR (Indian Council of Agricultural research) and Agriculture Ministry, Point of care testing devices to assess the levels of pesticides and heavy metals in the blood or urine, (Animal) Work to understand the molecular mechanisms and the efficacy of medications used to treat diabetes and vascular disease in the presence of agrochemicals. Therapeutics targeted at detoxifying diabetic agrochemicals, development of more "metabolic friendly" pesticides, and fertilizers.

We genuinely hope that this chapter has made a meaningful contribution to the health of our rural population. With more efforts, we believe that this work will be translational to make lives of millions of our rural population better.

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CHAPTER

53 Type 2 Diabetes: Lifestyle Management Protocol

Ashok Taneja

Abstract

It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 9.9% of the world's adult population (9.9%). Forty-six percent of people with diabetes remain undiagnosed till complications ensue. The problem is more grave in our country since our diet contains more carbohydrates than protein, chemical fertilizers, pesticides use is rampant. India will be Diabetes Capital by 2030 is a true and stark reality. As they say "Early Bird catches the worm", we should target the people with pre-clinical diabetes and people with clinical diabetes with alteration in food habits, enhanced nutrition (quality wise), encouraging people to do aerobic exercises, stopping of tobacco, alcohol moderation, good-healthy sexual life. We should guide people to adopt yoga, meditation, relaxation techniques to make their life happier and healthier. Remember, happiness comes through good quality of life. Happiness Index is directly proportional to good quality of life. Adopt these Top Ten measures for a wholesome improvement in quality of life.

Introduction

Type 2 diabetes mellitus (T2DM) is a global non-communicable lifestyle disease (NCD) prevalent all over the world. The unfortunate part of this disease is its ever increasing incidence in all socioeconomic groups of population. As per estimate of WHO, incidence of non-insulin-dependent diabetes mellitus (NIDDM) is 10% of population, the world over. Whereas in India, the incidence is 11–14%. It is manifested by a chronic hyperglycemic state in conjunction with other metabolic derangements. If left untreated or treated poorly, it leads to complications like end stage renal failure, heart failure, coronary artery disease (CAD), peripheral artery disease (PAD), strokes, retinopathy, erectile dysfunction, and many others. This leads to increased morbidity and mortality in general population.

T2DM is primarily due to either insulin deficiency or insulin resistance or both. Both the states result in increased hepatic glucose output, reduced utilization of glucose by various organs, increased renal reabsorption of glucose, reduced incretin hormones and increased production of glucagon among others.

Currently there is no known cure for the disease but can be controlled enabling the individual to have an improved quality of life. The main aim of management is directed at reducing acute and chronic complications, that is, microvascular and macrovascular.

Epidemiology: Prevalence in India and World

India: There are estimated 72.96 million cases of diabetes in adult population of India. The prevalence in urban areas ranges between 10.9% and 14.2% and prevalence in rural India was 3.0–7.8% among population aged 20 years and above with a much higher prevalence among individuals aged over 50 years (INDIAB Study). Kerala has the largest number of diabetes patients followed by Tamil Nadu and Punjab.

World: It is estimated that 415 million people are living with diabetes in the world, which is estimated to be 1 in 11 of the world's adult population (9.9%). Forty-six percent of people with diabetes remain undiagnosed till complications ensue. The figure is expected to rise to 20% worldwide by 2040. China, followed by India has the highest incidence of T2DM. Lithuania, Sweden, Estonia, Ireland, and 35 more nations have the lowest incidence.

Though, there is no sex preponderance in incidence of DM in males or females. Both are equally affected. Genetic effects, epigenetic mechanisms, nutritional factors, pregnancy and sedentary lifestyle affect the risk and complications differently in both sexes. However, obesity, psychological stress, higher incidence of myocardial infarctions are more prevalent in females.

Of concern, is the population above 18 years of age who are unaware of their diabetic status (52% of diabetics). The percentage of undiagnosed diabetes is highest among the Malays (53%) followed by the Chinese (49%) and the Indians (42%). In terms of diabetes control, only 23.8% of patients in primary care and 12.7% in tertiary institutions were able to achieve their specified glycemic targets.

Risk Factors

- *Biological risk factors:* Body mass index (BM)I; body fat distribution; Brown adipose tissue (BAT); metabolic syndrome (MetS); adipokines; imbalance of sex hormones; gestational diabetes mellitus (GDM), insulin resistance (metabolic syndrome).
- *Health related:* Smoking; alcoholism; lifestyle disorders including sedentary life; excessive intake sugar sweetened beverages.
- *Psychological:* Stress; economic status; sleep deprivation; drugs abuse.
- Pharmacological drug induced like steroids, etc.
- Genetics.

Management

T2DM is basically a combination of lifestyle disorder with genetic predisposition superimposed by pollution and other environmental factors. Obesity or metabolic syndrome further compounds the problem. Non-pharmacological measures are the most important faculties in managing diabetes. Next step is to add OHAs-Insulins. Surgery esp. in diabesity or stem cell or pancreatic transplantation is the other option, but reserved for highly morbid conditions. I hereby, postulate ten Commandants for the management of T2DM **(Box 1)**.

BOX 1 Ten commandments for lifestyle management in DM

• Nutrition therapy	• Alcohol
• Micro nutrition therapy	• Sex
• Exercise	• Stress management including sleep
• Sweetners	• Environmental pollution
• Tobacco	• Pharmacotherapy

TABLE 1 Recommended dietary composition for diabesity

Component	*Energy intake (%)*
Carbohydrates (Sucrose should be <10%)	40–50%
Proteins	20–30% (not to exceed 1 gm/kg body weight)
Fats	20–30%
n-6 PUFA	<10%
n-3 PUFA	<2%) Oily fish is the main source. Once a week
MUFA	10–20%
Saturated	7–10%

Nutrition Therapy (i.e., Diet)

Medical nutrition therapy (MNT) has a great role in preventing or delaying the onset of T2DM specifically with obesity. The basic idea is to control the calories intake as appropriate for the body weight of the individual. Calorie intake depends on work style, BMI, place of work, gender and ethnicity (decides muscle mass of the body). However, the calorie composition should be: Carbohydrates: Normal=60% (Diabesity=40–50%); Proteins: Normal=25–30% (Diabesity=30%, not to exceed 1 gm/kg body weight); Fats: Normal=25–30% (Diabesity≤30% of which MUFA=10–20%; PUFA=7–10% Saturated 7–10%) **(Table 1)**.

In weight reducing diets, a calorie reduction of 500–1,000 cal are planned with simultaneous increase in expenditure of 500–1,000 cal in the form of exercise. ADA, DCCT, RSSDI, Diabetes India recommend the healthy

BOX 2 Nutrition—broad guidelines

- Reduce saturated fats to abot 10% of total fat intake
- Increase MUFA by 40% of balance fat intake
- Increase PUFA by 40% of balance fat intake
- Eliminate transfats totally
- Increase viscous fibers in diet to min. 50 g/day
- Increase vegetable to 6 servings per day
- Reduce refined carbohydrates. Use complex carbohydrates
- Take at least one fruit per day. Daily the color of fruit must change. Preferably use low glycemic fruits
- Add plant/marine sterols or nuts to the diet
- Consume high quality proteins like soy, cold water fish, organic lean meat and poultry
- Exercie 60 minutes daily with aerobics and resistance training
- Achieve ideal body weight, BMI, waist circumference and body fat composition

choice of foods and good physical activity to decrease the risk of diabetes and prevention of CV morbidity and mortality. DASH, mediterranean, ketogenic diets are other concepts for control of diabesity **(Box 2)**.

Micronutrition Therapy

Although use of micronutrients as nutrition therapy is a cornerstone of the management of diabetes, but uncertainty prevails in its guidelines. Whether the micronutrients are causative agents of diabetes or its complications or just innocent bystanders.

Zinc, chromium, iron, vitamin D, alpha lipoic acid, carotenoids, vitamins E and C, selenium, and some of the B vitamins, notably folate, pyridoxine, and cyanocobalamin play an important role in managing diabetes.

Best source of micronutrients are: fruits, nuts, fresh vegetables, sprouts, seeds, sun-shine, fatty fish, egg, and supplements. Cooking oils, flours, rice, cereals, and juices are now being available in the market with fortified vitamin A, D, Calcium, etc. **(Box 3)**.

Exercise

Regular moderate exercise not only utilizes blood sugar but improves blood circulation removing oxidants from the body. It further reduces the development and progression of atherosclerosis; hence reduction in CVD related mortality. Exercise induces longevity by 1.1/2 years in moderate and 3.1/2 years in vigorous exercise

BOX 3 Ideal meal plan

- Reduce carbohydrates in your diet by 20%
- Change eating pattern
- Take fruits with highly glycemic index before the meal as meal prevents surge of glycemia. Daily change the color of fruit. Different antioxidants and high fibers which slow the absorption of carbs
- Nuts and dried fruits should be taken daily. This supplements Vit E & Omega FAs
- Pulses provide micro nutrients. Must include them in diet.
- Increase protein in diet: 2 Eggs or 1 cup chicken, fish, soyabeen, cheese, milk, tofu
- Substitute rice with brown rice or water drained rice
- Snacks in between meals: Should be made of less carbs, high proteins with some fat
- Curd must be taken daily as it keeps stomach healthy with probiotics
- Garlic-Ginger-Mint, Aloe Vera provide good antioxidants
- No Sugar/Jaggery/Palm Sugar—100% cut
- Refined flour—Replace with multigrain
- Increase millet, quinoa, bajra, besan in diet
- Increase high fiber veggies like beans, cabbage, spinach, etc.
- Sprouted beans, salads provide good working snacks
- **Before deciding the Diet/Meal Plan, calculate your Calorie needs**
- 20 Cals/kg Wt (Sedentary), 30 Cals (Moderate), 35–40 Cals (Heavy)
- Ideal Wt; Height in CMs-100 Maintain Proper BMI

individuals. The beneficial effects include reduction in HbA1c; blood sugar levels, triglycerides (TGs) (9.5%); LDL (13.7%), and increase HDL (9.6%). American College of Sports Medicine and AHA Current recommendation for exercise is:

- 30 minutes of moderate exercise (5–6 Scale*), that is, mild increase in HR and breathing—5 days a week.
- 20 minutes of vigorous exercise (7–8 Scale), that is, noticeable change in HR breathing—5 days a week.
- In addition resistance training (weight training × 10 minutes) daily. All major muscle groups should be involved using 8–10 repetitions.

*10-point scale: Sitting is 0 scale and all out effort is 10.
WALK WALK WALK & MORE WALK

WHO recommends 10,000 steps per day for a healthy living. Those who cannot walk should do sitting exercise,

exercise on bicycle ergometer, swimming, pushups, weight training, upper/lower body exercises depending on the deformity. Aerobic exercise especially jogging/cycling/swimming are considered the best.

Sweeteners

Sweeteners are the ingredients that are added to food to bring sweetness, which can be sugar (nutritive) or sugar (non-nutritive) substitutes. Nutritive sweeteners are those sugars which contain carbohydrates and provide calories, whereas, non-nutritive sugars provide only sweetness for taste and no calories. These are:

- Monosaccharides—Sugar, jaggery, khaand, etc.
- Disaccharides—Fruit sugars
- Polysaccharides—Honey, polyols
- Non-nutritive sugars (artificial sweetners)—Aspartame, sorbitole, stevia, tagatose, sucralose, etc.

Which Sugar to Use in DM

- Naturals: Polyols or Polysacchrides, Disacchrides with low glycemic index
- Artificial: Plant product—Stevia or Sucralose (Min. side effects)

Fresh or dried fruits can be used as adjuvants without much rise in blood sugar levels. Additional benefit is that these fruits add vitamins, minerals, and antioxidants to diet. One type (color) of fruit must be taken at least once a day. Fruits with moderate or high-glycemic index should be taken before meals as it does not increase the blood sugar levels much.

Tobacco: Chewing or Smoking

Tobacco smoking and chewing are the leading causes of preventive mortality. The acute effects of tobacco smoking are sharp rise in blood pressure acutely and enhanced risk of renovascular, malignant, and masked hypertension. The effect is due to stimulation of sympathetic nervous system. Whereas chronic use promotes atherosclerosis with fall in HDL, rise in LDL-C, rise in PFFAs levels, thickening of arterial walls, especially the peripheral arteries, increased levels of carboxyhemoglobins with resultant coronary insufficiency, high platelets adhesiveness, high plasma fibrinogen levels, increased risk of subarachnoid hemorrahges. A study from Canada indicated that women who smoke are more at risk of preeclamsia and eclamsia. Smoking in diabetes increases the risk of CV mortality and peripheral neuropathy.

Alcohol

Alcohol use has been a very debatable issue for a very long time. Safe limit, however, is no alcohol.

Mild level of alcohol intake lowers the risk of thrombosis due to decreased inflammation markers and increased HDL levels. Moderate to heavy drinking impairs insulin release and hyperglycemia with increase in CVD related mortality and liver failure and pancreatitis. Chronic and more than permissible alcohol intake is associated with increased LDL, TGs, increased inflammatory markers, insulin resistance, increased incidence of cardiomyopathy, vent, arrhythmias, and endothelial dysfunction.

One standard drink is 10 gm of pure ethyl alcohol. This amounts to 375 mL of beer (5% alcohol); 150 mL of wine (12% alcohol), and 45 mL of whiskey (40% alcohol). This is considered safe limit in a day for men. For women it is 75% of above values. Red wine offers better protection due to presence of plant sterol—resveratrol. But wines and beers contain high levels of carbohydrates, hence calorie count is must while taking alcohol.

Caution: No alcohol is the best option.

Sex

Studies show that men with diabetes often have reduced testosterone levels, which can affect their sex drive. Moreover diabetes damages the blood vessels, which affect blood flow to the penis leading to erectile dysfunction. Intimacy is ageless. It makes you young, energetic and you live longer with good quality of life. Tips for better sex in diabetics are:

- Approach sex like exercise with full emotional support.
- Use a lubricant. If a woman with vaginal dryness, a vaginal lubricant can make sex feel better.
- Creativity is sexy watch erotica together. Explore different ways to climax.
- Limit alcohol. A little alcohol may boost your desire, but drinking can also make your blood sugar level drop quickly.
- Get help for emotional issues. Depression, anxiety, poor self-image, and other emotional concerns can hurt your sex life.
- Relax: Be confident, be relaxed, do not try to force yourself. Be active.
- Use sildenafil or tadalafil, if ED is the problem.

Psychological Stress

Yoga, Meditation, Positive Thoughts Therapy, Laughter Therapy, Music, and Dancing. Stress result in imbalance of hormones and catecholamines, which has deleterious effects on blood sugar levels and blood pressure. Stress act primarily on hypothalamus pituitary axis to produce more steroidal hormones, decrease insulin sensitivity and alter calcium-vitamin D metabolism, increased sympathetic stimulation and decreased parasympathetic system. A variety of measures have been suggested to overcome stress and improve lifestyle. Yoga, meditation, music therapy, dancing, and laughter therapy are very helpful in alleviating stress. Professional counselors also play a very important role in managing stress. Enjoying holidays, family vacations, going to movies or theatres, doing arts, paintings, etc. also help in stress management. UKPDS over 12 years, observed the beneficial effects of stress management.

Lifestyle Heart Trial: Pranayam, Surya namaskar, Vrijasan asans; Meditation, Group support sessions, Music therapy all lead to correction of Glycosylated HbA1c levels, dyslipidemias with reversal of atherosclerotic plaques.

Meditation, sound sleep for 6–7 hours, listening to music, dancing all lead to reduction of stress hormones, relaxation of mind and body. This results in improving good quality of life.

Environmental Pollution

- *Air Pollution:* PM 2.5—SO_2, CO_2 are the main culprits from Prali burning, vehicles, thermal plants, increased construction activity.
- *Water Pollution:* Contamination of underground water table with heavy metals like arsenic-mercury, etc.
- *Earth Pollution:* Overuse of pesticides, chemical fertilizers, etc.
- *Noise Pollution:* Affects catecholamine secretion, stress hormones like corticosteroids, dopamine.

Pollutions affect the general health leading to anemia, hypocalcemia, Vit. D deficiency, and other micronutrients deficiency which alters sympathetic-parasympathetic axis dysfunction, and hence, poor control of T2DM. The pollutants increase stress levels also especially noise pollution. This leads to poor insulin secretion and efficacy.

BOX 4 Pharmacoltherapeutics: Oral hypoglycemic agents and insulin

- Biguanides
- Sulphonylureas
- Thiazolidines
- Meglitinides
- SGLT2 inhibitors
- Drugs working on Gut peptides
  - DPP IV inhibitors
  - Incretins
- Alpha Gluciside inhibitors
- Dopamine receptor agonist
- Others
  - Hydroxy chloroquin
  - Amylin agonist: Pramlintide
  - Probiotics like Akkermansia
- Insulins

Pharmacotherapy

It includes oral hypoglycemic drugs, incretins, insulins, surgery like bariatric surgery, duodenal mucosal resurfacing (DMR); islet cells and pancreatic transplants and genetic engineering to alter genes **(Box 4)**.

Conclusion

Goals of therapy for T2DM patients include evaluation of diabetic status, BMI, work style (i.e., sedentary or hard worker), socioeconomic status, presence of comorbidities and patient's willingness or compliance with the drugs management. Always start with lifestyle modification (LSM) followed by oral drugs with or without insulin, depending on the patient's condition and parameters. Diet prescribed to the patient must confirm to his/her tastes, availability, and affordability. Diet should be a balanced diet, rich in proteins, must include seasonal fruits. Drugs used, should also be easily available, affordable, and the regime should be tailor-made to the patient. If socioeconomic status is not good, there is no fun of writing fancy, expensive medicines, which, patient will not take in long run. Patient counseling is must so that he/she understands the modality of treatment and the need of initiating insulin therapy or undergoing surgery. The ideal target of control of diabetes is HbA1c of 6.5–7.0% in Indian population. Though, it may be difficult to achieve in elderly, but tight control always gives benefit in terms of reducing complications, and hence enhanced morbidity and mortality.

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CHAPTER

54 Top Three Knowledge Gaps in Diabetes

Amit Saraf

Abstract

It's a well-accepted fact that treatment of diabetic patients has some lacunas, which may range from non-compliant patient to a busy clinician. This chapter tries to encompass these gaps in the treatment of diabetes.

Traditionally the top three knowledge gaps in clinicians include:

- Type(s) of diabetes
- Insulinization: Too early/too late
- Complications of diabetes

Similarly the top three knowledge gaps in patients include:

- Diabetes: Remission OR Cure?
- Diet
- Social media prescriptions

Introduction

Top three knowledge gaps in diabetes can be divided into:[1,2]

- Top three knowledge gaps in Clinicians
- Top three knowledge gaps in Patients

Top three Knowledge Gaps in Clinicians

Knowledge gaps in clinicians can be divided into:

- Type(s) of diabetes
- Insulinization: Too early/Too late
- Complications of diabetes

Clinician Knowledge Gap I

- *Identifying* types of diabetes:[1,2] Many a times, especially in the "gray-zone area patients," for example, patients with newly diagnosed hyperglycemia and in the age group of 20–25 years, type of diabetes is not routinely attempted to be sought. This is very important as it dictates not only treatment but also prognostication. Some ready reckoners for the type of diabetes can be—
  - Young (15–25 year old) diabetic
  - Type I (GAD +, C Peptide +)
  - MODY (Young on OADs, Genetic link)
  - LADA (Type II, GAD -, C Peptide -)
  - Elderly Type I (GAD +, C Peptide -)

Type(s) of diabetes[3,4]—

- Type 1 diabetes
- Type 2 diabetes
- Genetic defects of β-cell function—
  - Chromosome 12, HNF-1α (MODY 3)
  - Chromosome 7, glucokinase (MODY 2)
  - Chromosome 20, HNF-4α (MODY 1)
  - Chromosome 13, insulin promoter factor-1 (IPF-1; MODY 4)

- Chromosome 17, HNF-1β (MODY 5)
- Chromosome 2, *NeuroD1* (MODY 6)
- Mitochondrial DNA

In some cases the diabetes is secondary to some other pathophysiological process, which if identified, will lead to better treatment protocols in the patient. For example—

- Syndromes of Extreme Insulin Resistance
- Transient Hyperglycemia
- Diseases of the exocrine pancreas
- Endocrinopathies
  - Acromegaly
  - Cushing's syndrome
  - Glucagonoma
  - Pheochromocytoma
  - Hyperthyroidism
  - Somatostatinoma
  - Aldosteronoma

Certain medical conditions can lead to diabetes themselves, such as—

- Glucagonoma
- Chronic pancreatitis
- Cystic fibrosis

Also, certain conditions linked with Type 1 DM, such as[4,5]—

- Celiac disease
- Rheumatoid arthritis
- Addison's disease
- Autoimmune thyroid disease
- Celiac disease
- Rheumatoid arthritis
- Addison's disease
- Autoimmune thyroid disease

Similarly, certain conditions are linked with Type 2 DM, such as—

- Alzheimer's disease
- Polycystic ovary syndrome (PCOS)
- Cushing's syndrome
- Pancreatic cancer

If the "gaps" enumerated above in the etiopathogenesis/pathophysiological conditions are ascertained in all patient right at the time of diagnosis, it helps in better treatment outcomes.

Clinician Knowledge Gap II

- Insulinization: Too early/Too late
- Targeting the "Dirty Dozen"

Insulinization: Too early/Too late[5,6]—

The following pie-charts demonstrate the overall blood sugar control in diabetics worldwide. As observed, the sugar control is not very optimal. **Figure 1** demonstrates worldwide prevalence of glycaemic control.

Worldwide studies have repeatedly proven that insulin is by far the most effective drug for sugar control, as seen by the following bar chart.[6,7] **Figure 2** illustrates that early Insulanisation is the need of the hour for an effective glycaemic control.

In spite all of the above, there is a lot of inertia for initiation of insulin therapy and this inertia is from clinicians and patients alike, this "gap" in the management of diabetics need to change.

Target the Dirty Dozen[7,8]—

ADA consensus statement of 2016 says, target the treatment of organ damage early on, irrespective of initial glucose levels. Most of the clinicians in routine busy out-patients practice tend to only observe and dictate therapy depending on the blood sugar reports. This 'gap' in the mind-set needs to change to allow routine assessment of 'ominous octave', to create a wholesome treatment for the patient.

Clinician Knowledge Gap III

Complications of diabetes—Complications of diabetes can be categorized in this scenario into complications due to "infections" and complications due to "vasculopathy."

Infections—

It is very imperative to look for infections leading to & associated with diabetic ketoacidosis—

For example—

- Mucormycosis
- External otitis media
- Emphysematous pyelonephritis
- Well controlled diabetic on a OPD follow-up, acutely becomes uncontrolled—look for underlying infections (do not only control BS).

Many times, especially targeting only sugar management may cause a "gap" in the treatment of a critically ill diabetic leading to morbidity and or mortality.

Vasculopathy[8,9]—

Clinicians should not forget to correlate between organ-specific vasculopathy:

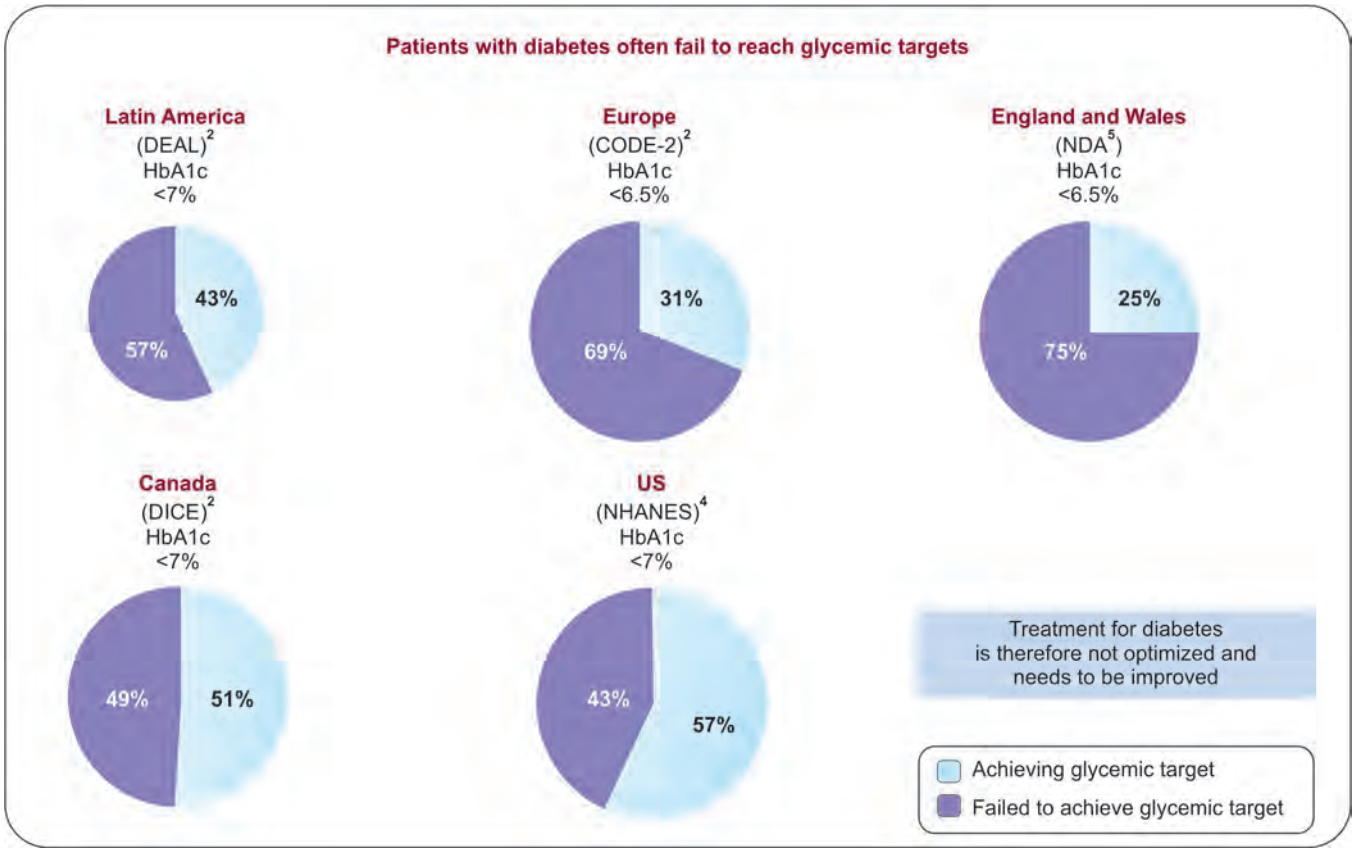

Fig. 1: Worldwide index of glycemic targets achieved

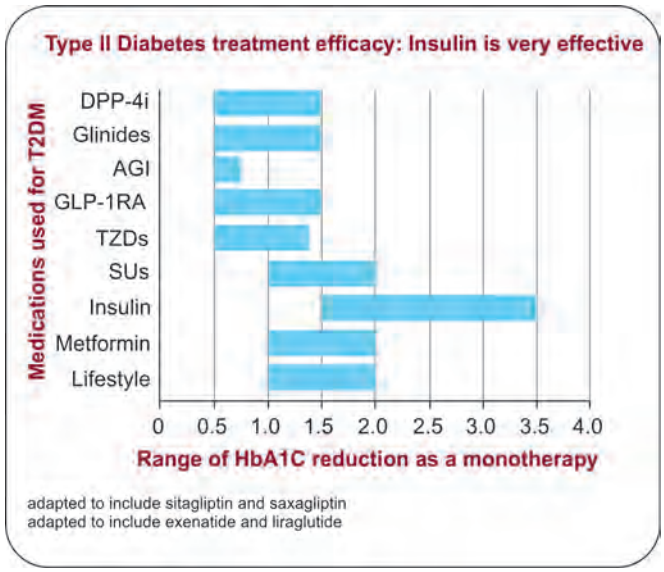

Fig. 2: Insulin effectively compared to OADs

For example—

- Retinopathy if present—look for nephropathy
- Microalbuminuria if present, retinopathy absent—look for causes beyond diabetes
- Erectile dysfunction if present—work up toward ischemic heart disease

Top three Knowledge Gaps in Patients

Knowledge gaps in patients can be classified as—

- Diabetes: Remission or Cure??
- Diet
- Social media prescriptions

Patient Knowledge Gap I

Diabetes: Remission or Cure??—Patients have to be clearly counseled that diabetes is a lifelong disease. Only remission is possible not cure!!, which in simple words means, a diabetic can go off drugs and can be controlled on

only lifestyle changes, but he does not become "Diabetes Free." This "gap" in patient knowledge will ensure better follow-up compliance.

Patient Knowledge Gap II

Diet[10]—Various diets such as intermittent fasting diet, crash diets, supplementary diet, etc. are advocated and are being followed. The "gaps" in knowledge of these diets are—

- Diet have to be under guidance—"no one single diet suits all."
- Sustainability—the patient should be clearly made aware that most of the individuals fail to keep up the dietary restrictions lifelong.

Patient Knowledge Gap III

Social Media Prescriptions—This "gap" in knowledge encompasses Doctor-Patient prescriptions over social media platforms. Though this is a very "convenient" method, it has its own inherent risks such as not involving physical examination of the patient; some medical parameters may get omitted during such communications, etc. The patient has to be made very clear that online consultation does not replace a physical consult and should be sought only in certain scenarios, such as lockdowns, etc.

Conclusion

Top three Knowledge Gaps in Clinicians:

- Type(s) of Diabetes
- Insulinization: Too early/Too late
- Complications of diabetes

Top three Knowledge Gaps in Patients:

- Diabetes: Remission or Cure??
- Diet
- Social media prescriptions

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CHAPTER

55 Candid and Equitable Diabetes Care: Beyond the Bounds of Possibility?

Supriyo Mukherjee

Abstract

The prevalence of diabetes in India is enormous and remained at 11.8% in last 4 years. Approximately 77 million people are living with diabetes while nearly 43.9 million (57%) of the cases of diabetes are undiagnosed. Moreover, challenges such as malnutrition, poverty, and socioeconomic burden precipitated by communicable diseases strain the already burdened health-care system of India. Adding to this, the Indian public health infrastructure can be characterized as chronically underfinanced since 1999. The Indian health sector received only 1–1.5% of the total GDP annually and even less is allocated to public health, health promotion, and awareness campaigns. There is lack of cohesion amongst a plenty of unregulated private centers with varying level of quality, poor coordination and communication, weak referral mechanisms, poor record-keeping, negligible accountability, and transparency which promotes distrust in medical establishment. Therefore, there is large-scale inequity in terms of accessibility and quality of service provision between rich and poor. Potential solutions are private and public sectors, especially public-PCC, need to be strengthened. A strong political will and a robust, evidence-based translational research, a bridge between theory and reality, achieve this beyond the broad structural characteristics of system and make the journey worthwhile for all the stakeholders.

Introduction

Dr. Amartya Sen reflected, "Health equity cannot be concerned only with health seen in isolation. Rather, it must come to grip with the larger issues of fairness and justice in social arrangements, including economic allocations, paying appropriate attention to the role of health in human life and freedom."[1]

Equitable diabetes care means that the individuals have access to affordable, high quality culturally and linguistically appropriate care in timely manner. This includes regular preventive care, in addition to emergency care, as well as mental health support.[2]

Inadequacies in Diabetes Care: Current Scenario in India

Diabetes is a complex, chronic disease recognized as an important cause of premature death and disability, and disproportionately affects socially and economically disadvantaged population, especially poor and young sub-populations of Third World Countries.[3,4]

The prevalence of diabetes in India is enormous and remained at 11.8% in last 4 years. Approximately 77 million people are living with diabetes while nearly 43.9 million (57%) of the cases of diabetes are undiagnosed.[5] To complicate the matters more, majority of the T2DM patients have uncontrolled diabetes with HbA1c around 9%.[6] Moreover, challenges such as malnutrition, poverty and socioeconomic burden precipitated by communicable diseases strain the already burdened health-care system of India. Adding to this, the Indian public health infrastructure can be characterized as chronically underfinanced since 1999. The Indian health sector received only 1–1.5% of the total GDP annually and ranks 184th out of 191 in terms of GDP percent-spend on health care. Even less is allocated to public health, health

promotion, and awareness campaigns; consequently there is large-scale inequity in terms of accessibility and quality of service provision between rich and poor.[7]

Economic model suggests that an additional 1% in GDP spent on precisely defined proven health schemes would save 480 million healthy life years.[8]

Fee for service health seeking prevails in India and public-private fragmentation of health system results in skewed distribution of human and financial resources. Additionally, with disparity in expenses, infrastructure and manpower, drug delivery, and training are ubiquitous in India.[9] Annual health expenditure in India, 80% of which is spent in private facilities, amount to trillion Indian rupees—greatest of which is perceived by the households.[8] Thus, those who cannot afford fee can only access services characterized by poor infrastructure, overworked, and yawning personnel. In other words, poor quality service provision is left for the unprosperous.[9]

Along with these lines the inverse curve law states that "the availability of good medical care tends to vary inversely with the need of it in a population served," which holds true in low- and middle-income countries.[10]

Also, direct specialist consultation is common in India and there is no obligation regarding continuity of care from either physician or patients. There is lack of cohesion amongst a plenty of unregulated private centers with varying level of quality, poor coordination and communication, and weak referral mechanisms.[9] Poor record-keeping, negligible accountability and transparency present opportunities for unethical practice promoting distrust in medical establishment. There exist many functionally illiterate populations with consequent poor health literacy.[11] Whatever the underlying causes, inadequate glycemic and comorbid risk factors manifest in seriously disabling and life-threatening complications.[12,13]

Majority of resource constrained Indians are deprived of annual routine monitoring of health indicators, BP, BMI, eye and feet examination, serum cholesterol, serum creatinine, HbA1c, urinary albumins, smoking review, mental health evaluation, etc. which form the regular elements of diabetes care along with the access to specialist health-care professionals including ophthalmologists, podiatrist, and dietitians.

However, the ambition is to achieve universal health coverage for successful diabetes care by making the health services accessible with the targets to provide essential medicines and diagnosis to at least three-fourths of the cases by 2025.[14]

Need and Awareness

It is essential to have person with diabetes as caregivers and sustain a multitude of daily self-management decisions that include:

- Compliance with medications regarding correct dose, frequency, route, and protection against adverse effects.
- Lifestyle modification: Adequate physical activity and daily exercise with a healthy diet.
- Cessation of smoking and harmful use of alcohol.
- Self-monitoring of blood glucose.
- Foot care.

Diabetes Self-Management Education and Support (DSME/S) for educating the patient on diabetes self-care is an intrinsic and vital segment of continuous care model of primary care facilities, which is very fruitful in improving diabetes-related health outcomes.

The ADA has endorsed measuring and tracking key results of DMSE/S, comprising self-management, clinical outcomes, health status, and quality of life.[15]

Challenges in Provision of Diabetes Self-management Support through Public Sector Primary Care as Candid and Equitable Diabetes Care

- Lack of readiness of Public sector—Primary Care Centre for diabetes self-management
- Lack of awareness and understanding among patients with diabetes
- Suboptimal prescription adherence and therapeutic inertia
- Poor diabetes clinical audits and prospective registries
- Lack of inclusion of mental health services with diabetes care
- Enablement of smoking and tobacco cessation
- Dearth of diabetes educator and dietitian at the point of care level
- Lack of private public partnership
- Lack of political will

Potential Solutions

Strengthening of public sector-PCC is the key. Diabetes care research should also focus on quality of care accorded in primary care facility, especially in resource constrained settings.

Feasibility of adherence, avoidance of clinical inertia, patient counseling, peer education, provision of uninterrupted drug supply through team based DSME/S for patients in primary care need high quality trained nurses, MPWs, and diabetes educators. A robust back up of laboratory investigations also help in maintaining the flow of patient care.[11]

Depression plays an important barrier in achieving optimum patient adherence to treatment. It can be effectively managed by planned community outreach programs, by setting up of yoga or meditation centers for the patients, using a proper peer support system.[11]

A valid and practical adherence assessment system is necessary to reduce clinical inertia to a certain extent. Proper and targeted training of health workers and adequate supply of insulin and insulin syringes to avoid out of pocket expenses is of paramount importance.[11]

This surely would help to balance the economic burden on the society and cost effectiveness of diabetes therapy.

Specific Models of Sustainable Health-care Delivery and Disease Prevention in Resource Constrained Environment

Professor V Mohan et al. demonstrated in MDRF, Chennai, how framework of systemic research may be applied to diabetes in developing countries to address deficiencies in knowledge and inequities in care. The MDRF and its associated clinical facility provide a good example of this. It illustrates the value of structured research in laying a foundation of policy development through assessing burden and translating evidence into practical responsive interventions, as well as harnessing the benefits of interventional collaborations and information technology.[9]

Alternative form of financing must be sought since the cost of health care is so burdensome in most developing countries draining family and societal resources. Charging fee relative to respective income may be feasible in a context of fee for service facilities which has been hugely successful for India's Aravind Eye Hospital (AEH).[16]

Research Centre for Diabetes Hypertension and Obesity (R.C.D.H.O.), established in 2002 in district of Samastipur, is focused on serving the impoverished population of North Bihar and around. The idea to set up a non-profit centre emerged from management of diabetes and related comorbidities with huge lapses in the follow-up due to complex interplay of poverty, lack of awareness and education, daily-wage loss, misinformation, and myths. Those resource-poor patients later landed in the same clinic with life threatening infections, CKD, heart failure stroke, or blindness.

The centre detects, treats, educates, and defines timely and necessary referral pattern, and undertakes clinical and epidemiological research in sustainable and equitable manner charging fee relative to respective income.[17] The role of private sector in diabetes care also needs to be made more accessible to the general population.[18]

Role of Private Sectors in Equitable Diabetes Care

As we aspire to grow to a 5 trillion US dollar economy by 2025, private sector has a crucial role to play not only in even-handed and objective diabetes care but also in universal health coverage (UHC). It is due to widely divided and dispersed health infrastructure the voice of private sector is muddled and often goes unnoticed. This needs to change and we need to align it to our national goals of a high quality, affordable, accessible, equitable health system made in India for India.[18] Unfortunately the cost of private health care is still about four to six times greater than our country's public health care. The public health services are hugely grant-aided and supported by Indian government through interest in free capitals, interest rate subsidy, free land, electricity, and a number of other rebates and grants, all of which make it difficult to compare the real efficiency and comparable cost of service deliveries. Thus, there is large private-public gap in logistics, capacity, and delivery of care.

Conclusion

Both private and public sectors, especially public-PCC, need to be strengthened. A strong political will and a robust, evidence-based translational research, a bridge between theory and reality, achieve this beyond the broad structural characteristics of system and demonstrate if the financial benefits are reproducible, have a fair distribution and are collaborative with hand in glove approach. All of it guarantees a minimum set of core services of equitable diabetes care backed by our unified

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common pool of national resources which make the journey worthwhile for all the stakeholders.

"Not everything that is faced can be changed but nothing can be changed until it is faced." **–James Baldwin**

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CHAPTER

56 Resistant Hyperglycemia—A Practical Approach

Raveendran AV

Abstract

Blood sugar level not responding to a reasonable dose of oral anti-diabetic medication or insulin or other injectable therapies is called resistant hyperglycemia which is common in clinical practice. We will briefly review the causes of resistant hyperglycemia and practical approach to tackle this issue.

Introduction

Hyperglycemia not responding to usual doses of oral anti-diabetic medication or insulin or other injectable therapies is a common clinical challenge. In type 2 diabetes mellitus (T2DM), most of the time its transient due to coexisting acute medical condition. Hyperglycemia not responding to usual doses of medication can be due to some rare conditions associated with severe insulin resistance.

Lots of people with diabetes are not achieving treatment targets and this contributes to increased risk of development of complications. Common factors contributing to worsening of diabetes control is given in **Box 1**.

In people with T2DM, failure to respond to oral hypoglycemic agent (OHA) is a common issue. Most of the time it shows the progression of the disease, with loss of beta cell function.

BOX 1 Factors that can contribute to worsening of glycemic control

- Decreased compliance with:
  - Diet
  - Exercise
  - Medical regimen
- Weight gain
- An intercurrent illness
- The use of medicines causing:
  - Increase insulin resistance
  - Interfere with insulin release
  - Increase hepatic glucose production
- Progression of the underlying disease process:
  - Decreased insulin secretion
  - Increased insulin resistance
- Undiagnosed type 1 diabetes with gradual destruction of the pancreatic beta cells:
  - "Latent Autoimmune Diabetes in Adults" (LADA)
- Therapeutic inertia

Oral Hypoglycemic Agent Failure

Failure to respond to OHA can be of two types: primary or secondary.[1]

- *Primary failure to OHA:* When a newly diagnosed patient initially classified as T2DM has little or no glycemic response to OHA, it is called Primary OHA failure.
- *Secondary failure to OHA:* In people with diabetes, who have a fair glycemic control on oral medications initially, may subsequently fail to achieve glycemic targets. This is called secondary OHA failure. When sulphonylurea (SU) and metformin (MET), in appropriate doses and diet, lose its capacity to produce

BOX 2 Factors associated with secondary oral hypoglycemic agent (OHA) failure

- Genetics
- Chronic hyperglycemia: Glucotoxicity, Lipotoxicity
- Amyloid deposition in the β-cells
- GAD positive
- ICA positive
- Low body mass index (BMI)
- Duration of diabetes
- Type of OHA used

a desired maximal therapeutic effect (FBG < 8.0 mmol/L or HBA1c < 7.0%) after administration in the absence of other conditions causing hyperglycemia, it is called secondary OHA failure.[2] Factors contributing to secondary OHA failure are given in **Box 2**.

Insulin Requirements and Insulin Resistance

The average total daily insulin dose (TDID) requirement for patients with T1DM is around 0.3–0.8 U/kg/day, except in teenagers where it is 1.0–1.5 U/kg/day. Anyone with a TDID of <1.0 U/kg/day is considered as having normal insulin sensitivity. The average TDID for patients with T2DM is around 1.0–1.5 U/kg/day, but, it can be as high as 2.0 U/kg/day. Anyone with a TDID of 1.0–2.0 U/kg/day is considered to have insulin resistance in the range of typical T2DM.[3]

Insulin resistance is characterized by an impaired response to insulin—either endogenous or exogenous.[4] Insulin resistance is defined as "a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal glycemic response."[5] According to TDID requirement, insulin resistance is divided into severe and extreme insulin resistance **(Table 1)**.[6]

Insulin Resistance: Measurement

Various methods to measure insulin resistance are briefly mentioned below:[6-8]

- *Insulin level at fasting:* Fasting serum insulin levels is usually less than 20 μμU/mL in normal individual whereas it is over 70 μμU/mL in those with severe insulin resistance.
- *Assessing the peak level of insulin achieved after oral glucose tolerance test (OGTT):* In normal individual peak post-OGTT insulin level is usually less than 150 μμU/mL, but it is greater than 350 μμU/mL in people with severe insulin resistance.
- *Measuring the index of insulin sensitivity (Si):* Si is the fractional clearance rate of glucose per unit change in the plasma insulin concentration. In normal individual Si is above 5 μμU/mL/min × 10^{-6} whereas in people with severe insulin resistance Si is below 2 μμU/mL/min × 10^{-6}.
- Gold standard technique is to measure insulin mediated glucose disposal, i.e., *MMM* rate by the euglycemic hyperinsulinemic clamp. In normal individual it is above 6 mg/kg/min, whereas in people with severe insulin resistance, it is less than 2 mg/kg/min.

Frequently sampled intravenous glucose tolerance test (FSIVGTT) and Homeostatic model assessment (HOMA) are also used for assessing insulin resistance.

Insulin resistance can be due to inability of the insulin to act effectively or increased destruction of insulin **(Box 3)**.

BOX 3 Mechanisms of insulin resistance

- Defects in insulin receptors:
  - Genetic defect
  - Insulin receptor antibodies
- Interference with intracellular insulin action:
  - Excess of counter-regulatory hormones
  - Inflammatory cytokines
- Increased insulin clearance

TABLE 1 Insulin resistance: Classification

Insulin resistance classification	*Total daily insulin dose (TDID) requirement (unit/kg/day)*
Insulin resistance	>1
Severe insulin resistance	≥2
Extreme insulin resistance	>3

Pseudoresistance

Insulin resistance has to be differentiated from pseudoresistance **(Box 4)**. It can be ruled out by conducting a

BOX 4 Pseudoresistance: Causes

- Nonadherence
- Poor injection technique
- Problems at the site of injection—Lipohypertrophy
- Improper insulin storage
- Malingering for secondary gain

BOX 5 Unexplained hyperglycemia: Causes

- Occult infection
- Recurrent ischemia
- Acute medical conditions
- Cushing's syndrome
- Acromegaly
- Hyperthyroidism
- Lipodystrophy
- Autoimmune diseases
- Hematological malignancy

TABLE 2 Extreme subcutaneous insulin resistance (SIR): Paulsen definition

Three criteria:
• Resistance to the hypoglycemic action of subcutaneous insulin, but not to intravenous insulin
• No increase in plasma-free insulin levels after subcutaneous insulin
• Increased insulin-degrading activity in the subcutaneous tissue

modified insulin tolerance test. During such a test, patients are administered a witnessed dose of short-acting insulin in the clinic, and their blood glucose level is monitored every 30 minutes for a period of 4–8 hours.[6]

After ruling out pseudoresistance, in people with T2DM look for cause of unexplained hyperglycemia, and correct it in order to control blood sugar level **(Box 5)**. Presence of antibodies to insulin and subcutaneous insulin resistance causes poor response to insulin **(Tables 2 and 3)**.[9,10]

Extreme Subcutaneous Insulin Resistance (SIR)

It is characterized by severe resistance to subcutaneous insulin with normal or near normal response to intravenous insulin.[11] Insulin degradation in subcutaneous adipose tissue and muscle result in extreme subcutaneous insulin resistance **(Table 2)**.

BOX 6 Causes of severe insulin resistance

Type A, due to defects in the insulin receptor gene
Type B, due to insulin receptor antibodies
Type C, cause unknown

- *Medications:*
  - Glucocorticoids
  - Atypical antipsychotics
  - Calcineurin inhibitors
  - Protease inhibitors
  - Oral contraceptives
- *Endocrine disorders:*
  - Acromegaly
  - Glucagonoma
  - Thyrotoxicosis
  - Cushing's syndrome
  - Pheochromocytoma
- Anti-insulin antibodies
- HIV-associated lipodystrophy
- Physiological causes:
  - Severe stress:
    - Trauma
    - Sepsis
    - Surgery
  - Diabetic ketoacidosis
    - Pregnancy
    - Puberty

TABLE 3 Antibodies to insulin

Insulin autoimmune syndrome	***Exogenous insulin antibody syndrome***
• Also called Hirata disease • Characterized by spontaneous hypoglycemia • Associated with the presence of insulin autoantibodies • In patients without previous insulin exposure	• Induced by exogenous insulin in diabetic patients • Associated with clinical events, such as hypersensitivity reactions, pregnancy, glycemia variability • Mainly with insulin resistance/hyperglycemia or hypoglycemia

Gustatory Insulin Resistance

Some people with diabetes who are not on diet control develop a special situation. They get into a vicious cycle of

unrestrained eating (hence the term gustatory), resulting in poor glycemic control, which leads to up titration of insulin dose, which in turn leads to further eating, and so on.[6] Because of unrestrained eating results in all these consequences it is called gustatory insulin resistance. This results in progressive weight gain, poor glycemic control, and, ever increasing, large doses of, seemingly ineffective insulin.

Lot of conditions can cause severe insulin resistance, including rare syndromes **(Box 6)**. Proper evaluation helps to find out the causes of resistant hyperglycemia.

Conclusion

Resistant hyperglycemia is a common clinical problem. Most of the time, it is due to severe insulin resistance. Modified insulin tolerance test helps to rule out pseudoresistance. In people with T2DM, any acute medical condition can precipitate resistant hyperglycemia. Severe hyperglycemia not responding to conventional therapy may be due to rare genetic condition associated with severe insulin resistance.

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CHAPTER

57 Blood Pressure Targets in Diabetes

Anil Kumar Virmani

Abstract

Hypertension is the major cause of cardiovascular mortality, and it forms a sinister alliance with diabetes, leading to catastrophic results. Besides achieving optimal glycemic goals, it is imperative to treat blood pressure to mitigate any complications. Various guidelines have been published in the recent past. There is a consensus that the threshold of initiating antihypertensive therapy is a blood pressure of 140/90 mm Hg. The goal of treatment is a blood pressure <130/80–85 mm Hg. Because of various reasons, Asians are more susceptible to cardiovascular risk as compared to Caucasians. While treating blood pressure to goals, individual characteristics and the total cardiovascular risk burden should be taken into account. However, the blood pressure should not be brought down to <120/70 mm Hg.

Introduction

There are three paradoxes in hypertension:

- it is easy to detect, but diagnosis rates are dismal; what we see is only the tip of the iceberg;
- it is easy to treat, but the treatment rates are disappointing;
- several potent drugs are available, but unfortunately very few patients are controlled to the recommended goals of 130/80 mm Hg, in fact not even 15%.[1]

Hypertension is the major cause of cardiovascular mortality (about 10 million deaths per year), and resulting in a higher prevalence of strokes, heart failure, and chronic kidney disease. Similarly, hypertension is 1.5–2 times more prevalent in diabetics versus non-diabetics.[2]

The prevalence of diabetes in India is increasing at a very rapid rate, thus increasing the hypertensive burden.[3]

T2DM and Hypertension—The Vicious Twins

The prevalence of diabetes globally is about 9.3%, that is, about 463 million adults (aged 20–79 years). In India, there are about 77 million people with diabetes.[4]

As per data from World Health Organization (13 September, 2019), more than two-thirds of the global population of about 1.13 billion people with hypertension live in the developing countries which generally have low- and middle-income. In India, hypertension is seen in about 29.8% of the population (33.8% in urban and 27.6% in rural).[5]

Between 40–80% of patients with diabetes have hypertension, and patients with diabetes are twice as likely to develop hypertension.

What is Normal Blood Pressure?

In patients without any risk factors, the cut-off level of "normal" blood pressure at which cardiovascular disease develops is not known. In the Multi-Ethnic study of atherosclerosis, 1,457 patients without any risk factors like diabetes (FBS >126 mg%), dyslipidemia (LDL >160 mg% or HDL <40 mg%), and not on any treatment or current tobacco abuse, and a Systolic blood pressure (SBP) between 90 and 129 mm Hg, underwent coronary calcium scoring to detect subclinical cardiac disease, during the period of 2 years from March 2018 to February 2020.

The study concluded that the risk of cardiac disease as per the coronary artery score appears as a stepwise increment right from a SBP of 90 mm Hg and gradually increases with rising systolic BP. These results further confirm that it is important to prevent rise in SBP even within the so-called normal levels of blood pressure, as there also occurs a similar graded increase in cardiac risk with rising SBP levels.[6]

Hypertension in Diabetes

The cardiovascular risk doubles with every 20/10 mm Hg increase in blood pressure.[7] SBP is a stronger predictor of cardiovascular disease and diabetic kidney disease than diastolic blood pressure. In fact, Systolic hypertension is more common (about 65%) in patients with diabetes, and more difficult to control.[8]

Blood Pressure Guidelines: Various guidelines have been published in the last couple of years, by the European Society of Hypertension (ESH 2018), American Heart Association/American College of Cardiology (AHA/ACC 2017), and the International Society of Hypertension (ISH 2020). ISH 2020 and ESH 2018 guidelines categorize the grade 1 hypertension when SBP 140–159 mm Hg and/or DBP 90–99 mm Hg while AHA/ACC 2017 categorize the stage 1 hypertension when SBP 130–139 mm Hg and/or DBP 80–89 mm Hg. *However, the Goal of blood pressure for patients with diabetes is same in all guidelines, that is, less than 130/80–85 mm Hg.*

All guidelines emphasize that in all patients with hypertension and associated diabetes, drug treatment should be initiated at a BP of 140/90 or higher, aiming at a goal of less than 130/80–85 mm Hg.

Cardiovascular Risk in Hypertension

The 2018 ESC & ESH Joint Guidelines for the management of arterial hypertension, published on 9th June, 2018, were the first international guidelines, which not only classified patients with diabetes (asymptomatic, without organ damage) as Stage 2 Risk & Symptomatic patients with diabetes and organ damage as Stage 3 (Highest Risk), but also for the first time classified Asians at a higher risk by 40% (multiplication factor of 1.4 for correction for cardiovascular risk.[9] The ISH guidelines also emphasize the racial and ethnic differences attributed to genetic differences along with a major contribution from life-style factors, which confer a higher risk for Asians.[10]

CV Risk in Hypertension—Are Asians Different?

The association between HTN and CVD is stronger in Asians as compared to the Western population, and occurs at an earlier age. Stroke is more common than CAD in Asian people, whereas the reverse is true in Western population (2.8 times higher—HONEST Study).[11] The slope of the association between rising BP levels and CV events is also steeper in Asians vis-à-vis the Western population.[12] Moreover, Asians are more susceptible for developing high BP even with mild obesity.

Asians also have a genetic predisposition to salt sensitivity, compounded by a high dietary salt intake[13] as well as a significant seasonal variation of BP, with a rise in BP during the winter season.

Asians are more likely to have morning surge and nocturnal hypertension leading to greater BP variability.[14]

The Mumbai/India cohort study showed a 16% rise in risk of deaths and cerebrovascular accidents when SBP was in range of 120–129, but jumped to 73% higher risk, when SBP was more than 130 mm Hg. Moreover, risk of ischemic heart disease rose to 16% & 19%, respectively.[15] Hence, a SBP of less than 130 mm Hg would be more beneficial for Asians.

How Aggressive should be the Treatment of Hypertension in DM?

Overall benefits of intensive BP treatment less than 120 mm Hg were only seen in ACCORD BP study participants receiving standard glycemic control (hazard ratio, 0.71; 95%, 0.56–0.90; P=0.005). Episodes of severe hypoglycemia have interfered with the intensive lowering of BP and probably cancelled out potential benefits of lowering SBP <120 mm Hg in patients with both DM and hypertension.[16]

The participants with DM in the ADVANCE trial benefitted from more intensive BP treatment regardless of baseline BP and of 10-year estimated ASCVD risk. This is consistent with recent guidelines recommending a lower BP target than the previous target of 140/90 mm Hg.[17]

In the ACCORD BP and SPRINT trials, BP was measured using Automated Office Blood Pressure, whose values are generally lower than typical office blood pressure by approximately 5–10 mm Hg. This implies that if protocols of the ACCORD BP or SPRINT are applied to routine clinical practice, then a SBP target higher than 120 mm Hg is required.[18]

Moreover, lowering the blood pressure to less than 110/75 had excess of risk for mortality at 3.5 years.[19]

A meta-analysis of 49 trials, including 73,738 patients by Mattais Brunstrom et al., showed that antihypertensive treatment in patients with SBP >150 mm Hg, reduced risk of all-cause mortality by 11%, CV mortality by 25%, stroke by 23% and end stage renal disease by 18%. For patients with baseline SBP of 140–149, additional treatment reduced risk of all-cause mortality by 13%, MI by 16% and heart failure by 20%. However, if baseline SBP is less than 140, additional treatment increased risk of CV mortality by 15%, and likely an increased risk of all cause mortality by 5%.[20] In another meta-analysis by Mueller et al., in patients with diabetes but without cardiovascular disease, patients with a SBP of 110–119 mm Hg had a lower risk of non-fatal MI by 24% and non-fatal stroke/CHD/total CHD by 15%, as compared to patients with SBP of 130–139 mm Hg. However, risk of heart failure was higher by 20% and all-cause death by 28% in the 110–119 group as compared to 130–139 group.[21]

This basically means that the baseline systolic BP <130 mm Hg conferred significantly lower risk for adverse CV events than did systolic BP 130–139 mm Hg—the current systolic BP treatment goal for this population. It also suggests the association between low baseline systolic BP and all-cause death is not due primarily to CV disease, but rather to concomitant disease or patient factors (not measured by this study) that lead to both low BP and excess risk.

Is there a J-Curve?

J-curve implies a higher risk of cardiovascular risk in patients both with a higher BP >140/90, as well as a lower BP <120/70 mm Hg. It is thus evident that in diabetics with a higher cardiovascular risk, there is a significant and lasting risk of subclinical myocardial injury and myocardial infarction, even when extensive adjustments have been made for any underlying disease burden.[22]

Hence, the available evidence from various well conducted scientific studies suggest that in patients with preexisting CVD, specifically CHD, it is prudent not to lower SBP ≤130 mm Hg. However, for those at higher risk of stroke (such as black and Asian patients) who do not have preexisting CHD, it may be beneficial to reduce SBP <120 mm Hg if this can be done without any harm.[23] The J-curve does exist, but only for patients with preexisting coronary artery disease.

Key Points

The ideal SBP goal for all is less than 130 mm Hg, irrespective of the presence or absence of diabetes. Those having a SBP of 130–139 mm Hg should first be treated non-pharmacologically with intensive life-style modification, and for those with high cardiovascular risk drug therapy should be initiated if resources allow.[24]

However, in the majority, if the goal BP of less than 130/80 is not achieved after 6 months with intensive life style modification, drug therapy should be initiated, irrespective of their cardiovascular risk.

Younger patients less than 40 years of age with SBP of 120–129 mm Hg, and a strong family history of risk factors like hypertension, dyslipidemia or diabetes, drug therapy should be initiated if after 6 months of intensive life style modification, the goal BP of less than 120/80 is not achieved and they are able to tolerate such levels of BP.[25]

Conclusion

It is time to move beyond conflicting evidences and guidelines, derived from clinical trials that have excluded many patients due to age, comorbidities, and various social factors to a more nuanced and individualized approach based on scientific evidence and ethical principles, that can be implemented in clinical practice.

We should be treating patients and not mm Hg!!

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CHAPTER

58 Keto Diets and Diabetes Reversal—Can Keto Diet Really Cure Diabetes?

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Abstract

Based on the science and the clinical studies that have been done over the last 100 years on Keto Diet (KD), KD has made a demonstrable impact on type 2 diabetes management. Such dietary modification led to improvements in glycemic control and medication reduction/elimination in motivated volunteers with type 2 diabetes. While larger, longer-term studies are needed, the data gathered thus far make a strong case for incorporating KD into treatment guidelines for type 2 diabetes. The ADA has recognized that reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia. The ADA also notes that reducing overall carbohydrate intake with a low- or very low-carbohydrate eating pattern is a viable option for those patients who are not meeting their glycemic targets or for whom reducing glucose-lowering drugs is a priority. However, the ADA does recognize that low-carbohydrate plans can be hard for diabetics to sustain in the long term and thus recommends that clinicians work with their patients and reassess their nutritional status through the life course.

Introduction

Diabetes mellitus, as defined by the American Diabetes Association (ADA), is a metabolic disease of consistent hyperglycemia, caused by either a defect in insulin secretion, a defect in insulin response, or both.[1]

The ADA has provided criteria for diabetes diagnosis as follows:[1]

- Symptoms of diabetes plus causal plasma glucose concentration more than or equal to 200 mg/dL (11.1 mmol/L). Causal is defined as any time of the day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.
- Fasting plasma glucose more than or equal to 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.
- Two-hour post-load glucose more than or equal to 200 mg/dL (11.1 mmol/L) during an oral glucose load test. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water.

The pathophysiology behind why diabetes occurs is complex. In type 1 diabetes, the primary cause is an absolute deficiency of insulin secretion. Individuals with type 1 diabetes have evidence of an autoimmune process in the pancreas, specifically the pancreatic beta cells. The specific markers of pancreatic beta cell destructions include islet cell autoantibodies as well as autoantibodies to insulin, glutamic acid decarboxylase (GAD65), and tyrosine phosphatases IA-2 and IA-2β. There are also genetic factors include mutations in the HLA DQA and DQB genes.

In type 2 diabetes, it is multifactorial: there is a combination of insulin resistance and inadequate insulin secretory response to combat signals that there is high blood glucose. The majority of these persons with type diabetes are obese, which in of itself is a metabolic

condition that can cause insulin resistance. Even in those not classified as obese, the extent of insulin resistance, when reaches a critical threshold, can lead to the beginning signs of disease.

The degree of hyperglycemia varies by the individual and can vary over time and with the circumstances. How a particular person goes from an asymptomatic state to one where there is multiple-organ involvement is moderated by both genetics and the environment.[1] Especially with type 2 diabetes, continued elevations in blood glucose with inability to upregulate insulin secretion and insulin resistance can lead to deleterious consequences in the short- and long-terms (including macrovascular and microvascular complications).

To combat and ultimately reverse type 2 diabetes requires a multi-pronged approach customized to each individual's physiology. Insulin resistance can be improved with a combination of pharmacologic treatment as well as weight reduction. Over the past decade, there have been significant advancements in diabetic pharmaceuticals with new medications specifically focused on getting more insulin responsiveness. There have also been significant improvements in bariatric surgical techniques with improved patient outcomes. While nutrition therapy (via low-carbohydrate diet) has been considered to be the tried-and-true method to modifying carbohydrate metabolism and endorsed by many professional medical societies around the globe, diligent adherence, and continued compliance to this diet regimen remain major obstacles.

Recently, the ketogenic diet (KD) has been proposed as a potential means to achieve euglycemia and reverse diabetes altogether. This diet was initially used to treat children with refractory epilepsy in the early 19th century. However, over the last 35 years, KD has been promoted in the diet world as a fast and easy way to lose weight.

In this review, we will go through the pharmacology of ketogenesis and evaluate the origins of KD. We will also review the current evidence in humans demonstrating the effectiveness of KD in diabetes type 2 reversal as well as the potential complications. We will also review low carbohydrate high fat (LCHF) diets.

Ketogenesis: The Basics

Physiological ketosis means that the body is able to optimize its fat utilization, reducing lipogenesis, and increasing lipolysis and fat oxidation. By consuming below-average amounts of carbohydrates, the body starts to deplete its carbohydrate reserves (in the form of glycogen). Once those reserves have been exhausted, the body then starts to generate its own glucose (gluconeogenesis). After that route is exhausted, the body is put into a state of ketosis. As a result, there is a high concentration of free fatty acids (FFAs) in the bloodstream, which are directed to the liver. In the liver, these FFAs are oxidized into ketone bodies (KBs). The KBs generated include β-hydroxybutyrate (βHB), acetoacetate (AA), and acetone. The beta-oxidation of these KBs in conjunction with the FFAs can generate a large amount of energy compared to just carbohydrates alone. βHB (100 gm) can yield 10,500 gm of ATP (the main currency of energy in the body), whereas 100 gm of glucose can generate 8,700 gm of ATP. Moreover, 108 ATPs are produced per 16 carbon FAs, as compared to 32 ATPs per unit of glucose.[2] This energy-efficient process makes KBs and FFAs a good substrate for cells, especially in low-oxygen environments. These KBs are also able to cross the blood-brain barrier and can serve as energy source for brain cells, providing up to approximately 70% of the brain's energy requirements.[3] KBs are stable chemical structures and can remain in circulation for years. FFAs are especially effective in exercise, enhancing the skeletal muscle's ability to oxidize fat.[2]

It should be noted that while a person can get sufficient calories from KD, it does not necessarily mean that the body is optimally using KBs and FAAs for fuel. The body has to be primed to exclusively use KBs and FAAs. Keto-adaptation is the term used to describe the changes the body has to make metabolically to be able to completely depend on KBs and FAAs as the primary energy source.[2] For the body to be able to "keto-adapt" requires carbohydrate restriction for an extended period of time. The exact amount of time required to reach that point where multiple organs in the body have reached KB/FAA homeostasis is unclear. Goedecke et al. attempted to do a time-course of metabolic adaptations to KD among 16 elite cyclists and found that changes in glucose tolerance were identified in these cyclists between 5 and 10 days of starting the KD.[4] Looking at keto-adapted among elite athletes in the long-term (between 9 and 36 months), Volek and colleagues found that those on the KD had twofold greater peak fat oxidation rate and a higher serum KBs (indicating upregulated ketogenesis and lipolysis) compared to those on the high-carbohydrate group.[5]

The Origins of the Ketogenic Diet

KD is a eucaloric diet composed of high fat and low carbohydrates with normalized protein intake, resulting in the production of KBs.[2] This process is able to keep the body in a continued state of KB production.

KD as a diet had not been fully formulated until the mid-1930s, but only after a series of discoveries had been made.[6] Multiple clinicians in the early 1900s had observed that fasting their epileptic patients would eliminate the seizures altogether. This was formally introduced to professional medical society by H. Rawle Geyelin, an endocrinologist at New York Presbyterian Hospital. Dr. Woodyatt, another clinician from the same time period, had noted that βHB and acetone appeared in a normal subject by starvation or a diet containing too low a proportion of carbohydrate and too high a proportion of fat. It was Dr. Wilder at the Mayo Clinic who was able to put it all together: he hypothesized that a diet should be as effective as fasting for treating epileptic patients and could be maintained for a much longer period of time. Wilder conducted a small trial of patients treated with the ketone-producing diet at the Mayo Clinic and then called the diet the "ketogenic diet."

There are many types of KDs currently in use around the world (including the popular Atkins diet). However, there is no uniform guideline or professional consensus on what specific ratios of fat to carbohydrate to protein constitutes a "true" KD.

The first physiologic study looking at the long-term metabolic effects of KD was by Phinney et al. in the early 1980s.[7] This study consisted of cyclists who were given a eucaloric balanced diet for 1 week (which provided 35–50 kcal per kg per day and 1.75 gm of protein per kg per day, with the remaining calories provided as two-thirds carbohydrate-based calories and the remaining one-third fat-based). Then the cyclists were put on a eucaloric KD for 4 weeks. This diet provided less than 20 gm of carbohydrates per day but the protein was matched to the balanced diet (1.75 gm per kg per day) so that the reduction in carbohydrate-based calories was replaced with an increase in fat-based calories. The goal was to evaluate whether there was a change in maximal oxygen uptake and pedal efficiency with the KD in comparison to the balanced diet group. The study authors found that there was neither any clinical nor biochemical evidence of any hypoglycemic event occurring during the time the cyclists were on the KD, demonstrating that aerobic endurance was not compromised by 4 weeks of KD. Moreover, the there was an across-the-board reduction in blood glucose (by about 15%) as well as in glucose metabolism (by about 30%).[7,8]

Today in most nutrition circles, a KD is a state of increased fat consumption, which leads to ketosis. In the average person, the upper limit of carbohydrate intake is approximately 50 gm per day and protein intake ranges anywhere from 1.2–2 gm per kg per day in order to maintain this ketotic state.

Effectiveness of KD in Diabetes Type 2 Reversal

The potential to utilize KD in the management of type 2 diabetes has been explored primarily in small clinical populations. Even with major medical and technological advancements, the greatest challenge has been trying to control post-prandial glycemia. Focusing on the type of carbohydrate consumed and how it is metabolized has been the driving force behind the pursuit of a carbohydrate-modified diet specifically suited for type 2 diabetics.

But to understand the impetus behind KD and diabetes type 2 management, one needs to review Dr. Atkinson's work. Dr. Atkinson, a professor of Medicine at Eastern Virginia School of Medicine and Chief of the Division of Clinical Nutrition had written a series of papers and authored many books and book chapters from the late 1970s through the 1990s looking at the use of low and very low calorie diets which were low in overall calories, low in carbohydrates, and high in protein.[9] While many of them were linked to fad diets, the science behind a diet more in-line with a traditional KD had gained traction in the diabetic research community and the principles have been utilized to create targeted interventions focused on glycemic control.

There have been multiple studies looking at variations of KD and impact on hyperglycemia in type 2 diabetics.

To determine whether obese type 2 diabetics would achieve better glycemic control on a high-ketogenic very-low-energy diet (VLED) versus a low-ketogenic VLED, Gumbiner et al. conducted a small study among 13 patients over 6 weeks.[10] Gumbiner and his study colleagues enrolled seven patients and put them on the high-ketogenic VLED for 3 weeks and compared them with six patients treated with a low-ketogenic VLED. The patients were then

crossed over and treated with the alternate diet for another 3 weeks. The study authors ensured that the caloric intakes for both diets were the same, but compared to a normal diet, the protein amounts were 55% higher.[8,10] Both these diets created ketotic states, but the low-ketogenic VLED (which had more carbohydrates) reduced ketosis by about 60% compared to the high-ketogenic VLED. After dieting, the amount of weight loss was not different between the groups but fasting and oral glucose tolerance test glycemia among those on the high-ketogenic VLED were lower than those on low-ketogenic VLED.

To evaluate how a low-carbohydrate KD could be effective way to improve glycemia and ultimately reduce the number of medications in type 2 diabetics, Yancy and associates conducted the following study: 28 patients from an outpatient clinic were selected to be part of a 16-week single-arm pilot diet intervention trial.[11] The low-carbohydrate KD had a target carbohydrate amount of 20 gm per day or less. Twenty-one of the 28 participants who were enrolled completed the study. Twenty participants were men; 13 were white, 8 were African-American. The mean age was 42.2 years (BMI was 56.0). Hemoglobin A1c decreased by from an average of 7.5 to an average of 6.3 ± 1.4% to 6.3 from baseline to week 16. Diabetes medications were discontinued in 7 out of the 21 participants, reduced in 10 out of the 21 participants, and unchanged in 4 out of the 21 participants. The end results: glycemic control in patients with type 2 diabetes was optimized for the majority of the patients enrolled. However, given the rapid changes in hyperglycemia, patients on diabetes medication who use this diet were advised that they should be under close medical supervision to ensure that there were no major complications.

To be able to identify if a diet lower in carbohydrate would lead to greater improvement in glycemic control in patients with obesity and type 2 diabetes mellitus over the course of 6 months, Westman and associates recruited 84 community volunteers with obesity and type 2 diabetes from the outpatient setting.[12] These individuals were randomized to either a low-carbohydrate KD (defined as 20 gm or less of carbohydrate daily) or a low-glycemic, reduced-calorie diet (500 kcal/day deficit from weight maintenance diet). The main outcome was glycemic control (as measured by hemoglobin A1c). Out of the initial 84, 49 completed the study. While both interventions led to improvements in hemoglobin A1c, fasting glucose, fasting insulin, and weight loss, the low-carbohydrate KD group had more significant results. The low-carbohydrate KD group had an average of 1.5% reduction in Hemoglobin A1c (compared to 0.5% in the low-glycemic group), an average weight loss of 11.1 kg (compared to 6.9 in the low-glycemic group, and reduction/elimination of diabetes medications in 95.2% of the low-carbohydrate KD group (compared to 62% in the low-glycemic group).

LCHF diets had become a contentious area of nutrition, especially as it pertains to diabetes and diabetes reversal.[13]

An LCHF diet is defined as one that restricts carbohydrate intake to 130 gm per day or less whereas a very LCHF (ketogenic) diet restricts carbohydrate intake to between 20 and 50 gm per day.[14]

There have been recent studies looking at LCHF in the management and potential reversal of diabetes type 2.

In one trial, 363 overweight and obese patients were allowed to choose either a ketogenic LCHF diet or a "low calorie, high nutritional value" diet and were on their respective diets for 24 weeks.[15] About 220 (59 men and 161 women) were on the ketogenic LCHF diet and 143 (27 men and 116 women) were on a low-calorie diet, with102 of the participants had established type 2 diabetes. After 24 weeks, HbA1c and fasting blood glucose concentrations decreased significantly more with the LCHF diet (down from an average of 7.7 mg/dL to an average of 6.7 mg/dL, a 1-point drop in HbA1c).[15]

A randomized trial enrolled 34 prediabetic or type 2 diabetic patients to a calorie-restricted diet consistent with ADA guidelines or very LCHF diet.[16] The very LCHF group showed a significant reduction (6.6–6.0%) in HbA1c values compared with unchanged values (6.9% at baseline and follow-up) in the ADA group. A significant number of more participants in the very low LCHF group decreased their use of diabetic medications as compared to the ADA group. The very low LCHF group also lost more weight (–5.5 kg) as compared to the ADA group (–2.6 kg).[16]

Tay and colleagues randomized 115 obese type 2 diabetics to adults to either LCHF or LFHC diets for 1 year.[17] The outcomes measured included: HbA1c, fasting blood glucose, glycemic variability assessed with use of 48-hour continuous glucose monitoring, diabetes medication, weight, blood pressure, and lipids assessed at baseline, 24, and 52 weeks. While there were no differences in HbA1c and blood glucose levels among the groups, the LCHF-diet group achieved greater mean reductions in the diabetes medication score, and there was less glycemic variability.[17]

Conclusion

Based on the science and the clinical studies that have been done over the last 100 years on KD, KD has made a demonstrable impact on type 2 diabetes management. Such dietary modification led to improvements in glycemic control and medication reduction/elimination in motivated volunteers with type 2 diabetes. While larger, longer-term studies incorporating more people of color (including African-Americans and Hispanic-Americans, who are disproportionately affected by type 2 diabetes as compared to other racial/ethnic groups) are needed, the data gathered thus far make a strong case for incorporating KD into treatment guidelines for type 2 diabetes. The ADA has recognized that reducing overall carbohydrate intake for individuals with diabetes has demonstrated evidence for improving glycemia.[18] The ADA also notes that reducing overall carbohydrate intake with a low- or very-low-carbohydrate eating pattern is a viable option for those patients who are not meeting their glycemic targets or for whom reducing glucose-lowering drugs is a priority. However, the ADA does recognize that low-carbohydrate plans can be hard for diabetics to sustain in the long-term and thus recommends that clinicians work with their patients and reassess their nutritional status through the life course.

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CHAPTER

59 Metformin: The Enigma of Diabetes

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Abstract

Metformin is the drug of choice for type 2 DM as recommended by most of scientific society dealing in diabetes. Although being one of oldest hypoglycaemic agents, the mechanism of action is still to be revealed completely, currently it is best correlated with AMPK activation and altering redox state to reduce hepatic gluconeogenesis. Recent implication of metformin in meta inflammation has opened a big vista for its use not just as a hypoglycemic agent but in other states such as dementia by decreasing effect of MPTP, in cancer by inhibiting mitochondrial respiratory chain complex 1, anti ageing by inhibiting mTORC 1, in chronic infection like mycobacterium tuberculosis by inhibiting the mammalian target of rapamycin targets p70S6K and 4EBP1, in PCOS by increasing SHBP, by reducing pulmonary fibrosis via down regulating TGFβ1-mediated fibrogenesis and most important its cardiovascular modulating actions in CHF, DCMP, cardiac fibrosis, and hypertrophy. And the story does not commence here without mentioning its noble effect on thyroid health, obesity, and osteoporosis too. Below is a concise narrative of metformin and its expanded scope in medicine.

Introduction

Metformin is the preferred first-line oral blood glucose lowering agent to manage type 2 diabetes mellitus (T2DM) by almost all diabetic and cardiological societies all over the world either ADA or ECS. Galega officinalis (also known as goat's rue), a traditional herbal medicine in Europe was found rich in guanidine. Metformin was introduced in 1920s, but came into US market in 1960s and gradually became one of the first-line oral antihyperglycemic drugs.

Pharmacokinetics and Pharmacogenetics

Drug is administered orally. It has low bioavailability 40–60%.[1] Absorption predominantly occurs in the small intestine. Drug is not metabolized and excreted unchanged in the urine. After a dose of 500 mg it gets distributed systemically within 6 hours. Peak plasma concentration occurs after 3 hours. Half-life is 4–9 hours.

Mechanism of Metformin and Hepatic Glucose Regulation

Liver is the centrally acting body in glucose lowering effect of metformin.[2]

Metformin-induced AMPK Activation

AMPK (5-AMP activated protein kinase) is a regulator of energy homeostasis. Metformin lowers hepatic gluconeogenesis through activation of AMPK. Due to metformin the ratio of ADP/ATP; AMP/ATP increases as a result of AMPK activation. Lack of energy inhibits gluconeogenesis.

Alterations of Redox State

Metformin also decreases hepatic gluconeogenesis independently of AMPK mediated and energy charge mediated effects through direct inhibition of

mitochondrial glycerol 3 phosphate dehydrogenase (G3PDH). Inhibition of this shuttle decreases the glucose production from reduced substrates but not from already oxidized substrates.

What Makes Metformin the Oldest, Most Trustful, and Still an Enigma?

Metformin and Meta Inflammation

Chronic low-grade inflammation associated with obesity is known as meta inflammation. It leads to insulin resistance, impaired lipid, and glucose homeostasis in metabolic syndrome and metformin have all potentials to reduce this meta inflammation.[3]

Metformin Action in Intestine

Gut is the primary target of metformin. It inhibits glucose absorption from intestine along with increased glucose utilization by enterocytes by the upregulation of GLUT-2 and SGLT-1.[4] Decrease glucose absorption in upper small intestine makes more glucose available in ileum, which further leads to more release of glucagon like peptide 1 (GLP-1). Fineman et al. showed primary action of metformin is in human gut. They demonstrated delayed release metformin which releases drug until pH was 6.5 in small intestine or beyond where the systemic absorption of metformin is low, resulted in more blood glucose lowering as compared to immediate releasing composition. Metformin also possess action on *gut-brain-neuronal axis*.[5] It results in more release of GLP-1, which acts on GLP receptor on vagal afferent nerves innervating gut mucosa and augments the glucose lowering effect. Metformin plays role in modulating the *gut microbiota*.[6] It causes increase in Escherichia species, lactobacillus and decrease in intestinibacter species, Bacteroides fragilis. Studies showed that altering the gut microbiota may contribute to glucose lowering effect of metformin. Metformin is also effective in type 1 diabetes as evidenced by REMOVAL TRIAL.[7]

Metformin Therapeutic Repurposing

Neurodegenerative Diseases

The search for treatments for neurodegenerative diseases is a major concern in light of today's aging population and an increasing burden on individuals, families, and societies. Therapeutic factor might be how metformin is able to balance *survival and death signaling in cells* through pathways that are commonly associated with neurodegenerative diseases.[8] Metformin has the potential to interfere with neuronal longevity mechanisms.[9] Insulin resistance and diabetes are increasingly recognized as a contributor to disease development especially in the field of dementias. Therefore, rationale for using metformin is its potential to slow aging processes. Most common dementia is *AD (Alzheimer's dementia)*. Neurofibrillary tangles and amyloid plaques (derived from amyloid precursor proteins (app)) are pathological hallmarks. Insulin signaling and glucose tolerance are altered in app in rat models. Diabetic rats showed increased levels of app, a-beta, phosphorylated tau.[10] Metformin has shown to reduce tau phosphorylation, improves memory, and cognition. Metformin *reduces the damaging effect of MPTP* (methyl phenyl tetrahydropyridine) on dopaminergic neurons shown by tyrosine hydroxylase staining (a marker of dopaminergic neurons) in the substantia nigra, pars compacta, striatum or both. ALS (Amyotrophic Lateral Sclerosis) is characterized by degeneration of first and second order motor neurons resulting in spasticity and muscle atrophy. Neurochemical imbalance and genetic mutations are known to cause ALS. A protective role of diabetes in elderly and increased risk of developing ALS in young with diabetes has been described.[11]

Cancer

Various evidences have provided that metformin has utility in cancer prevention and/or treatment.[12] It has the potential for *inhibition of tumorigenesis* as it inhibits mitochondrial respiratory chain complex.[1] In recent years, epidemiological data have shown that diabetes increases the risk of breast cancer, colorectal cancer, pancreatic cancer, endometrial cancer, and other malignant tumors. Metformin likely has an inhibitory effect on tumor progression in patients with T2DM, which can reduce the risk of tumor and tumor-related mortality of patients, improving their survival rate. *I SPY trial* is aiming that metformin hydrochloride may prevent or lower risk of breast cancer and decrease cancer cells, lower risk of cancer spreading. Metformin may also cause eradication of cancer stem cells, induction of cell cycle arrest, and inhibition of unfolded protein response, which further aids in its anti-tumorigenesis property. Recent data

suggest that diabetic patients taking metformin have a lower incidence of certain cancer, including prostate carcinoma

Aging

Metformin is likely to hold the three promises—Longevity, Rejuvenation, and Health Span. The *Targeting Aging with Metformin (TAME) clinical trial* was designed to investigate the effects of metformin on several age-related diseases in humans.[13] As supportive evidence for the TAME trial, it was stated that "metformin modulates the biology of aging and health span in model organisms." Caenorhabditis elegans showed a good evidence for metformin as a potential anti-ageing drug. *Inhibition of mTORC1 via blockage of lysosomal ATPase (V-ATPase)* was postulated as an anti-ageing mechanism of metformin. *A megatrial*, sponsored by the Veterans Administration (NCT02915198; VA-IMPACT), started on February 19, 2019. This trial plans to study 7,868 subjects with prediabetes and established atherosclerotic disease for 4.5 years in a double-blind fashion with metformin extended release versus placebo for a combined primary endpoint. Time-to-events for oncology-related diseases and diabetes are secondary endpoints.

Mycobacterium Tuberculosis Infections

Evidence has emerged that metformin significantly decreases mortality during treatment for *M. tuberculosis* infection, suggesting a role for the drug as a host-directed therapeutic adjuvant.[14] Metformin has a range of potentially beneficial effects on cellular metabolism, immune functions, and gene transcription involved in innate host responses to tuberculosis. Metformin enhances in vitro cellular metabolism while inhibiting the mammalian target of rapamycin targets p70S6K and 4EBP1, with decreased cytokine production and cellular proliferation and increased phagocytosis activity. Metformin also induces shift in myeloid cells from classical to nonclassical monocytes.[15]

Polycystic Ovarian Disease

There is excessive production of androgens that cause some of the most common clinical symptoms of hyperandrogenism (acne, hirsutism, and alopecia).[16] It is often associated with obesity and the metabolic syndrome. Metformin decreases insulin resistance and hyperinsulinemia, improves dyslipidemia and meta-inflammation, decreases blood pressure, and exerts cardioprotective benefits through pleiotropic action on the vascular endothelium.[17] In combination with lifestyle intervention, metformin treatment is also associated with a lower body weight and improved menstrual cyclicity and fertility potential in women with obesity and polycystic ovary syndrome (PCOD). Possible mechanism is increase in hepatic production of sex hormone binding globulin (SHBG), which decreases androgen levels. Alternatively, the drug directly inhibits androgen synthesis in theca cells, which decreases testosterone levels.[18]

Lung Fibrosis

A study in 2018 found that therapeutic concentrations of metformin accelerated the resolution of established fibrosis in a mouse model of lung fibrosis by promoting AMPK activation and apoptosis in fibroblasts. Metformin induces lipogenic differentiation in myofibroblasts to reverse lung fibrosis. Metformin induces lipid accumulation in IPF lung fibroblasts, inhibits TGFβ1-mediated fibrogenesis in vitro.[19]

Premature Pubarche

It refers to precocious appearance of pubic hair without other signs of puberty in girls less than 8 years, boys less than 9 years. In a study done at Ibanez et al., metformin showed to have favorable effects on abdominal adiposity, androgen levels, and insulin resistance.[20]

Cardiovascular Effect

Role in Cardiac Fibrosis

Metformin decreases cardiac fibrosis by AMPK activation and decreasing TGF beta. It inhibits myofibroblasts differentiation by suppressing reactive oxygen production by inhibition of NADPH oxidase.[21]

Role in CHF

It decreases oxidative stress induced cardiomyocyte apoptosis, improvement in insulin resistance, and left ventricular end diastolic pressures. To date metformin is the only anti-diabetic drug which has shown to decrease *the macrovascular complications by reducing the risk for MI.*

Role in DCMP

Majority of ATP for cardiomyocytes is derived from fatty acids. Normally fatty acids are oxidized as it inhibits glucose catabolism via Randle cycle. In DM heart loses this regulation and leads to development of DCMP. Metformin acts to channelize the ATP coming from fatty acids and glucose in appropriate proportion and prevents or decreases the morbidity and mortality resulting from DCMP.[22]

Role in Cardiac Hypertrophy

Anti-hypertrophic action of metformin is due to AMPK activation. It leads to negative regulation of

- protein synthesis via Motor inhibition
- gene transcription including mitogen activated protein kinase and calcineurin nuclear factor of activated T cell pathways.[23]

Non-alcoholic Fatty Liver Disease (NASH)

Non-alcoholic fatty liver disease (NAFLD) related to insulin resistance (IR) is a growing global health concern. Metformin inhibits lipogenesis, increases fatty acid oxidation in liver and adipose tissue. Metformin improves liver function, HOMA-IR and BMI to some extent, but not histological response in NAFLD patients. Studies have indicated that metformin could improve IR and may be beneficial in the treatment of NAFLD.[24]

Thyroid and Metformin

Individuals with hyperinsulinemia have larger thyroid gland and a higher prevalence of thyroid nodules and cancer. Accordingly, patients treated with metformin have a smaller thyroid volume and a lower risk of incident goiter, thyroid nodule. Metformin can inhibit thyroid dysfunction irrespective of thyroxine replacement and presence of thyroid autoimmunity. Perhaps, metformin has central action.

Obesity

It reduces the body weight independent of dosage. The mean body weight lost is in the range of 1–5 kg or 1–3% in both diabetic and non-diabetic patients. Metformin also helps to counteract the weight gain caused by sulfonylurea (SU), thiazolidinediones, and insulin.[25]

Abbreviations

AMPK, Amp activated protein kinase
CHF, Chronic heart failure
DCMP, Dilated cardiomyopathy
MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mTORC, Mammalian target of rapamycin
SHBG, Sex hormone binding globulin
TGF, Transforming growth factor

Conclusion

Metformin is first-line agent in management of type 2 diabetes mellitus. It also possesses potential for management of other conditions like cancer, neurodegenerative diseases, obesity, ageing. Upcoming studies may change the perspective of its usage. So in true senses we can say metformin is an enigma of diabetes, which still have many more things to reveal.

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CHAPTER

60 SGLT2 Inhibitors—Where to Use? Where not to Use?

Aarathy Kannan, Chandrakumar

Abstract

Diabetes mellitus is a worldwide serious health issue and an economic burden, rising in epidemic proportions over the last few decades. Although several treatment options are available, only half of the global diabetic population achieves the recommended or individualized glycemic targets. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of antidiabetic agents with a novel insulin-independent action. SGLT2 is a transporter found in the proximal renal tubules, responsible for the reabsorption of most of the glucose filtered by the kidney. Inhibition of SGLT2 lowers the blood glucose level by promoting the urinary excretion of excess glucose. Due to their insulin-independent action, SGLT2 inhibitors can be used with any degree of beta-cell dysfunction or insulin resistance, related to a very low risk of hypoglycemia. In addition to improving glycemic control, SGLT2 inhibitors have been associated with a reduction in weight and blood pressure when used as monotherapy or in combination with other antidiabetic agents in patients with type 2 diabetes mellitus (T2DM). Treatment with SGLT2 inhibitors is usually well tolerated; however, they have been associated with an increased incidence of urinary tract and genital infections, although these infections are usually mild and easy to treat. SGLT2 inhibitors are a promising new option in the armamentarium of drugs for patients with T2DM.

Introduction

Diabetes is a growing epidemic due to population growth, ageing, urbanization, and westernization. Hereby, the burden of diabetes translates into substantial social and economic problems.[2] The alleviation of hyperglycemia, often by oral antidiabetic drugs, leads to improvement of insulin sensitivity, b-cell function, and reduction of microvascular complication such as retinopathy, neuropathy, and nephropathy.[1] The standard antihyperglycemic treatments do not necessarily confer full protection against coronary artery disease (CAD), stroke, and peripheral vascular disease as shown in several large, long-term outcome studies, partially explained by the risk at hypoglycemic events. Furthermore, in order to effectively reduce cardiovascular (CV) events in diabetic patients, comorbidities such as obesity, hypertension, and hypercholesterolemia must be cotargeted, in conjunction to the maintenance of glycemic control. [3] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are approved for glucose lowering in patients with type 2 diabetes mellitus (T2DM) since 2012.[4] These agents have shown benefit in cardiovascular as well as renal outcomes in T2DM patients, which make them an excellent therapeutic option and have opened a vast area of research.[5]

Mechanism of Action

Glucose reabsorption is mainly mediated by the SGLT2 transporter. The SGLT2i reduce blood glucose by blocking its reabsorption in the proximal convoluted tubules of kidneys leading to glucose excretion via the urine.[6] Apart

from the above it also causes reduction in SBP of 4–6 mm Hg and DBP of 2–4 mm Hg. Osmotic diuresis reduced renin-angiotensin-aldosterone system (RAAS):

- Reduction in body weight 1–5 kg: calorie loss in urine, dehydration in short term, fat mass loss and lesser insulin requirement
- Increase in hematocrit: dehydration, increased erythropoietin
- Lower urate concentration
- Lower triglycerides: calorie loss, glucosuria

Currently Available SGLT2i

The currently available SGLT2i are discussed in **Table 1**.

Natural History of Diabetes

Onset of macrovascular complications occurs early in metabolic dysregulation[7] **(Fig. 1 and Flowchart 1)**.

Mechanisms of Cardiovascular Benefits with SGLT2i

Mechanisms of cardiovascular benefits with SGLT2i have been discussed in **Table 2**.

Cardiovascular Benefits of SGLT2i—Evidence

- The EMPA-REG outcomes trial was the first to show not only non-inferiority but also superiority over

TABLE 1 Currently available SGLT2i

Name	*Empagliflozin*	*Canagliflozin*	*Dapagliflozin*
Available doses	10 mg, 25mg	100 mg, 300 mg	5 mg, 10 mg
Daily dosing	Od before breakfast	Od before breakfast	Od before breakfast
Food interaction	None	None	None
Renal dose adjustment**	EGFR>45: no dose adjustment EGFR<45: NR EGFR< 30 : C/I	EGFR> 60: no dose adjustment EGFR 45–60: canagloflozin 100 mg eGFR< 45: NR EGFR< 30: C/I	EGFR> 60: no dose adjustment EGFR< 60: NR EGFR< 30: C/I
Other agents approved in india	Remogliflozin		
Other agents	Ertugliflozin (FDA approved, EMA authorized) sotagliflozin (SGLT2, 1 dual blockade FDA CRL, EMA authorized)		
Approved in japan	Tofogliflozin, luseogliflozin, ipragliflozin		

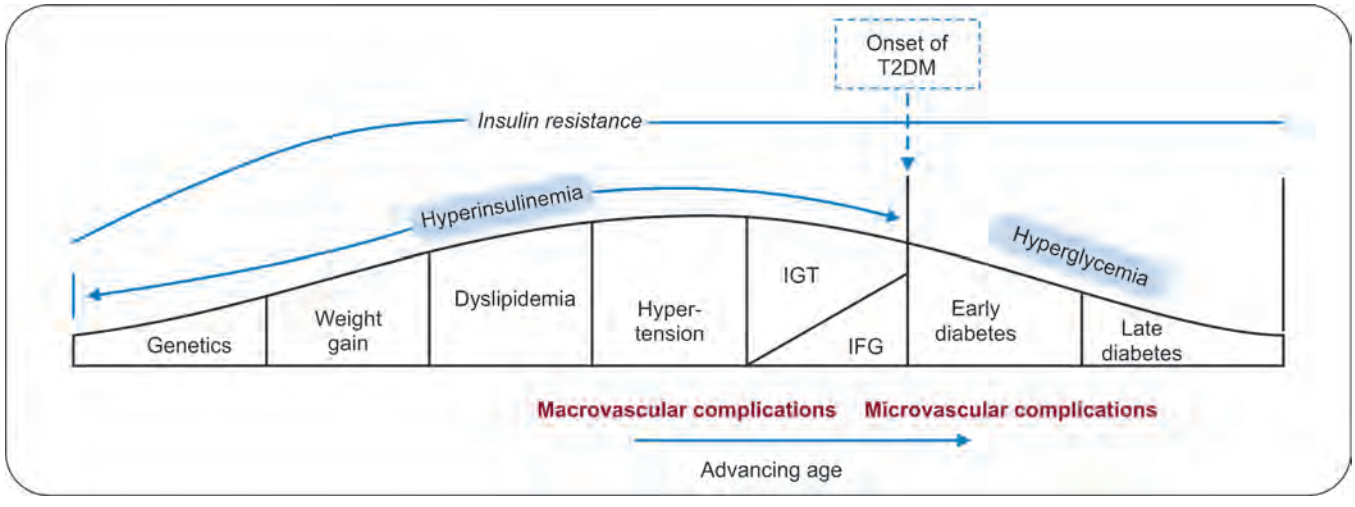

Fig. 1: Natural history of diabetes

Flowchart 1: Metabolic adaptations following SGLT2i therapy

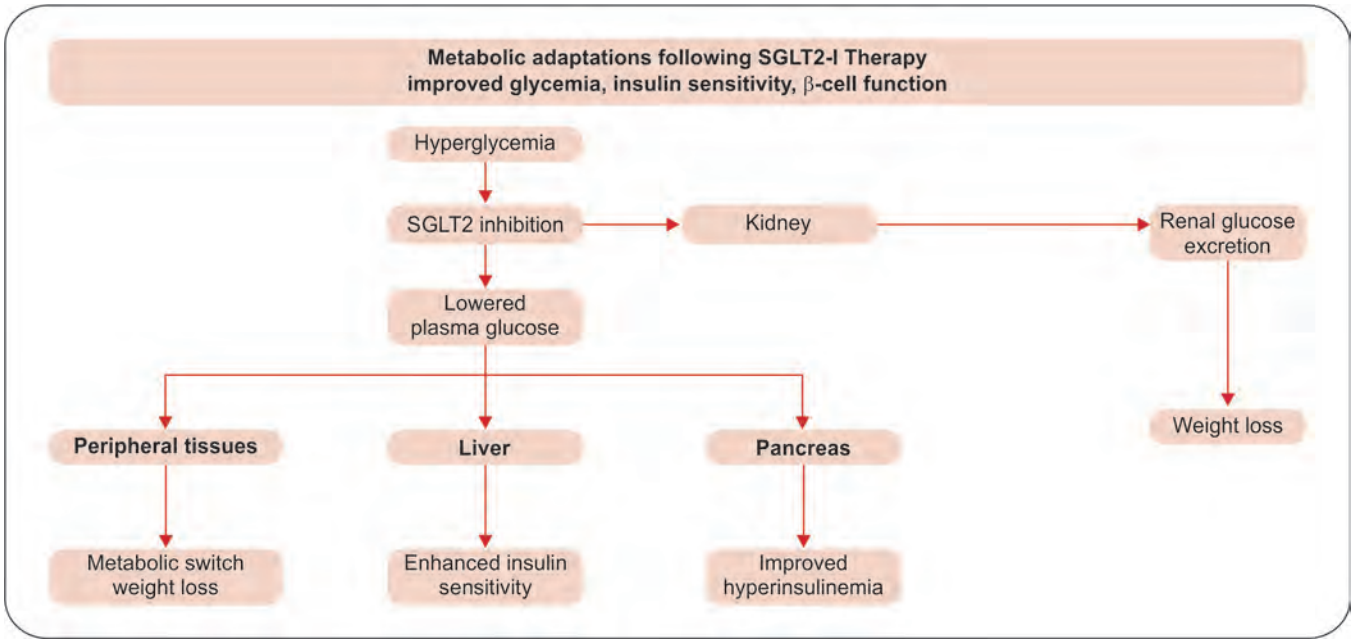

TABLE 2 Potential mechanisms of cardiovascular benefits with SGLT2i

Hemodynamic effects	*Metabolic alteration*
Osmotic dieresis and reduced preload	Glycemic control
Bp reduction	Weight loss
Local (renal) and systemic raas activity inhibition	Ketone body generation and energy efficient utilization of ketone bodies over glucose by a failing myocardium—the " thrifty fuel" hypothesis
Neprilisyn inhibition	Uricosuria
Alternation in intra and extracellular Na^+ distribution by inhibition of Na^-h exchanger in cardiomyocetes (sodium hypothesis)	Increased erythropoietin production due to reduced glycemic exposure of macula dense improved hematocrit and O_2 carrying capacity
Decreased sympathetic nervous system activity	
Improved arterial relaxation and decreased after load	

placebo in CV outcomes in patients with T2DM receiving either doses of empagliflozin (10 mg or 25 mg).

- The primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke was reduced by 14% with empagliflozin. Interestingly, this was driven mainly by a significant decrease in CV death.[8]
- There was a non-significant reduction in nonfatal MI but a slight increase in nonfatal stroke with empagliflozin.
- There was also significant reduction in all-cause mortality by 32% and hospitalization due to heart failure by 35%.
- The CANVAS program integrated data from two trials—CANVAS and CANVAS-R patients with T2DM

on standards therapy at high cardiovascular risk were randomized to receive either canagliflozin (100 mg or 300 mg) or placebo.[9]

- Around one-third patients had high risk for CV disease while 65.8% of patients had already established CV disease.
- In the canagliflozin group, the relative risk of the primary composite outcome (3-p mace) significant decreased by 14%. There was however no significant difference in CV death, nonfatal MI, or nonfatal stroke.
- In the DECLARE-TIMI 58 trial, which was CVOT designed to satisfy the US FDA criteria of safety for dapagliflozin, 40.6% with atherosclerotic CV disease and 59.4% with risk factor for atherosclerotic CV disease.
- Though the trial showed the non-inferiority of dapagliflozin in 3-p mace but dapagliflozin did not result in a lower rate of mace than placebo in contrast to was seen in EMPA-REG and CANVAS trials.[10]

Comparison of Landmark CVOTS with SGLT2i

Comparison of landmark CVOTS with SGLT2i has been discussed in **Table 3**.

Renal Benefits with SGLT2i—Mechanisms

The mechanisms for renal benefits with SGLT2i could be multifactorial including both direct renal vascular and hemodynamic effects **(Table 4)**.

Renal Benefits—Evidence

- The EMPA-REG outcome also investigated renal outcomes in patients with T2DM, established CV disease, and an estimated glomerular filtration rate (eGFR) 30 mL/min/1.73 m^2. In spite of an initial decline in eGFR in the first 4 weeks of empagliflozin treatment, overall, there were a 39% reduction in the relative risk of worsening nephropathy, a 38% reduction in the progression of macroalbuminuria, 44% reduction in the doubling of serum creatinine, and a 55% reduction in the initial of the renal-replacement therapy.
- CANVAS-R trial was predominantly aimed to study renal outcomes with canagliflozin treatment. It showed significant reduction in the risk of progression of albuminuria, requirement for renal-replacement therapy, or renal death by 23% and 40% respectively.[11]
- Credence trial, the primary outcomes, which was a composite of ESRD , doubling of serum creatinine or

TABLE 3 Comparison of the landmark CVOTs with SGLT2i

Trial	*EMPA- REG outcome*	*Canvas program*	*DECLARE – TIMI 58*
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analyzed	10 mg, 25 mg	100 mg, 300 mg	10 mg
Median follow- up (yrs)	3.1	2.4	4.2
No of participants	7020	10142	17160
Mean age (yrs)	63.1	63.3	63.9
Patients with established CV disease (%)	100	65.6	40.6
Patients with heart failure (%)	10.1	14.4	10
Patients with eGFR <60 mL/min/1.73 m^2	25.9	20.1	7.4
Reduction in 3-p mace (HR with 95% cl)			
In patients with atherosclerotic CVD	0.86 (0.74- 0.99	0.82 (0.72-0.99	0.9 (0.79-1.02)
In patients with multiple risk factors for ASXCVD		0.98 (0.74-1.30)	1.01 (0.86-1.2
Reduction in CVD/HHF (HR with 95% cl)			
In patients with atherosclerotic CVD	0.66 (0.55-0.76)	0.77 (0.65-0.92)	0.83 n(0.71-0.98)
In patients with multiple risk factors for ASCVD		0.83 (0.58-1.19)	0.84(0.67-1.04)
AMI/CVD	↓↓	↓	↓
Stroke	↑	↓	↓
Hospitalization due to heart failure	↑	↓	↓

TABLE 4 Probable mechanisms of renal benefits with SGLT2i

Hemodynamic hypothesis (or the tubular hypothesis)	Reduced Na reabsorption in PCT (SGLt2 inhibition) – increased Na delivery to macula densa– activation of tubuloglomerular feedback – reduced hyperfiltration
Reduction of serum glucose and glucotoxicity hypothesis	Reduced glycemic exposure – reduced glucotoxicity mediated damage of proximal tubular cells
Improvement of renal oxygenation hypothesis	Exaggerated glucose (and sodium) reabsorption in T2DM – increased energy consumption and tubular cell damage – secretion of inflammatory cytokines and fibrosis- decreased production of erythropoietin (epo) SGLT2i prevent this and increase epo production
Thrifty substrate hypothesis	Energy efficient utilization of ketone bodies compared to glucose by PCT cells

TABLE 5 Comparison of two main renal trials with SGLT2i

Trial	*Canvas-r*	*Credence*	
Inclusion criteria	Established vascular complications or >+2 CV risk factors	Stage 2 or 3 CKD + macroalbuminuria	T2DM, eGFR>+60 mL/min and established ASCVD or multiple risk factors for ASCVD
No. of patients	5700	4401	
Primary composite outcomes	Progression of albuminuria	ESRD, serum creatinine doubling renal/CV death	
Renal specific secondary outcomes	Regression of albuminuria, change in eGFR	Composite of ESRD serum creatinine doubling, renal CV death Dialysis/renal transplant or renal death	Composite of 40% reduction in eGFR, ESRD, renal or CV death Pre-specified additional renal composite outcome included all the criteria described for the secondary renal outcome except for cardiovascular death
RR% reduction of primary composite outcome		30	
HR primary composite outcomes (95% cl)		0.70 (0.59-0.82)	
RR % reduction of renal specific secondary outcome		34	23
HR renal specific outcome (95% cl)		0.66(0.53-0.81)	0.76(0.67-0.87)

death from renal/CV diseases was reduced by 30% with canagliflozin in patients meeting the inclusion criteria two of which were the presence of macroalbuminuria and an eGFR as low as 30 mL/min/1.73 m^2. The best results were seen in those with eGFR 45–60 and those with baseline urine ACR >1,000 mg.

- Overall, canagliflozin has shown renoprotective effect in T2DM patients, especially those at high CV risk.
- Declare-trial with dapagliflozin, the renal composite outcome (40% decrease in eGFR to <60 mL/min/1.73 m^2, ESRD, or death from renal or cardiovascular cause) significantly favored dapagliflozin with an incidence of 4.3% in the dapagliflozin group and 5.6% in the placebo group.
- Remogliflozin—the robust developmental program conducted globally for remogliflozin till its first approval in India[12] **(Table 5)**.

SGLT2i and CV Outcomes—Real World Evidence

- Real world evidence is captured in natural, uncontrolled settings and can provide date on effectiveness and safety during routine care and complement date from RCTS.

- CVD-real: compared the rates of hospitalization due to heart failure (HF) in individuals with T2DM who newly initiated on SGLT2i (canagliflozin, dapagliflozin, or empagliflozin) versus other oral hypoglycemic agents.[12] Data for 160,033 people on SGLT2i and 1,226,221 on other agents were available from six different countries (US, UK and Nordic countries). Canaglifloxzin was used in 53% of the population, 37% received dapagliflozin and 10% received empagliflozin. Results favored SGLT2i over other agents for HF or death by any cause.
- CVD real looked at CV and mortality outcomes from an additional six countries (four from Asia pacific, plus Canada and Israel). Up to 75% received dapagliflozin. Results were similar to CVD-real, with a lower incidence of the composite of HF or death by any cause.
- Embrace—real world effectiveness and tolerability of remogliflozin.[13]

Remoglifozin

Remoglifozin is an intensively researched molecule in 26 clinical studies conducted globally.

The phase III pivotal registration trial in India has demonstrated non-inferiority of remoglifozin 100 and 250 mg BID to dapagliflozin 10 mg OD.[14]

- The reduction in HbA1c at 24 weeks in RE 100 g vs. Dapa 10 mg was 0.72 vs. 0.58 (p <0.001) for non-inferiority.
- The reduction in PPG was seen to be numerically higher (39.2 vs. 32.4 g/dL) at 24weeks.
- The reduction in FBG was comparable at 24 weeks.

The reduction in non-glycemic parameters was seen comparable to dapagliflozin.

The adverse event profile was comparable to dapagliflozin 10 mg. Remoglifozin is demonstrated to be well tolerated.

Remoglifozin has equivalent PD (assessed by UGE), glycemic efficacy and real world clinical effectiveness as with other SGLT2i.

The economical costing of remoglifozin empowers for larger access to Indian T2DM patients.

The real world experiences from large scale utilization are/would be presented in various scientific forums, which underscore the efficacy and safety profile in real clinical practice.[15]

The ongoing and future studies are expected to be generated to further strength the evidence exclusively in Indian patients.

The phase III pivotal registration trial in India has demonstrated non-inferiority of remoglifozin to dapaglifozin, with comparable result in all glycemic and non-glycemic parameters.[16]

The adverse event profile of remoglifozin was comparable to dapaglifozin and is well-tolerated by patients.

Cardio-renal benefits are consistently seen with all agents of this class, and explained by mechanistic hypothesis of effective SGLT2 inhibition.

Efficient SGLT2 receptor blockage would potentially provide these benefits observed with this class of drugs.

Remoglifozin is equivalent but economical SGLT2i that would offer access to clinical benefits of SGLT2 inhibition to larger set of Indian patients.[17]

Safety Concern around SGLT2i

Safety concern around SGLT2i has been discussed in **Table 6**.

Place of SGLT2i in current guidelines: as per the 2020 guidelines, apart from affordability issues, there is possibly no reason why agents other than SGLT2i or GLP-1RA should be preferred over these two agents as the second drug of choice after metformin[18] **(Figs. 2 to 4, Flowchart 2)**.

TABLE 6 Safety concern with SGLT2i—results from landmark CVOTs

Adverse event studied	*Higher rates than placebo?*
Major hypoglycemias	No
Euglycemic diabetic ketoacidosis	No, most events in patients with autoimmune diabetes
Genital mycotic infection	Yes, all agents
Urinary tract infection, pyelonephritis	No
Lower limb amputation	With canagliflozin
Fractures	With canagliflozin
Strokes	With empagliflozin
Pancreatitis	No
Acute kidney injury	No
Cancers (bladder, renal cell, breasts)	No
Venous thromboembolic events	No

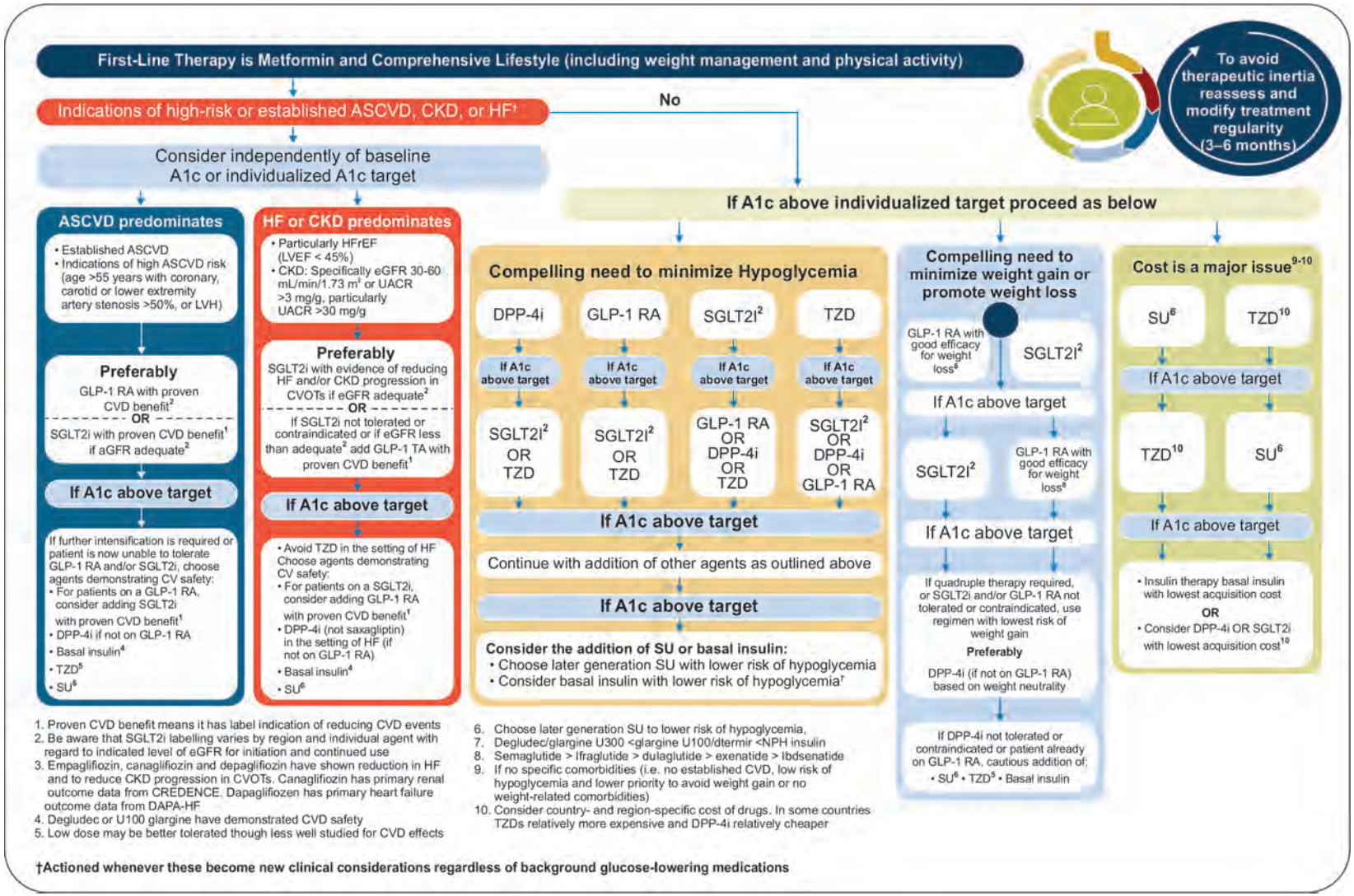

Fig. 2: Algorithm for T2DM management from ADA 2020 guidelines
LVH, left ventricular hypertrophy; HFrEF, heart failure reduce ejection fraction; UACR, urine albumuin-to-creatinine ratio; LVEF, left ventricular ejection fraction

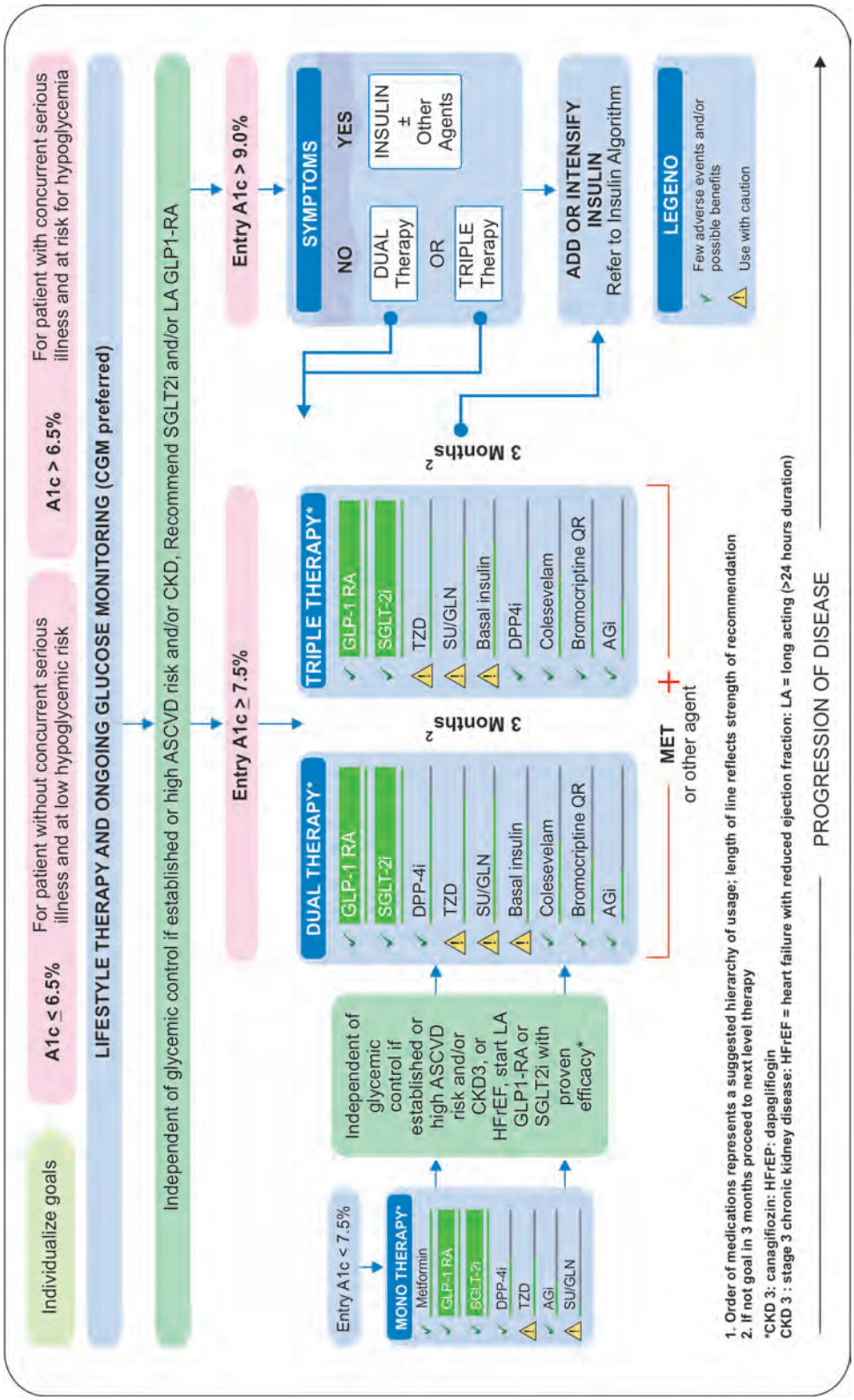

Fig. 3: Algorithm for T2DM management from ACCE 2020 guidelines

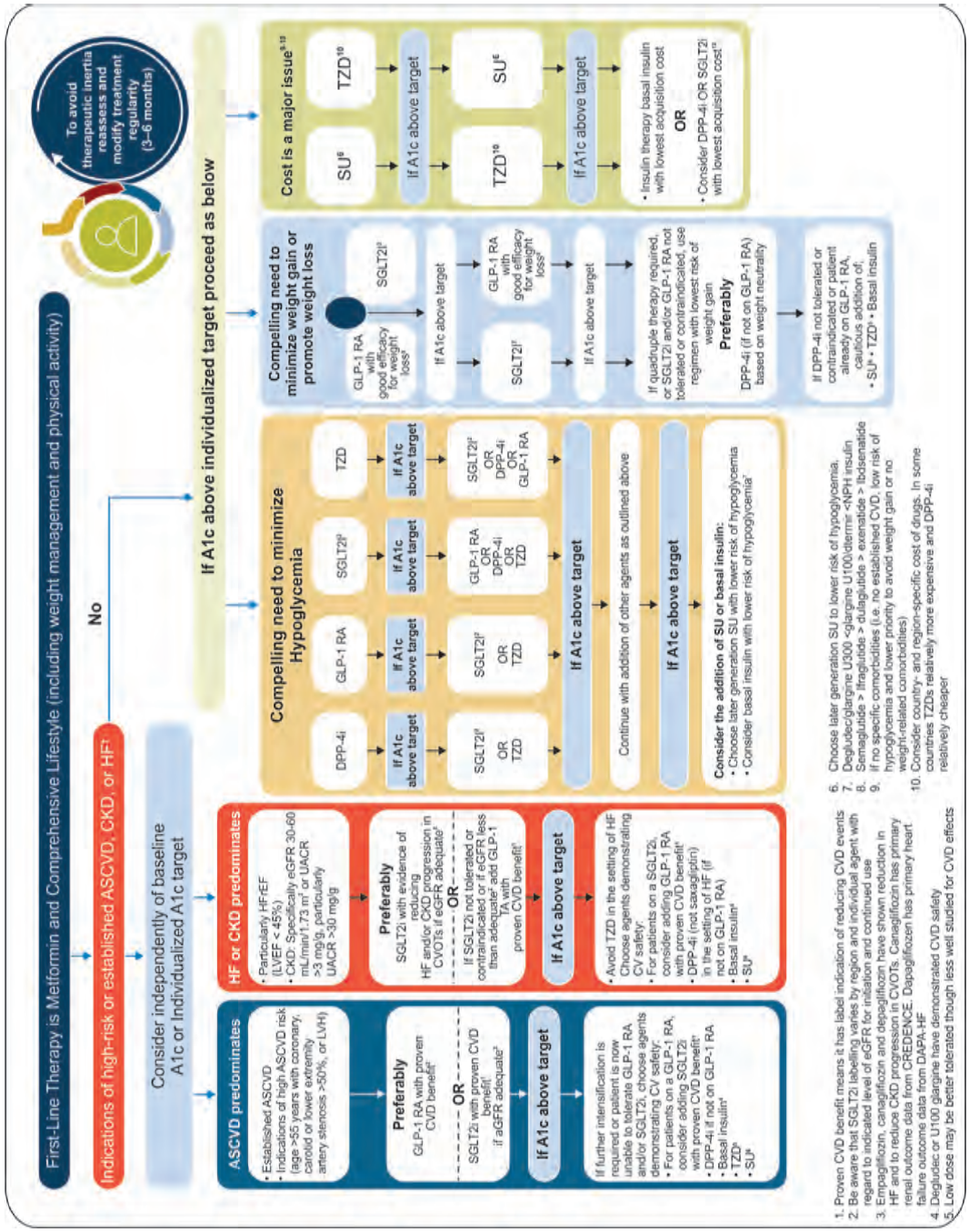

Fig. 4: Algorithm for T2DM management from EASD 2020 guidelines

LVH, left ventricular Hypertrophy; HFrEF, heart Failure reduce ejection fraction; UACR, urine albumuin-to-creatinine ratio; LVEF, left ventricular ejection fraction

Flowchart 2: Algorithm for T2DM management from ESC 2020 guidelines

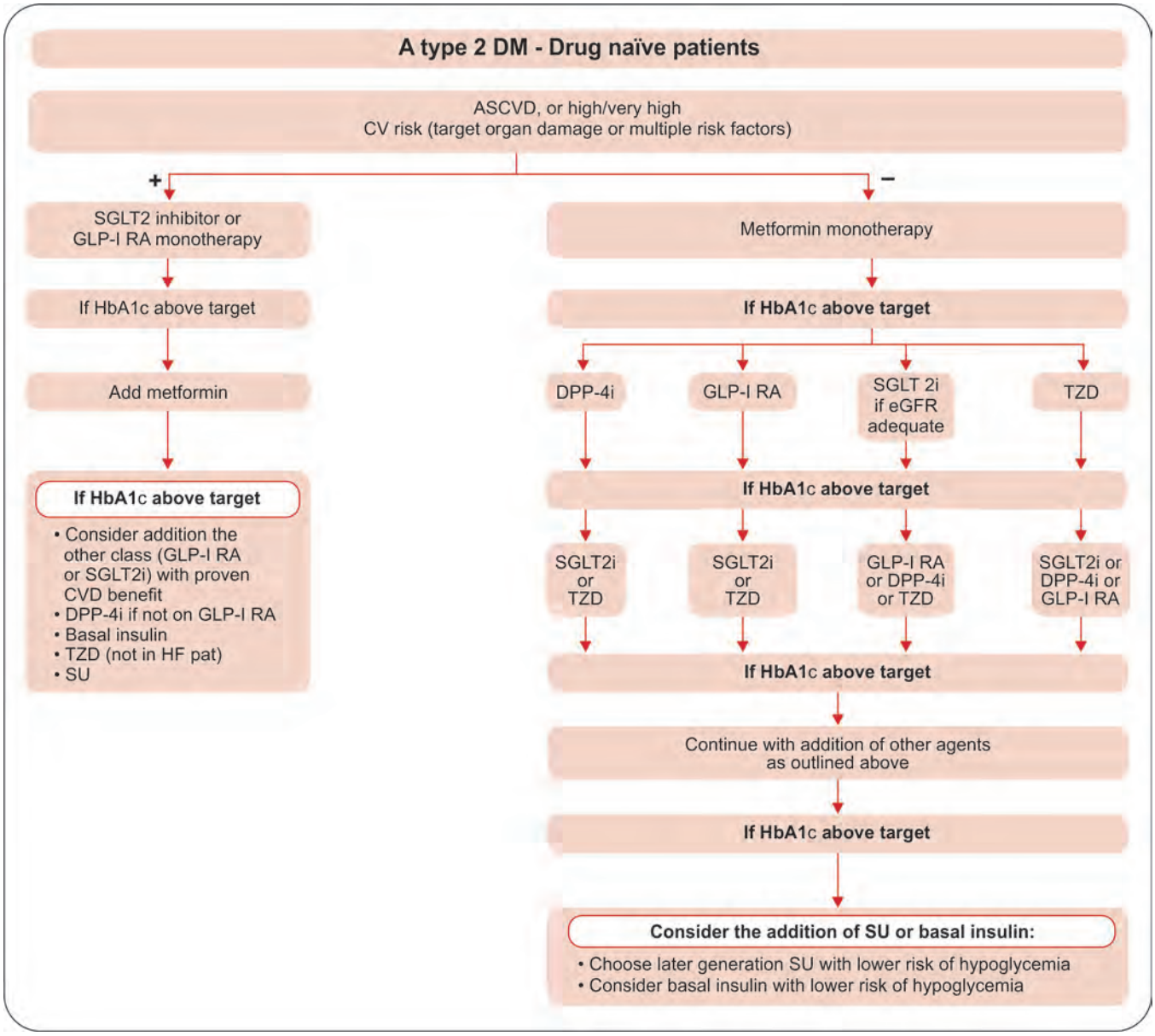

TABLE 7 SGLT2i—ongoing trials

Trial name	*Drug*	*Aim*
Vertis – CV	Ertugliflozin 5 mg, 15 mg vs placebo	To assess CV safety of ertugliflozin in T2DM
Dapa-CKD	Dapagliflozin 10 mg, or 5 mg vs placebo	To assess the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease
Emperor preserved	Empagliflozin 10 mg vs placebo	To assess the risk of CV death and heart failure related hospitalization in patients with heart failure with preserved ejection fraction, with and without diabetes
Scored	Sotagliflozin vs placebo	CVOT of sotafgliflozin
EMPA kindey	Empagliflozin vs placebo	To assess renal disease progession and CV dealth in diabetics and non-diabetics with eGFR> 20-45 or eGFR> 45 + urine ACR > 200 mg/g

SGLT2i—The Future

See **Table 7**.

Where to Use SGLT2i

- Type 2 diabetic patients with good renal function.
- Diabetic patients with hypertension.
- Overweight and obese type 2 diabetic patients.
- Type 2 diabetic patient with recurrent hypoglycemic episodes.
- Type 2 diabetic patients experiencing therapy related limiting adverse events. For example GI side effects with GLP-1 analogs or with AGI use. Type 2 diabetic patient with poor glycemic control while on monotherapy or combination therapy.[19]

Conclusion

- SGLT2i are one of the most attractive therapeutic options in T2DM management with reasonably acceptable safety profile.
- SGLT2i offer a very second-line option following metformin monotherapy especially in individuals with established renal or CV disease or at high risk for the latter. The most common side effect is genitourinary infection, which is however easily treated.
- Canagliflozin reduced the burden of the first and total HHF events by 39% and 36% respectively in patients with T2DM and CKD.
- SGLT2i recommended as monotherapy if metformin is contraindicated or not tolerated in T2DM with unmet needs of glycemic control with metformin monotherapy.
- SGLT2i as monotherapy/add-on to metformin effectively reduce A1c, FPG, body weight and BP in patients with T2DM.
- SGLT2i significantly reduce the risk of CV morbidity and mortality; and associated with reno-protective effects—viz. slower progression to kidney disease and progression of albuminuria, and reduction of eGFR.
- SGLT2i—potential benefits on β-cell function and reduction of insulin resistance may be more useful in Indian T2DM patients.
- Insulin independent action, hence greater durability of glycemic control.
- Efficacious in all stages of T2DM.
- Additional benefits of weight loss, BP reduction.
- Beneficial for combating multiple comorbid diseases associated with T2DM.
- Requires appropriate patient selection and adequate counseling.

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CHAPTER

61 Untold Story of SGLT2 Inhibitors

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Abstract

The journey of SGLT2 inhibitors is unimaginable. As new trials keep surfacing, tremendous potential of SGLT2 inhibitors becomes obvious. Not only unmet needs in diabetes therapy, but also indications in non-diabetic conditions have come to light. Use in non-diabetic heart failure has given new hope. We have now evidence to prevent new onset diabetes, lowering gout risk, and new modality for NAFLD/NASH treatment. It has also become a new ray of hope for cardio-renal protection. In type 1 diabetic patients, taking SGLT2 inhibitors with insulin act as insulin dose modifier. Many other new indications might be visible in the coming days. The ever changing untold science of SGLT2 inhibitors has posed challenges for learned societies to make clear guidelines. Clearly, a diabetologist's drug group is becoming favorite of cardiologists and nephrologists.

Introduction

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2i) are perhaps the most exciting newer anti-diabetics, which now have garnered attention even beyond its traditional indication for type-2 diabetes mellitus (T2DM). The clinical dimension of SGLT2i is increasing apart from frontline metabolic, cardiovascular, and renal therapeutics.[1,2] A plethora of extra cardiac and renal effects are on the horizon and has not been told. Some of these untold stories related to beyond glycemic lowering need serious considerations after they have been found to have some unique features and indications in some landmark trials **(Tables 1 and 2)**.

Historical Perspective

SGLT2i has a remarkable history dating back more than 150 years. It was first isolated from the root bark of apple tree as a substance called Phlorizin as early as 1835. The first clue about how kidneys reabsorb glucose came in the early 1980s. The first SGLT2i, which was approved by FDA was canagliflozin in year 2013. Later dapagliflozin and empagliflozin were approved by FDA in January 2014 and August 2014, respectively. Ertugliflozin got approved by FDA in 2017. Remogliflozin is approved by health regulatory authority in India in 2019. Today SGLT2i are being successfully being used to treat diabetes by harnessing the kidneys. This journey of SGLT2i is going through an unimaginable curve showing tremendous benefits to meeting the multitudes of unmet needs of diabetic patients.

New Exciting Indications

Prevention of Diabetes

First evidence emerges by DAPA-HF trial with 32% reduction in new onset diabetes shown by Dr Inzucchi's new analysis. In non-diabetic subjects dapagliflozin reduced the risk of developing new onset type 2 diabetes. Remarkably it was 32% reduction in comparison to

TABLE 1 Twelve most emerging new vistas about SGLT2i[1,2]

12 most emerging new vistas about SGLT2-inhibitors
• Use in non-diabetic herat failure
• Evidence now to prevent new onset diabetes
• Nephrologist and cardiologist's love with SGLT2-inhibitors
• Gout-Lower risk with SGLT2-inhibitors
• Abdominal obesity
• NAFLD/NASH—A new ray of hope
• Role in controlling difficult hypertension and nocturnal non-dipping resistant hypertension
• Why not to use in type 1 diabetics for cardio-renal protection
• Opening new vist for primary cardio-renal prevention if used from beginning?
• Use as insulin dose modifier
• Reduce the risk of new-onset obstructive sleep apnea
• May reduce AF and flutter risk in type 2 diabetes

TABLE 2 SGLT2i, some unique facts[1,2]

SGLT2-inhibitors—Some unique facts
• SGLT2-inhibitors rduce eGFR decline in subjects with well-regulated diabetes mellitus, pre-diabetes or even non-diabetic CKD
• The data from recent trials show a pattern that suggests SGLT2-inhibitors are cardiovascular and renoprotective in patients with lower renal functions, in patients with lower HbA1c levels and in patients with non-diabetic kidney disease
• The first completed CVOT with SGLT2-inhibitors empagliflozin, the EMPA—REG presented at EASD Stockholm in 2015 is considred historic whcih changed the perspective of diabetes
• CANVAS study with cangliflozin was found to have doubled the risk of below-the-knee amputations and shoked the diabetes world but later studies do not substantiate it
• In December 2018, the American College of Cardiology issued an "expert consensus decision pathways" as a guide for cardiologist in using SGLT2-inhibitors and stressed for a "paradigm shift" away from just glycemic control
• Renal outcomes were secondary outcomes in the cardiovascular disease trials of the SGLT2-inhibitors, but the favorable results were just as surprising
• CREDENCE trial led Janssen pharmaceutical to apply FDA for a new indication for Canagliflozin to reduce the risk of end-stage kidney disease, the doubling of serum creatinine, and renal or cardiovascular death in adults with type 2 diabetes and chronic kidney disease
• Boehringer Ingelheim and AstraZeneca have launced new clinical trials aimed at expanding the use of their SGLT2-inhibitors beyond people who have diabetes
• In DAPA-HF trial 55% chort were non-diabetic and had only 0.003% Hb1Ac change from the base line at 4 months. In non-diabetic reduction is approximately 0.12% only
• DECLARE TIMI58 is the first trial using SGLT2-inhibitors in which hospitalization for heart failure was included in a primary endpoint

placebo. Just after 18 months, in placebo group 7.1% developed diabetes but in dapagliflozin group only 4.9% developed new onset of diabetes. Implications of this new finding need to be translated.[3]

Prevention of Non-diabetic HF

EMPA-REG OUTCOME trial, CANVAS trial, and DECLARE -TIMI 58 trial have brought new ray of hope in diabetes management. These trials brought a historic change and led to change in guidelines. Today diabetologist are saying goodbye to glucocentric concept. Needless to say, we give top priority to cardiovascular and renal protection. We want reduction in hospitalization for heart failure. In 2019 DAPA-HF trial results amazed the scientific community. It showed 26% relative risk reduction in primary end point, which was composite of cardiovascular death, hospitalization to heart failure or urgent heart failure visit in patients with. It also showed 30% relative reduction in worsening heart failure. Cardiovascular death reduction was 18%. It is worth to note that DAPA-HF constituted 55% non-diabetic cohort. Both diabetics and non-diabetics cohorts got benefitted in equal proportion. It clearly tells that dapagliflozin efficacy was not related to glycemic reduction. Even the all cause death reduction was 17%. The message is clear and loud. Dapagliflozin can be used as a novel therapeutic drug to treat heart failure with reduced ejection fraction (HFrEF), irrespective of the presence of diabetes. It is a great news for heart failure patients (both diabetic & non-diabetic population). Latest Canadian guidelines have already included this benefit and extended use of dapagliflozin in non-diabetics.[2]

Emerging as Nephrologist's Favorite to Treat Diabetic Kidney Disease

The evidence has emerged from unique RCTs and meta-analyses. In a patient with full blown kidney disease and base line eGFR up to 30 mL/min/1.73m^2, renoprotective

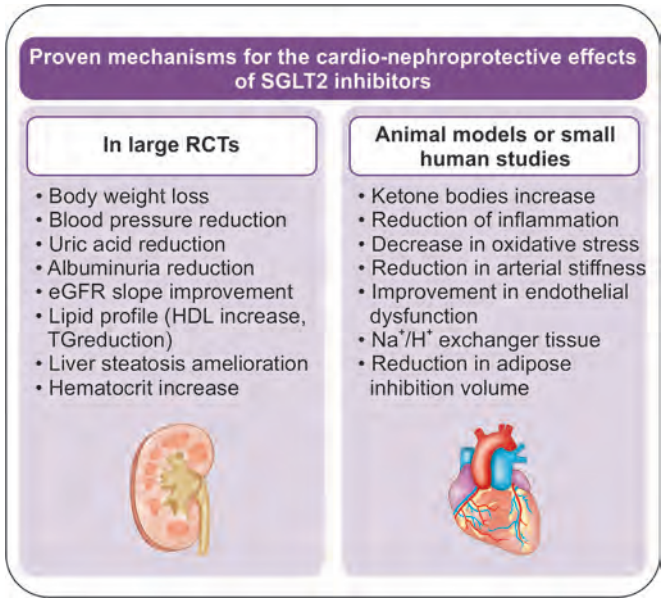
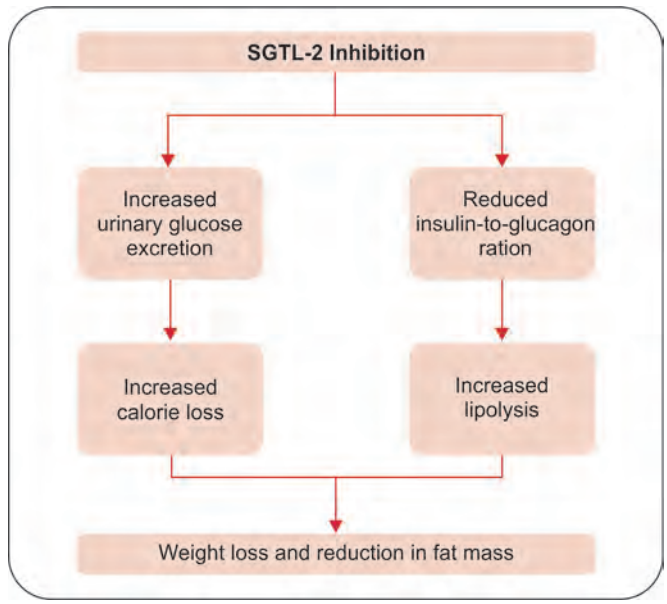


Fig. 1: Proven mechanisms for the cardio-nephroprotective effects of SGLT2i[3,4]

Flowchart 1: Proposed mechanisms of effects of SGLT2i on body weight and fat mass[6]



and cardioprotective effects of SGLT2i are maintained. Scientific societies have moved to recommend the preferential use of SGLT2i in patients with DKD. It is expected that regulatory authorities will increase the range of eGFR at which SGLT2i can be used, as well as modify the indications to include nephron protection **(Fig. 1)**.[4]

Lowering Gout Risk by SGLT2i

A meta-analysis of 62 studies, comprising 34,941 patients shows that any of the SGLT2i significantly decreased serum uric acid levels compared to control. When compared with GLP-1 RA, clear benefits of SGLT2i have been found. It was 4.9 events per 1,000 person-years in SGLT2i group and 7.8 events per 1,000 person-years in GLP-1 RA group. [HR of 0.64, 95% CI, 0.57–0.72]. Empagliflozin resulted in superior reduction. SGLT2i might be beneficial for diabetic patients with hyperuricemia as per this meta-analysis.[5]

Abdominal Obesity

Now it is well known that SGLT2i reduces body weight and visceral opacity. They also reduce ectopic fat deposition. Thus, they improve adipose tissue function. We have today an evidence-based therapeutic option for management of overweight and obese patients having type 2 diabetes **(Flowchart 1)**.[6]

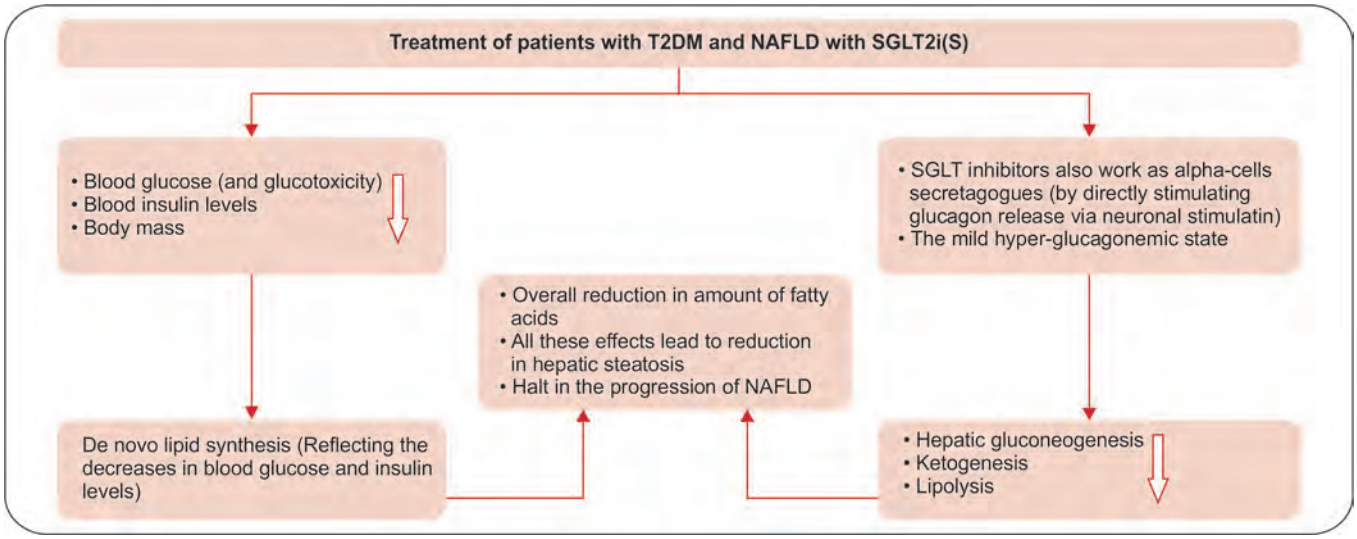
Evidence in Hypertension

SGLT2i can bring modest reduction in blood pressure. Most of studies point that 5–6 mm Hg reduction in systolic blood pressure occurs. The diastolic blood pressure reduction has been found 1–2 mm Hg. This reduction is not dependent on blood sugar control. Initial reduction is due to diuretic mechanisms. Improvement of vascular stiffness could be another mechanism later on. Interestingly SGLT2i could be beneficial in difficult to control hypertension. Non-dipping resistant hypertension is a very difficult situation in day-to-day practice. Now, SGLT2i have been found to modulate such cases. It is worth to note that SGLT2i mediates osmotic diuresis. It leads to more electrolyte-free water clearance. Thus, more prominent fluid loss from interstitial spaces ensues.[7,8] No sympathetic nervous system activation occurs while reducing blood pressure by SGLT2i. This is in contrast to GLP-1 RA, which cause increase in heart rate. Reduction in preload and afterload is unique to SGLT2i. It is thus beneficial in reducing cardiac work load and also myocardial oxygen demand. Nevertheless, BP reduction is unlikely to explain all cardiovascular benefit.[9]

Use in NASH/NAFLD

SGLT2i are showing promising results in non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver

Flowchart 2: Proposed mechanisms of effects of SGLT2i on NAFLD and NASH[10]



disease (NAFLD). Various studies have already shown that SGLT2i improve serum level of liver enzymes, decrease liver fat, and fibrosis. And also, improvement in various metabolic parameters in type 2 diabetes patients with NAFLD. Many more studies are on the way in this aspect and indicate that SGLT2i should be used for all NASH, NAFLD cases at least in diabetics. We have to watch for more studies, research in cases of non-diabetics as well **(Flowchart 2)**.[10]

SGLT-2i in Type 1 Diabetes

At present SGLT2i are being used as off label drug in type 1 diabetes although some recent trials like DEPICT 1,2. EASE 1,2,3, and in-Tandem 1,2,3 clearly head to new indication to use SGLT2i with insulin in type 1 diabetes. In future SGLT2i may be included in guidelines to enable people with type 1 diabetes to achieve their glycemic goals. Dapagliflozin has credit to being the first SGLT2i to be approved in Europe. It has got approval from NICE (National Institute for Health and Care Excellence, UK) and SMC (Scottish Medicines Consortium) as an adjunct to insulin for people with T1DM if glucose levels are not adequately controlled with insulin alone. SGLT2i should be avoided if high risk of DKA is suspected. It should be used with utmost care if patient has difficulty in adhering to insulin regimen or having difficulty understanding and following treatment instuctions.[11] European Medicines Agency (EMA) approved dapagliflozin for use in some patients of type 1 diabetes but FDA has not approved it in the USA. Ipragliflozin has been approved in Japan for use together with insulin in adult with type 1 diabetes. The dual SGLT2i, sotagliflozin has shown improvements in Hb1Ac, weight loss and systolic blood pressure and reduction in insulin dose when added to insulin therapy.

Primary Prevention of Cardiorenal Complications in T2DM

It is now a proven fact that SGLT2i have a great affect in reduction to hospitalizations due to heart failure. DECLARE-TIMI58 trial data has thrown light that dapagliflozin has tremendous benefits in primary prevention. Taken together, cardiovascular death and hospitalization due to heart failure (HHF), we have now exciting data. The relative risk reduction in CV death was 17% and in HHF it was 27% in DECLARE-TIMI58 trial. ACC subgroup analysis further suggested and showed 16% reduction in MACE in subgroup analysis. Further, subgroup analysis of DECLARE-TIMI58 trial showed a reduction of 47% in renal outcomes. In nutshell, these drugs have shown a great promise in primary prevention of cardiorenal complications by dapagliflozin.[12]

Use in HFpEF

SGLT2i are yet to show proven benefits in HFpEF patients. Some important trials are on the way—DELIVER and

DETERMINE-preserved trials with dapagliflozin and EMPEROR-preserved and EMPERIAL-preserved with empagliflozin. It shall be a landmark development and another big feather in cap of SGLT2i if these trials show positive trend.[13]

Some Emerging Indications

- In cases of artificially-induced syndrome of inappropriate ADH secretion (SIADH), DIVE study has been done. It was done with empagliflozin. It gives an insight that SGLT2i can be used in diseases, which are associated with hyponatremia. It is so due to its effect on free water clearance.[14]
- In polycystic ovarian syndrome (PCOS), use of SGLT2i resulted in weight loss and anthropometric parameters also improved. This was shown in a small study. When metabolic and hormonal outcomes were compared with metformin, no significant difference was seen.[15]
- Now a very interesting data has emerged showing that empagliflozin can be very useful in reducing the requirement of insulin by 59%. This paper was presented at ADA virtual meeting 2020 (new-initiation of insulin, or >20% increase in insulin requirement in EMPA REG OUTCOME study). It appears SGLT2i are emerging as insulin dose modifier![16]
- The risk of new onset obstructive sleep apnea can be reduced by SGLT2i. In EMPA REG OUTCOME study, this risk was reduced by 52%. This data was presented at ADA 2020 virtual meeting.[5,17]
- In type 2 diabetes cases, dapagliflozin has been shown to reduce the risk of atrial fibrillation and flutter. In a new study it has been shown. Its effect remained consistent. There was not much effect on this regardless of previous history of atrial fibrillation, atherosclerotic cardiovascular disease or heart failure.[18]

Under-Prescription and Cost-Effective Issues

In spite of being rated among as only anti-diabetic oral drugs capable of cardiorenal prevention and having potential for primary prevention, SGLT2i remains under-

TABLE 3 DARE-19 trial[21]

Why they have DARE-19
• AstraZeneca and Saint Luke's Mid America Heart Insititue have initiated Phase II DARE-19 trial (completion date - December 2020) with Farxiga in COVID-19 patients
• An international, parallel-group, randomized, double-blind, placebo-controlled, investigator-sponsored phase III trial evaluating the efficacy and safety of Dapagliflozinin addition to background local standar of care therapy, on the riks of all-cause death or disease progression and complications in adults who are hospitalized with COVID-19
• They include 900 sickets patients of COVID with patient's history of at least one of the following: – Hypertension – T2DM
– Atherosclerotic cardiovascular disease
– HF and/or
– CKD state 3 to 4 (*eGFR ≥25 mL/min/1.73 m)
• There is a growing argument that dapaglifolzin, in particular, has shown to decrease lactic acidosis and thus has the potential to reverse acid-base balance inside the cells during hypoxi, which can prevent cell injury during the cytokine storm of COVID-19 illnes, in patients with diabetes
• Both pre-clinical and clinical studies suggest that SGLT2i may favorably impact the underlying mechanisitic processes dysregulated in the setting of acute major illness (such as COVID-19) and include favorable effect on endothelial function, inflammation, oxidative stress, tissue hypoxia, energy metabolism, and autophagey
• Some view it as a dangerous proposition as ketoacidosis in COVID-19 is associated with hypercoagubility

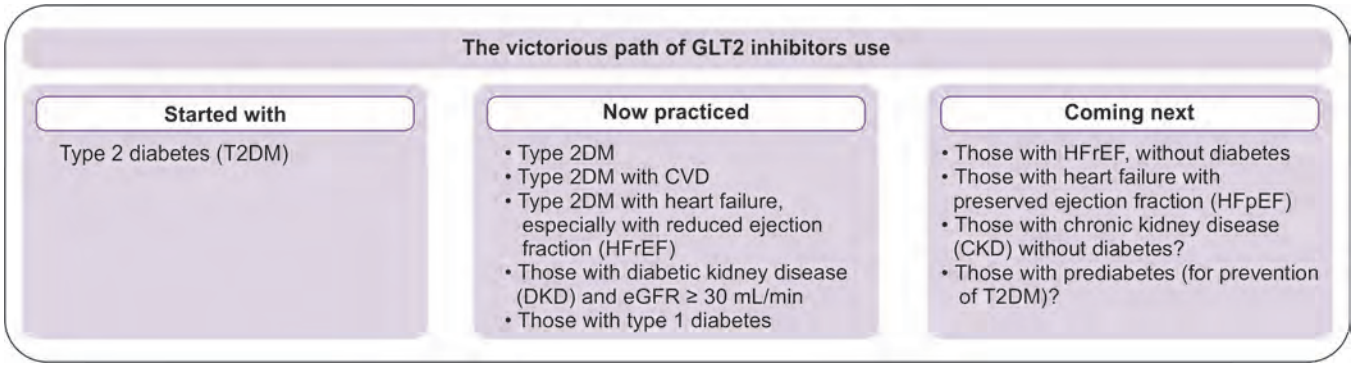


Fig. 2: The victorious path of use of SGLT2i[13]

prescribed worldwide. In the USA in patients with diabetes and CVD only 9.3% were prescribed SGLT2i as per one study.[19] As a matter of fact these are significantly cost-effective in long term by preventing cardiovascular and renal complications.

Class Effect Dilemma, are all SGLT2i not Same?

Much awaited VERTIS CV (ertugliflozin CVOT trial) was presented at ADA virtual meeting 2020 on 16th June. VERTIS CV trial did not superiority for MACE and cardiovascular death. Although the cohort population was almost similar to EMPA REG outcome trial.

There was a trend for lower HHF risk among ertugliflozin-versus placebo, with rates 2.5% versus 3.6%, but the difference was not statistically significant due to hierarchical testing sequence used. Still consistent class effect in HHF can be interpreted. It is worth to note that MACE reductions were only statistically significant only for empagliflozin and canagliflozin.

Now this trial gives suspicion that all SGLT2i are not the same. Many factors might be operating. No clear-cut answer exists. Some of debated factors are—a difference in patient population between trials, a true biological difference in drug efficacy or any other factor might be operating.[20]

DARE-19 Study with Dapagliflozin in COVID-19

You can raise your eyebrow. While consensus today is to stop SGLT2i due to fear of DKA in COVID-19, DARE-19 trial is daring to use SGLT2i in COVID-19.

Final results are expected in March or April 2021 **(Table 3)**.[21]

Conclusion

Usual indications of SGLT2i keep changing in light of latest clinical trials. Some stories are well known but immense potential has not been yet explored. SGLT2i which started its anti-diabetic journey with huge controversies has now emerged as an amazing weapon to fight not only in prevention of secondary cardiorenal complications but also in primary cardiorenal protection along with hosts of other metabolic disorders. Many new indications are emerging and these must be considered in clinical perspective **(Fig. 2)**.

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CHAPTER

62 Evolution of Insulin: Old Insulin versus Insulin Analogs

Arvind Gupta, Banshi Saboo

Abstract

Insulin was available for the treatment of diabetes for human use for almost 100 years after the discovery in 1921by Prof. Macleod and Dr. Fredrick G. Banting with the help of Dr. Charles Best and Prof. J.B. Collip. The different types of insulins available today are the fruits of various innovations and modern state of art DNA recombinant technology. Evolution of insulin has been shown to start from crude animal extract insulins to the recent pure and precisely controlled formulations of insulin analogs. The modifications of the insulin formulation and of the insulin molecule have made it in such a way that approximate the natural endogenous insulin secretions. These modern designer insulins provide the peak less basal level of insulin or mimicking the spikes of meal insulin release. We have discussed in this review how pharmacokinetics and pharmacodynamics of old insulin molecules have been modified to be converted into modern new insulins. Hence, various insulin formulations like rapid-acting, short-acting, intermediate-acting, and long-acting insulins, as well as mixtures and concentrated formulations have been produced.

Introduction: Evolution of Insulin

The management of diabetes has changed significantly over the past century after the discovery of insulin around the year 1921.[1] Insulin was invented by Frederick Banting, John Macleod, and Charles Best from animal pancreas.[2] The earliest insulin preparations were largely animal-based, having either bovine or porcine origin. Eli Lilly was the major producer of animal-based insulin, which soon started falling short with the demands. To overcome this, insulin analogs gradually emerged in the picture. The main objective for developing analogs was to prolong the duration of action of insulin, which required several shots during the day. Achieving this, in the year 1983, the use of recombinant human insulin was approved, and insulin analogs were gradually developed.

Newer types of insulin or insulin analogs offer better replacement of insulin because of closer simulation to the human physiology. When compared with regular insulin, insulin analogs such as lispro, aspart, and glulisine have faster onset of action. Other analogs like glargine and degludec have longer duration of action. Both of these types have evidenced reduction in the risks of hypoglycemia.[3] The most recent advancement in insulin has been the development of the insulin pen device, which allows better patient compliance and thereby corresponds with fewer side effects. It was developed in the year 1985 marking the era of better glycemic control for patients.

This chapter compares the old types of insulin with newer insulin formulations or insulin analogs. The discussion will be along the lines of safety and efficacy and will be supported by trial data and pharmacokinetic studies.

Old Insulin

Earliest preparations of human insulin were extracted from human cadaveric pancreas (refer to **Figure 1** for its

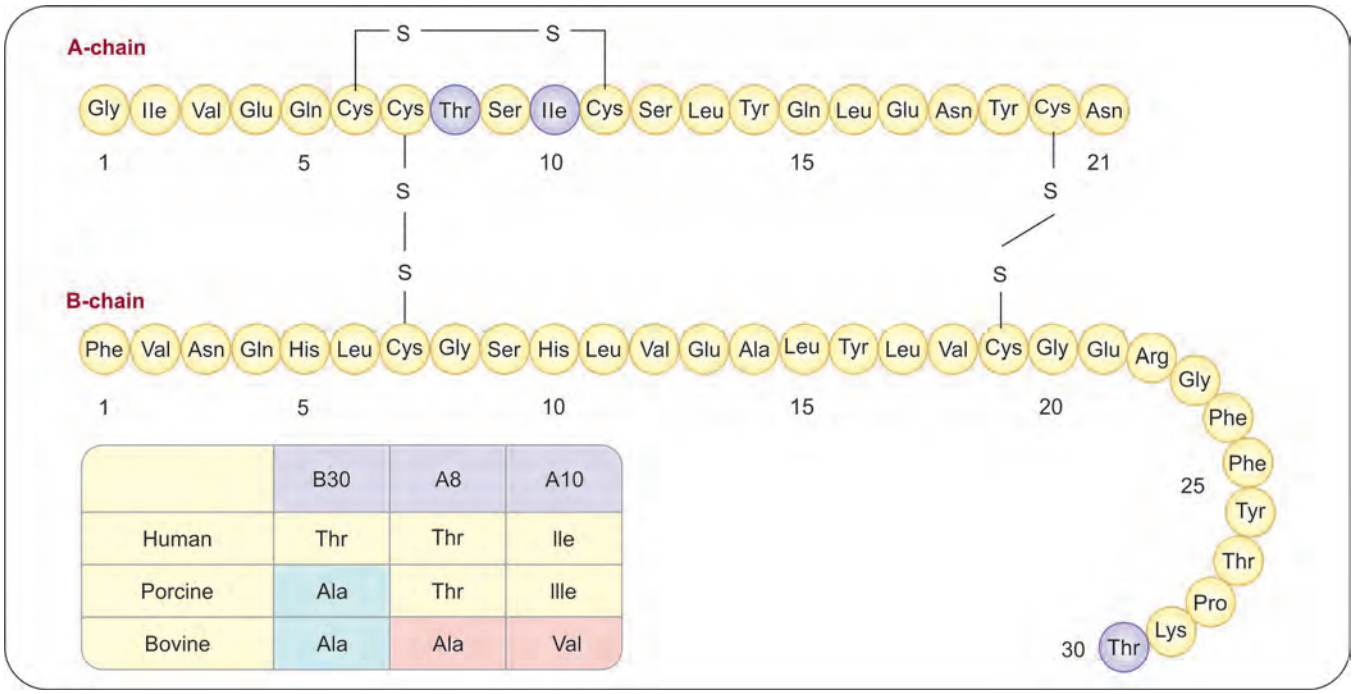


Fig. 1: Structures of animal and human insulin—old insulin types

structure) and its use was limited because of the risk of allergic reactions and lower availability. The first synthetic human insulin that was biologically equivalent to the hormone required significantly higher time and costs for production and also had lower rates of productivity (6–10%) thereby not offering higher success in terms of glycemic control of the patients. With subsequent productions, these drawbacks and side effects were gradually met.

Regular (rapid-acting), neutral protamine hagedorn (NPH) (intermediate-acting) and premixed insulin (long-acting)[4] are human insulin preparations that are now also prepared by recombinant DNA technology. They have a slow onset of action (peak after 3 hours of dosage) and may also have variability in their effects resulting in a lower predictability of the clinical outcomes of the patient.

Human insulin formulations, particularly, intermediate-acting types like NPH (reaches a peak after 4–6 hours of administration) have a major limitation concerning the risk of hypoglycemia.[5] Most particularly, nocturnal hypoglycemia is common in patients receiving this type of insulin. So, human insulins are not preferred for long-term use in patients for the stabilization of their HbA1c profiles. But, their combination with new insulin analogs supports better glycemic control in some patients and they are thus not completely obsolete.

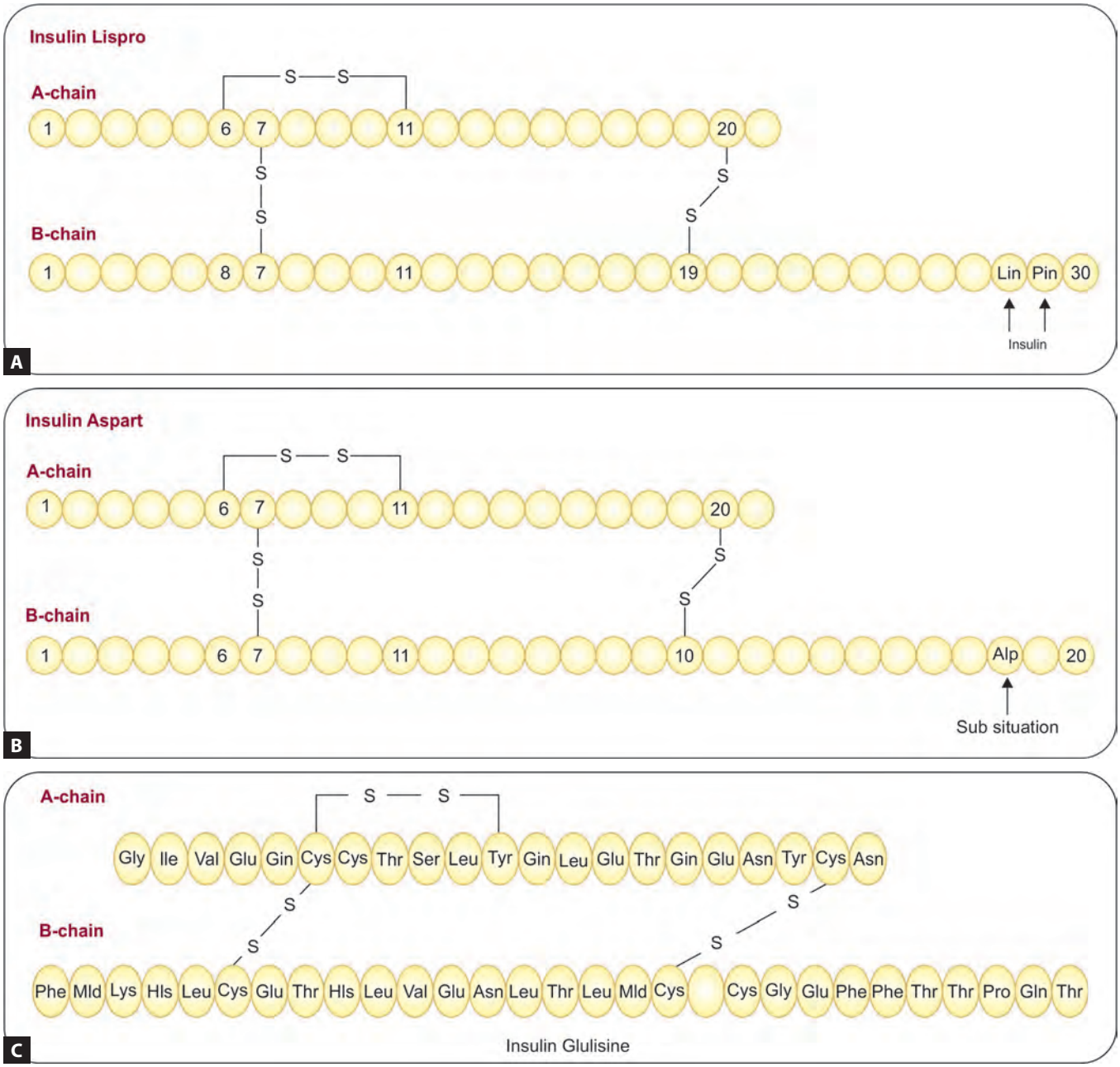
New Insulin

Insulin analogs were formed with the help of recombinant DNA technology in the presence of either *Escherichia coli* or *Saccharomyces cerevisiae*. Analogs are produced with altered pharmacokinetic and absorptive properties through the modification of binding affinity for insulin and insulin-like growth factors to meet the drawbacks of human insulin such as slow onset and limited efficacy or duration of action.

Rapid-acting Analogs

Insulin analogs such as insulin lispro (Humalog), insulin aspart (Novolog), and insulin glulisine (Sanofi) function as rapid-acting agents having a faster onset of action **(Figs. 2A to C)**.

When compared with regular insulin, rapid acting insulin had lesser risk of both postprandial hypoglycemia and nocturnal hypoglycemia thereby having a better safety profile. HypoAna trial of type 1 diabetic patients showed that treatment of patients with insulin detemir and aspart was associated with a 66% lower risk of nocturnal



Figs. 2A to C: Structures of insulin lispro, aspart, and glulisine

hypoglycemia when compared with human insulin. Other than HypoAna, 17 other clinical trials conducted worldwide have evidenced this effect.

Findings from systematic review and meta-analysis intended to compare the safety and efficacy of rapid-acting insulin analogs with regular insulin have demonstrated similar results. Insulin analogs were found here to reduce 7% of total hypoglycemic episodes, 32% of severe hypoglycemic episodes, and they also reduced nocturnal hypoglycemia by 45%.

Other than reducing hypoglycemia, the use of rapid-acting insulin analogs over prolonged periods led to more stabilized blood sugar levels because of the capability of rapid-acting insulin to closely imitate the properties

TABLE 1 The onset, peak, and duration of action of rapid-acting insulins

Insulin type	Onset (min)	Peak (min)	Duration (h)
Insulin lispro	5–15	30–40	4–6
Insulin aspart	5–15	30–90	4–6
Insulin glulisine	10–20	30–90	4–6[6]

TABLE 2 The onset, peak, and duration of action of long-acting insulin analogs

Insulin type	Onset (h)	Peak (h)	Duration (h)
Insulin degludec	1–2	No peak	>42
Insulin glargine	2–4	No peak	Up to 24
Insulin detemir	2	No peak	Up to 24

of insulin hormone in its physiological state.[7] Since postprandial fluctuation of blood glucose levels is primarily responsible for 50% of the hypoglycemic episodes and rapid-acting insulin prevents these episodes, it also results in better patient compliance to the treatment, which determines long-term glycemic control.

In a study comparing the rates of patient compliance, it was found that while only 7% of the patients adhered with the administration protocol of regular human insulin 30 minutes before their meals, for insulin lispro, the compliance rate was as high as 98% due to a more flexible protocol (0–15 minutes before meals).[8] This is a significant advantage favoring better treatment efficacy with the use of insulin analogs **(Table 1)**.

Indian data also depicts similar advantages of insulin lispro and other rapid-acting agents over regular human insulin. It confirms that the use of rapid-acting insulins more effectively manages postprandial spike in blood glucose levels and is thus associated with better glycemic control due to flexibility offered with both meals and insulin dosage.

Long-acting Analogs

Glargine and degludec are soluble long-acting analogue, which have a long duration of action (24 hours or more) **(Table 2)**. They are newer forms of insulin analogs and have also been labeled as second-generation insulin analogs **(Fig. 3)**.

Because of a long duration of action, insulin glargine only needs to be administered once daily resulting in a much higher rate of patient compliance. Since it does not have a distinct peak of action, it also has a lower risk of hypoglycemia. When compared with human insulin formulations, insulin glargine has depicted lower risk of hypoglycemia in clinical studies. At similar HbA1c levels, patients receiving glargine were found to have fewer episodes of nocturnal hypoglycemia when compared with patients receiving NPH insulin because of its favorable pharmacodynamic and pharmacokinetic properties.

As per the findings of a meta-analysis report of 15 clinical trials, it was determined that insulin degludec was superior to insulin glargine.[10] This can be attributed to its long-lasting basal insulin actions, which have twice more duration of effect than glargine, and much lower individual variability. Degludec can be administered at any time of the day without the risk of hypoglycemia in subjects, and can also be carefully combined with other types of insulin analogs such as aspart for managing the individual treatment needs of the patient. Further, it was stated that degludec resulted in lower rates of hypoglycemia in both type 1 and type 2 subjects.

The effectiveness of insulin analogs can also be judged through the results of clinical trials in insulin-naïve patients. CONFIRM trial, a large-scale non-interventional trial analyzing data from 4,056 patients depicted that the administration of degludec/glargine U300[11] significantly improved HbA1c profiles of adult type 2 diabetes patients (refer to **Table 3** to understand the implications of diabetic control on the overall health status of the patient). Further, the administration of long-duration insulin analogs even lowered the risks and frequency of hypoglycemia as well as it minimized the possibility of treatment discontinuation, which is a common finding in insulin-naïve subjects.

Compared with IGlar, IDeg is associated with equivalent glycemic control and a statistically significantly lower rate of nocturnal hypoglycemia in patients with T1DM and T2DM. In T2DM patients, IDeg also provides better results in terms of overall hypoglycemia.

Critical View of Old Insulin versus New Insulin

Human insulin is considered to be less superior to newer insulin formulations in managing blood glucose levels of the patient as well as in reducing the risks of hypoglycemia,

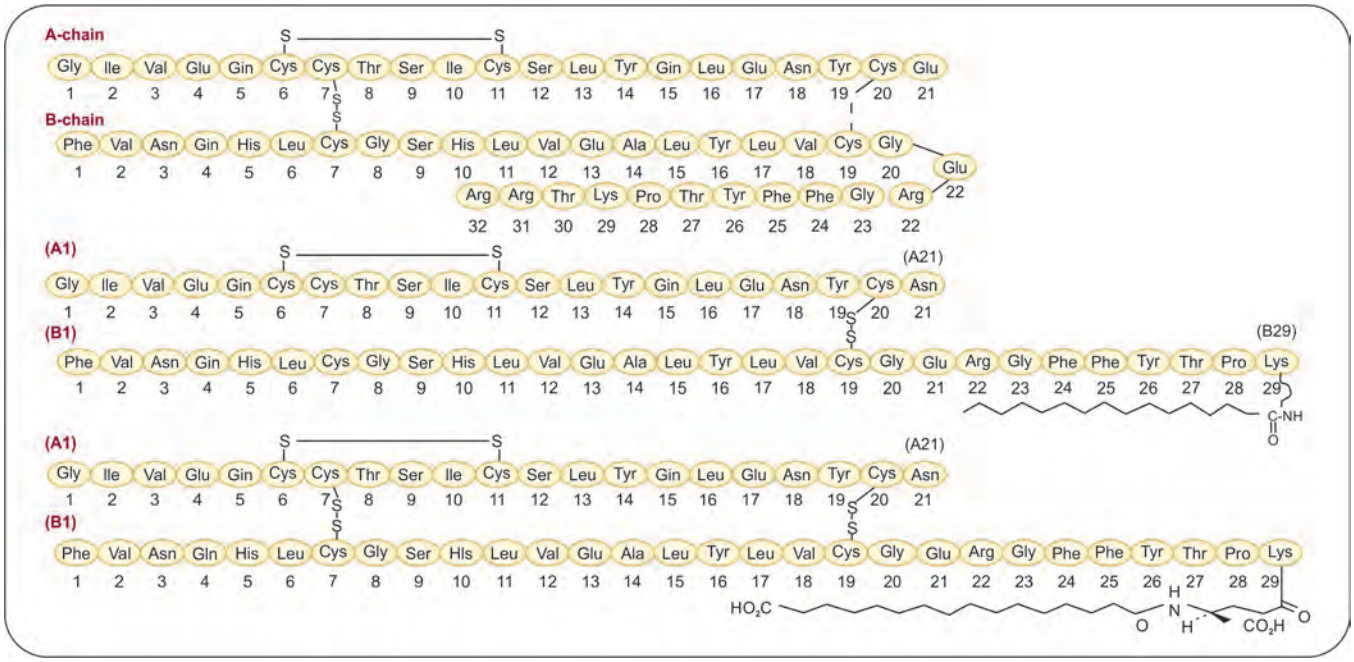


Fig. 3: Structures of insulin glargine, detemir, and degludec[9]

TABLE 3 Long-term effects of better HbA1c control on patients with type 2 diabetes

Risks	*Risk reduction for each 1% reduction in HbA1c levels*[12]
Death due to diabetes/diabetic complications	21%
Microvascular complications	37%
Risk of amputation due to diabetes or peripheral vascular disease	43%
All-cause mortality	12%
Myocardial infarction	14%
Stroke	12%
Heart failure	16%

which is a major concern hindering the long-term management of diabetes. Despite this, a recent clinical trial involving 40 pediatric type 1 subjects affirmed that regular and NPH insulin showed similar efficacy to insulin glargine and aspart.[13] In terms of glycemic control, it was noted that HbA1c levels were similar for both the groups of patients. While fasting blood glucose was better controlled for the group assigned to the glargine treatment, the result was not statistically significant implicating that human insulin could be as effective as newer insulin analogs. However, since this was a small-scale study involving only pediatric subjects and the risk of hypoglycemia was not evaluated at all, no derivations can be made in the favor of traditional insulin formulations over new insulin on the basis of this singular trial.

Because of this, it has been largely debated whether insulin analogs are better than regular or NPH insulin keeping in mind the clinical outcomes of the patient and their pre-existing awareness of old insulin. In this regard, greater evidence has been found in the favor of the use of insulin analogs when compared with regular or NPH insulin. This is because of its ability to reduce nocturnal hypoglycemia by 48% when compared with NPH, as well as severe hypoglycemic effects in patients compared with regular insulin. Both in type 1 and type 2 diabetes, detemir has proven to be better than NPH in several studies of 16–52 weeks of duration since it does not contribute to weight gain in patients.

Comparison among Insulin Analogs

Insulin degludec is an emerging treatment agent, which has is so far considered to be superior to human insulin

and analogue insulin. Findings from the multi-Centre, multi-national randomized controlled study BRIGHT trial are awaited to state with certainty that which of the insulin analogs is the most superior.

According to the large-scale blinded randomized control trial ORIGIN,[14] optimal stabilization of fasting blood glucose levels of patients and a high rate of adherence to the treatment (85%) was found with the use of degludec. Furthermore, the previous claims of the risk of cancer and cardiovascular complications with the use of insulin analogs were largely refuted by this trial. However, the risk of hypoglycemia was higher in the glargine arm when compared with the placebo, which is a considerable risk for the patient.

Insulin degludec when used alone is associated with lower risk of hypoglycemia in both type 1 and type 2 subjects as per the findings of several phase 2 trials.[15] It also has a low variability and thus is a safer alternative for individuals with blunted hypoglycemic awareness. Despite its benefits, one of the risks of insulin degludec is that it is an ultra long acting type and can be a potential risk for patients with renal or hepatic impairment. Overcoming this drawback, recent trial studies have demonstrated that the combination of degludec with rapid-acting insulin such as aspart results in significantly lesser hypoglycemia and can be regarded a safe alternative.

Pre-mixed formulations combining lispro and aspart have also been recently available, but their use is not recommended over other types of insulin.[16] This is because of their highly rigid dosage structure, which interferes with the lifestyle activities of the patient and elevates their risk of hypoglycemia. It can only be administered in elderly patients or those with social problems where maintaining A1c levels less than 7.0% is not of utmost priority. Even in them, it must be used cautiously.

Insulin Pen Devices

According to the consensus guidelines of diabetic management experts in India, insulin pen devices have considerable advantages over the conventional vial and syringe methods because of better patient compliance and higher accuracy of administration achieved through its use. FlexPen offers lower injection force and dose force and is thereby associated with fewer side effects such as pain. On the other hand, NovoPen offers higher treatment accuracy. Regardless of the insulin delivery system used, pen devices, overall, facilitated about 2.1% higher reduction of hypoglycemia when compared with vials and syringes.[17]

Conclusion

New insulin or analogue insulin including both rapid-acting and long-acting analogs are better than older insulin such as regular insulin or NPH. They correspond with better glycemic control (both HbA1c and fasting) and lower risk of hypoglycemic events, most particularly nocturnal or postprandial hypoglycemia. This concludes that insulin analogs have a higher safety and efficacy than old insulin and is also associated with better treatment compliance by the patient due to flexibility of treatment offered to them. Among insulin analogs, degludec is the most promising agent having a long duration of effect and no apparent peak. However, a combination of degludec and aspart is recommended in patients as a safer alternative.

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CHAPTER

63 Insulin Regimens for Initiation in Type 2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) has emerged as the global epidemic. It is a relentlessly progressive disease resulting in various dreadful complications. These complications, however, can be delayed/prevented by modifying risk factors and optimizing glycemic control. The optimization of glycemic control often requires using multiple pharmacological agents including oral antidiabetes drugs (OADs) and insulin. Insulin has the unmatched HbA1c lowering capacity. Therefore, in clinical situations where achieving HbA1c goal has not been possible despite using multiple OADs, insulin initiation seems logical. A basal regimen may be ideal to start with because of its simplicity and favorable impact on weight and lower risk of hypoglycemia. However, intensification of this regimen may be required later to maintain proper glycemic control.

Introduction

There is a tsunami of diabetes mellitus sweeping across the globe. In 2019, approximately 463 million adults (20–79 years) were living with diabetes. By 2045 this figure is likely to rise to 700 million.[1] Type 2 diabetes Mellitus (T2 DM) accounts for around 90% of cases. Nearly 1 million Indians die due to diabetes every year. T2DM has emerged as a major cause of blindness, stroke, heart attacks, kidney failure, and lower limb amputations. So T2DM is a chronic progressive disease associated with multiple complications that can be prevented or delayed by modifying risk factors and attaining proper glycemic control. UKPDS shows that at the time of diagnosis β-cell function is already markedly compromised by up to 50%, with β-cell function continuing to deteriorate in the years following diagnosis. So β-cell function progressively declines in T2DM, and there is increasing difficulty in maintaining glycemic control. In many patients, achieving HbA1c goal may not be possible despite using multiple OADs.[2]

Due to unprecedented explosion in the number of cases of T2DM globally, diabetes-related complications are posing a major challenge both at the individual and social level. Insulin initiation early in the course of disease may be an important measure to meet this challenge.[3] Unfortunately, clinical inertia exists and insulin is used quite late despite the benefits of timely glycemic control and guidelines encouraging earlier use of insulin. That is one important reason for increase in complications in T2DM. There are *several barriers* to initiation of insulin—both at the levels of the patient and the treating physician.[4] At the level of patients, important factors are—fear of injections, risk of hypoglycemia, difficulties in managing insulin therapy. Physicians also contribute to clinical inertia by their concerns about potential side effects (particularly hypoglycemia), difficulties in training patients and absence of clear-cut guidelines. However, early institution of insulin therapy has shown beneficial effects on β-cell function and may cause remission in various studies.

Ryan et al. demonstrated in a study that if insulin is used early in the course of disease even for a short period of 2–3 weeks to achieve intensive glucose control, it may cut down glucotoxicity drastically. This may lead to improvement in β-cell function and high-remission rates even at the end of 1 year.[5]

In a landmark multicentric randomized study, Weng et al. compared the effects of short-term intensive control of blood glucose by multi-dose injections of insulin or CSII (continuous subcutaneous infusion of insulin) versus effects of multiple OADs. The insulin group showed marked improvement in β-cell function. In addition the insulin group also showed significantly higher remission rates even at the end of 1 year.[6]

In another important metaanalysis, Krammer et al. demonstrated that intensive insulin therapy for even a short period of 2–3 weeks had a positive impact on glycemic control, insulin resistance, and remission rates.[7]

Most patients with T2DM have inadequate glycemic control on one or more oral antidiabetes drugs (OADs). In these circumstances, it may be a vital decision to add another OAD or initiate insulin.

It is well known that insulin has the greatest and unparalleled glucose lowering effect. While OADs have limited capacity to decrease HbA1c by around 1–1.5% only. So patients with HbA1c of 8.5% or higher are good candidates for insulin initiation. Indian (RSSDI-ESI) guidelines suggest that insulin should be considered in those T2DM patients who have failed to achieve normal glycemic control despite using three OADs. These guidelines also recommend insulin initiation in significant hyperglycemia (fasting plasma glucose more than 270 mg/dL or HbA1c more than 9%) and patients having symptoms of polyuria, polydipsia, polyphagia, and loss of weight. RSSDI-ESI guidelines also advocate use of insulin in unstable states, severe infections, and ketosis. Patients put on insulin need to be monitored and titrated. In selected cases intensification of insulin regimen maybe done.[8] One important thing to keep in mind is that OADs should not be suddenly stopped on initiating insulin therapy because of the risk of rebound hyperglycemia.[9]

Before discussing the different insulin regimens for T2DM, it may be worthwhile to know insulins, which are readily available in Indian market and their duration of action, onset, and peak of action **(Table 1)**.

Analogues may be preferred because of less risk of hypoglycemia particularly during night. However, cost consideration is also very important in poor country like ours. Education/counseling about timing and monitoring of different insulins to the patient is very important.

TABLE 1 Insulins available in Indian market

Type of insulin	*Preparation of insulin*
Rapid acting insulin	Lispro
	Aspart
	Glulisine
Short acting insulin	Regular/soluble insulin
Ultra-fast acting insulin	Aspart (Fiasp)
Intermediate acting insulin	NPH or isophane insulin
Long acting insulin	Glargine Detemir Degludec (longest acting) Toujeo (Glargine-300 U/mL)
Premixed human insulin	30% Regular plus 70% NPH 50% Regular plus 50% NPH
	25% Lispro plus 75% NPL 50% NLP 50% Lispro 30% aspart plus 70% protamine aspart

NPH, neutral protamine hagedorn; NPL, neutral protamine lispro

OADs During Initiation of Insulin

Continuing OADs should be considered during initiation of insulin. Combination of therapies not only lowers daily insulin requirement but results in effective HbA1c reductions. Combination of most of OAD with insulin is usually safe and effective. In analysis of different studies—no increased risk of adverse effects was evident on combining insulin with OADs with few exceptions. When insulin is used with pioglitazone, there are more chances of fluid and water retention, edema, and weight gain.[10] So one needs to be very careful and pioglitazone is better avoided. There is more chances of gastrointestinal disturbances if insulin is used with acarbose.[11] Combination of insulin with sulfonylureas/secretogogues are better avoided because of the increased risk of hypoglycemia.[12,13]

However, it is known that glycemic and metabolic control can improve morbidity and mortality in T2DM, the impact of insulin and different regimens on cardiovascular outcomes remains unknown.

Basal Insulin Regimen

Adding once a day, long acting basal insulin to the OADs will help achieve not only optimum glycemic control but

also may prove to be easy for early facilitation to insulin in T2DM. Once a day basal insulin regimen is effective and safe in patients with T2DM with HbA1c of 8.5%. For this purpose, NPH insulin (once or twice a day) may be used. Alternatively a long acting analogue insulin—detemir, glargine, or a newer insulin like degludec or toujeo (high strength insulin glargine 300 U/mL) may be used. It has been found useful for symptom relief if tight control is not a major issue. Potentially there is less weight gain and less frequency of hypoglycemia. The starting dose may be 10 units/day or 0.1–0.2 U/kg/day and is titrated by 10–15% or 2–4 units to optimize fasting plasma glucose level.[11]

The advantages of long acting analogue insulins particularly degludec over NPH insulin are longer half-life, lesser glycemic variability and lower incidence of nocturnal hypoglycemia.[14]

Due to its flatter curve and lesser day-to-day variability, degludec promises to reduce risk of hypoglycemia as compared to other basal insulins. DEVOTE study demonstrated non-inferiority of degludec over glargine as far as cardiovascular outcome is concerned. At the same time there were significant reductions in the episodes of hypoglycemia particularly nocturnal ones in patients taking degludec.[15]

Basal-plus Insulin Regime

When a rapid acting bolus insulin is added before the main meal of the patient who is already on basal insulin regimen it is known as "basal-plus" strategy.[15] This may be an effective step to insulin intensification before implementing the gold standard basal bolus regimen. Careful evaluation of the patient's life style, eating habits, and self-monitoring of glucose are important for adopting this regimen.[16]

Basal Bolus Regimen

Basal bolus regimen is invaluable in uncontrolled severe hyperglycemia, and in life threatening or organ/limb threatening clinical situations. This regimen comes closest to normal physiological pattern of insulin secretion from a healthy pancreas. In this, long acting basal insulin takes care of the metabolism in the fasting state, whereas the rapid acting insulin prior to meals takes care of postprandial surge of glucose.[17] Fifty percent of the total calculated insulin requirement is taken as basal insulin and rest 50% is distributed before major meals as bolus insulins. However, patients require education and counseling regarding self monitoring of blood glucose (SMBG), and carbohydrate insulin ratio and management of hypoglycemia.[18]

Insulin dose adjustment is done as shown in **Table 2**.

TABLE 2 Insulin dose adjustment according to SMBG during insulin therapy

Type of insulin	*Time of SMBG*
Basal insulin	Fasting blood glucose before breakfast
Pre-breakfast bolus insulin	Blood glucose 2 hours after breakfast or before lunch
Pre-lunch bolus insulin	Blood glucose 2 hours after lunch or pre-dinner
Pre-dinner bolus insulin	post-dinner or bedtime blood glucose

Premix Insulin Regimen

Premixed insulins are fixed premixed formulations of short-acting or rapid insulin and intermediate- or long-acting insulin for control of both fasting and postprandial glucose. These formulations may be a combination of short and long acting conventional human insulins or short and long acting insulin analogues. Premix insulin formulations are useful for those patients who have consistent lifestyle and find it difficult to count carbohydrates. They may be started as once or twice daily and intensified to three times a day in some cases. Premixed regimen has less complicated & less demanding glucose monitoring. Initiating with premix insulins offers improved efficacy and safety and offers the advantage of simplicity. Insulin analogues offer more predictable onset of action and lesser incidence of hypoglycemia. In some studies they have shown better glycemic control particularly postprandial glucose.[19]

Conclusion

T2DM is a chronic progressive disease associated with decline in β-cell function and multiple complications. Proper glycemic control is important to slow down or prevent the process. Insulin has shown maximum efficacy in reducing HbA1c and early insulin therapy can help reduce long-term complications. There are different insulin regimens to choose according to

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the individual characteristics and factors of the patient. Basal insulin regimen is simple, effective, and easy as augmentation therapy with OADs. Later intensification may be required. Treatment needs to be individualized based on discussion with the patient and his family members on glucose control, cost, side effects, and QOL (quality of life) while choosing optimum insulins and regimens. Premix insulins have the advantage of simplicity in patients with routine life style and consistent eating pattern. Basal bolus regimen offers optimum flexibility in terms of diet and activity but it requires multiple insulin injections, is more complicated to support and teach and needs knowledge of carbohydrate counting. Problems of hypoglycemia and weight gain need to be kept in mind. So full patient motivation is required with regular monitoring of blood sugar.

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CHAPTER

64

CGM Guidelines in 2021

Amit Gupta, Saurabh Srivastava

Abstract

Until recently mainstay of blood glucose monitoring was mainly dependent on SMBG and HbA1c; however, both the modalities may not serve as measure for glycemic variability. Intensified diabetes management requires accurate determination of blood glucose concentrations. Continuous glucose monitoring helps to detect trends and tracking pattern of glucose values, aids in detection of hypo- and hyperglycaemia, and help in minimizing glucose excursions, thus help in acute and long-term therapy adjustments.

Introduction

Blood glucose monitoring has entered a new era. The traditional methods of measuring glycemic control with glycated haemoglobin-HbA1c has been used for years and till date glycemic goals are defined by HbA1c, however HbA1c has many limitations. HbA1c though provides an average of blood glucose over a period of 8 to 12 weeks, it doesn't provide an estimate of intraday and interday glycemic variations and excursions. Glycemic Excursions i.e hypoglycemia or hyperglycemia have been linked to both microvascular and macrovascular complications of diabetes. Continuous glucose monitoring (CGM) depends upon the measurement of the interstitial glucose levels and track glucose levels in real time.[1]

Limitations of HbA1c

Elevated HbA1c is associated with increased risk of microvascular and macrovascular complications of Diabetes Control and Complications Trial (DCCT). United Kingdom Prospective Diabetes Study (UKPDS) has emphasized the importance of good glycemic control in improving the health outcomes in patients living with diabetes. A target HbA1c of less than or equal to 7 is recommended by most of the global organizations; however, all the guidelines equivocally recommend that HbA1c goal should be individualized for every person living with diabetes according to age, duration of diabetes, comorbidities, and life expectancy. The HbA1c has several limitations like it only provides an average over 2–3 months and it does not provide any information on hypoglycemic or hyperglycemic events.[2] HbA1c measurement may be unreliable in certain clinical settings like anemia, pregnancy, hemoglobinopathies, and iron deficiency. It does not provide data that can facilitate the decision to choose one drug over another. Studies have also reported variable glycation rates in people with different ethnic and racial backgrounds. HbA1c should be measured by a method certified by National Glycohemoglobin Standardization Program (NGSP). However, in spite of all the limitations, HbA1c remains an indispensable marker of glycemic control, a reliable marker for population health and a validated marker linked to diabetes complications.

Continuous Glucose Monitoring

It is important to understand some of the terminology often used for CGM.[3] There are CGM devices, which provide real-time unblinded data (real-time continuous glucose monitoring—rtCGM) with alarms and alerts for hypoglycemia and hyperglycemia to the users.[4] Such CGMS devices are used in most of the published randomized controlled trials. Interstitial glucose, which is measured by the rtCGM correlates well with plasma glucose and provides near real-time data on blood glucose. The glucose data received in real time allows the patient or the caregiver to take a treatment decision and allows for the timely intervention to avert severe hypoglycemic episodes. Some devices have options of sharing the glucose values with family members and friends enabling the timely alert for hypoglycemia.

The other types of devices are the ones which provide data to the patients and their health-care providers retrospectively for the analysis—intermittently viewed CGM (iCGM). The CGM device has to be physically scanned by a health-care provider **(Fig. 1)**.

iCGM is also called flash CGM.[4] There are studies to show that there is an improvement in overall time spent in hypoglycemia with rtCGM when compared to iCGM. Some rtCGMs require calibration, and frequency of calibration is variable based on the type of the device. CGM systems for which self monitoring of blood glucose (SMBG) is required to guide treatment decisions are called adjunctive while the one that does not require SMBG is called non-adjunctive. SMBG alone improves glycemic control and quality of life; however, it cannot predict impending hypoglycemia.

CGM Devices Working

CGM measures interstitial glucose levels with a delay of 5–15 minutes with rapidly changing plasma glucose levels; however, it correlates well with the plasma glucose.[5] CGM devices can measure glucose levels every 5–15 minutes. An electrochemical enzyme sensor is placed subcutaneously by the applicator and glucose readings are transmitted automatically to a receiver, which can be a smartphone, smartwatch, or any other smart device. Some CGM devices use fluorescence based sensors implanted subcutaneously with a transmitter either placed on or worn over the skin for transmitting the receiver. The sensor can record interstitial glucose values for 90 days.[6]

Interpretation of CGM Data

Data from the CGM devices can be downloaded for analysis. The glucose data is displayed in the form of current glucose values as well as in the form of trends and the direction of glucose change.[7] The data is very helpful in titrating the doses and helps in fine tuning the treatment. The ambulatory glucose profile (AGP) represents a standardized glucose reporting format in the form of mean glucose, percent of time in rage (70–180 mg/dL), percent of time spent in hypoglycemia (<70 mg/dL) and percent of time spent in hyperglycemia, that is, more than 180 mg/dL.[8]

Variability in glucose levels is reported in the form of standard deviation and percent coefficient of variation. A minimum of 10 days of data is required to accurately predict or estimate the HbA1c levels as calculated from glucose management indicator (GMI). Estimated HbA1c calculated by GMI uses a conversion based formula.[9] The estimate is based on data from clinical trials and modern CGM devices and estimated HbA1c may be the same, low or more than the laboratory HbA1c. CGM devices are also used with insulin pump therapy and are helpful in identifying glycemic patterns and deciding the insulin dose and rate for continuous subcutaneous insulin infusion.

When blood glucose levels rise rapidly the interstitial glucose concentration takes time for equilibration between the venous and interstitial fluid compartments and because of this reason CGM may yield lower glucose readings. The CGM values are less accurate at the extremes of hypoglycemia (<40 mg/dL) and hyperglycemia (>400 mg/dL) with a mean absolute relative difference of less than 11%.[10] It is difficult to compare the variability between different devices due to different sample sizes, study designs, methodologies, etc.; however, the reliabilities of newer CGM devices are improving **(Fig. 2)**.

It has been found that patients on high-dose vitamin C and on paracetamol may show falsely elevated CGM glucose values (in some CGM devices acetaminophen is oxidized by CGM electrodes).

Glycemic Variability

Glycemic variability is an independent risk factor for diabetes complications.[11] It represents the amplitude, frequency, and duration of glycemic excursions. Glycemic variability also has an effect on quality of life and cognitive

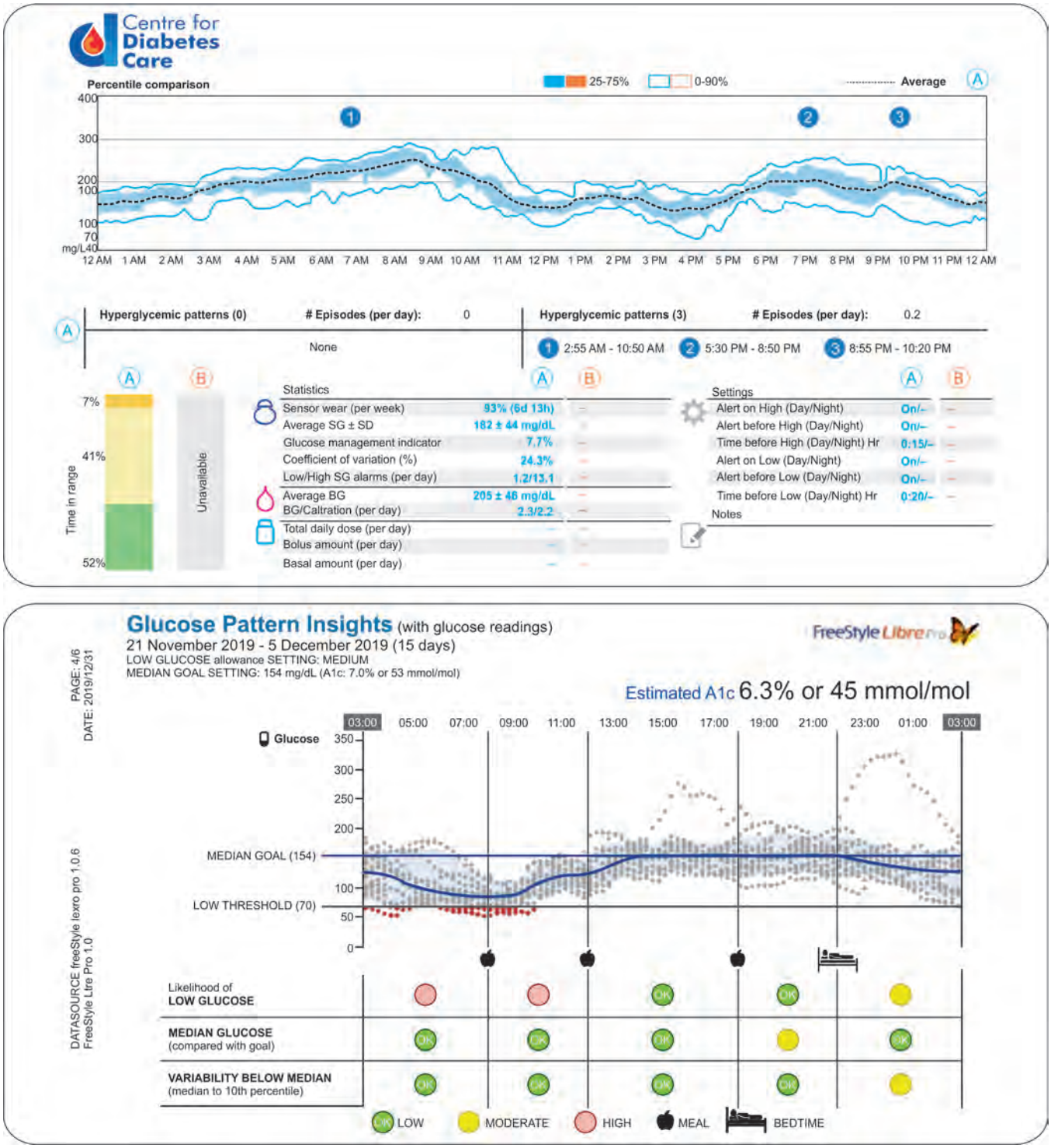

Fig. 1: The glucose patterns shown by a real-time continuous glucose monitoring (rtCGM) (above) and Intermittently scanned CGM (iCGM) (below)
(*Source:* Centre for Diabetes Care)

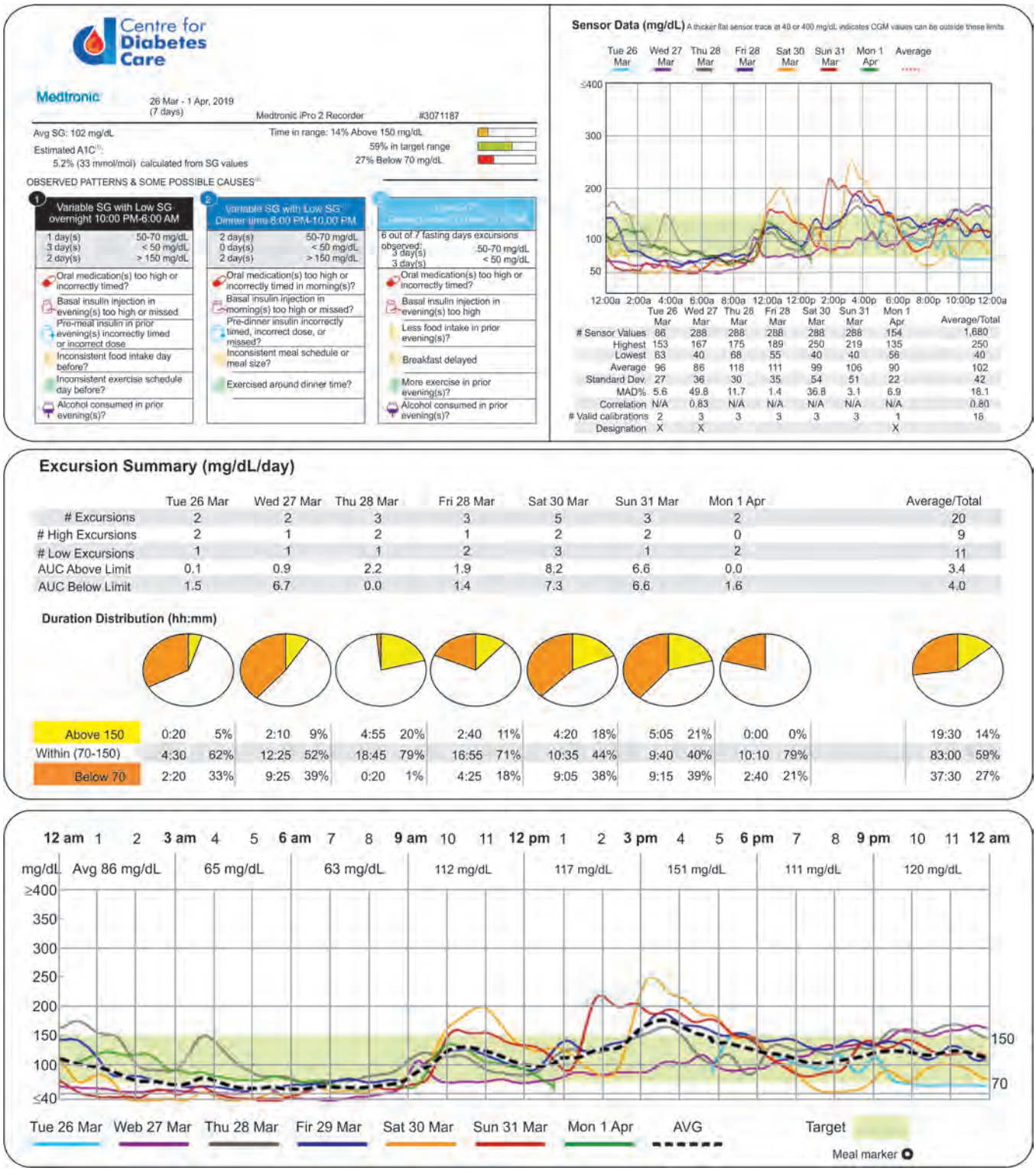

Fig. 2: A typical CGM report describes several metrics depicting glucose data
(*Source:* Centre for Diabetes Care)

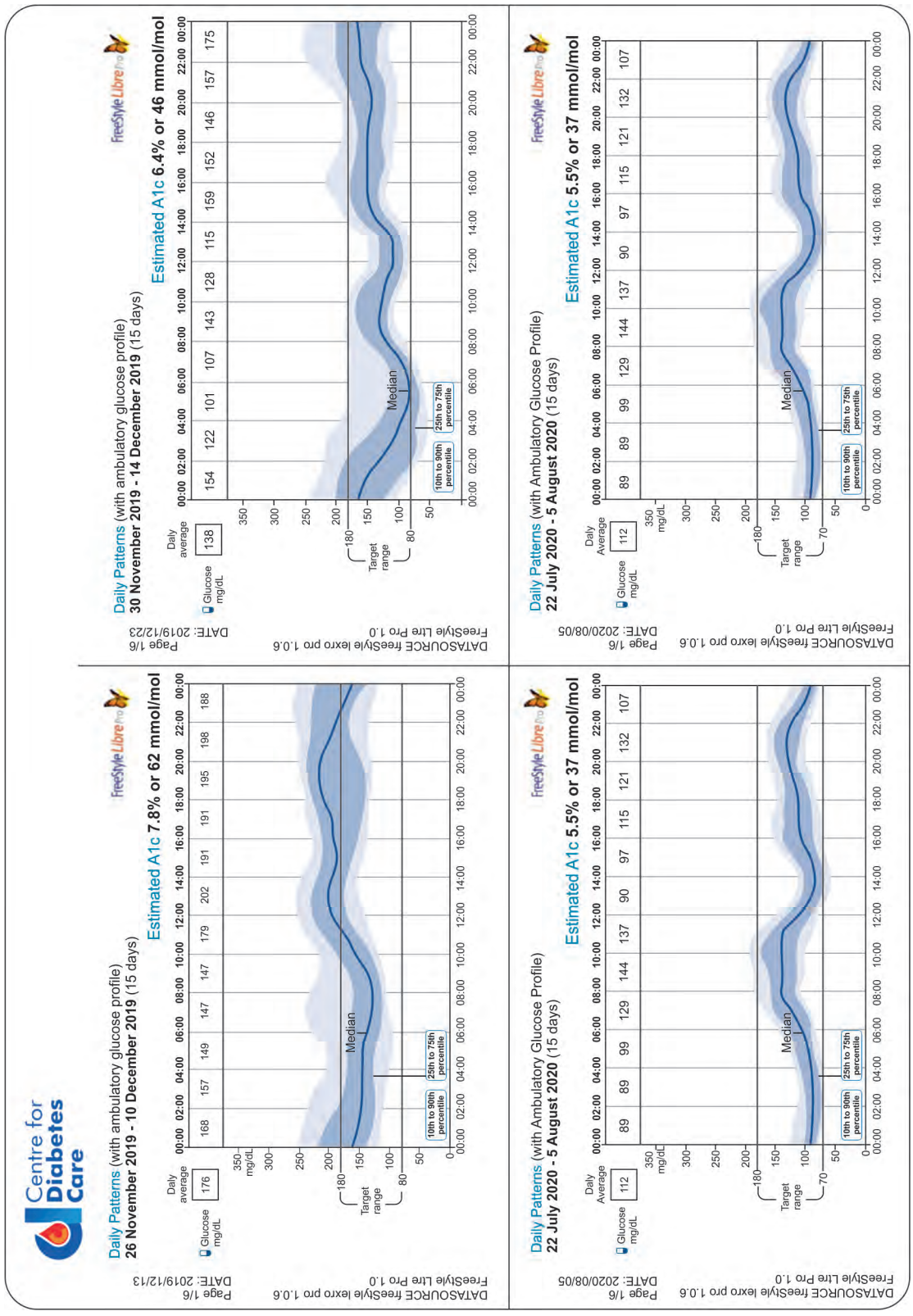

Fig. 3: Glycemic variability in four different patients
(*Source:* Centre for Diabetes Care)

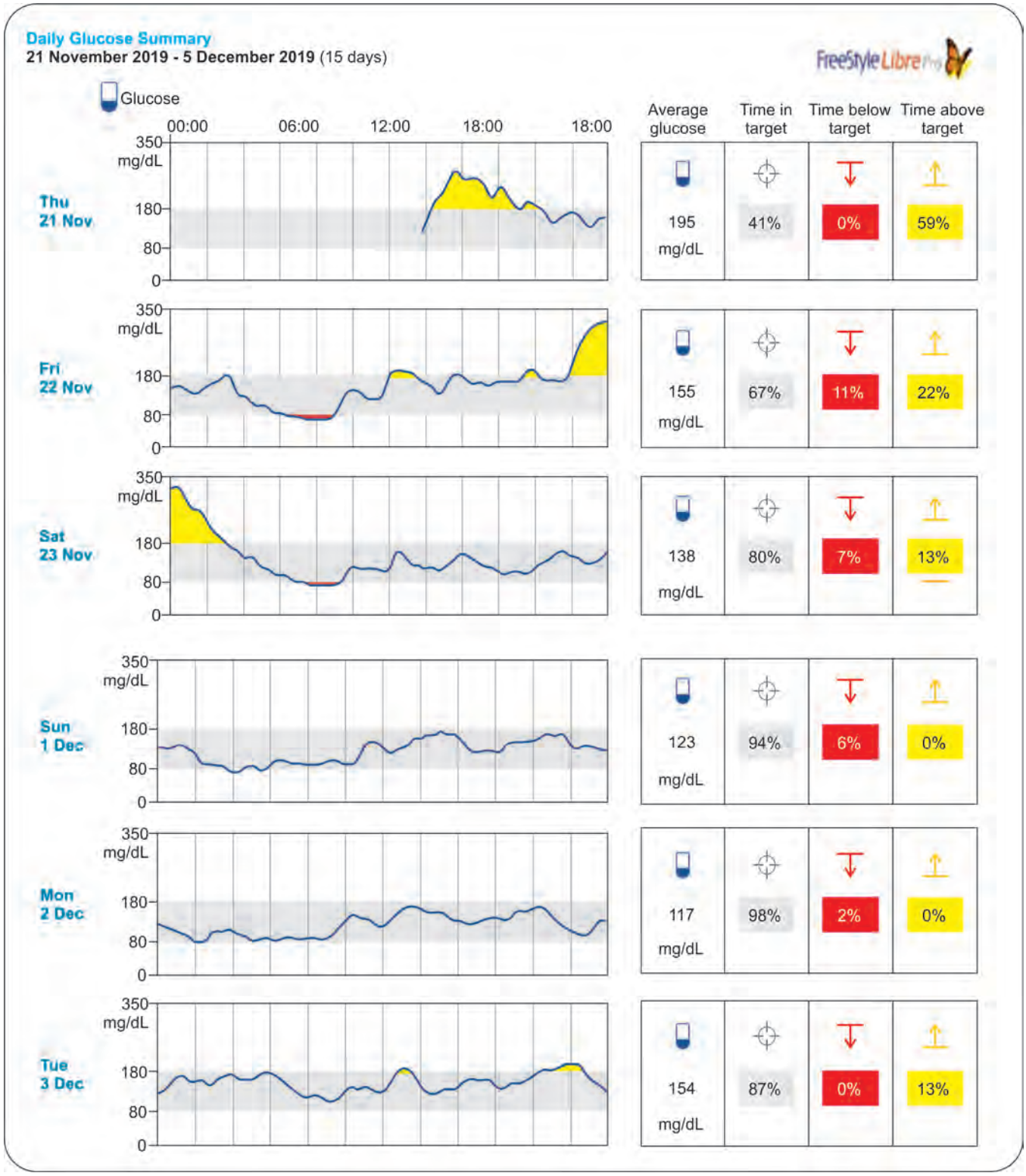

Fig. 4: Time in range values in a patient
(*Source:* Centre for Diabetes Care)

functions and is now a well-accepted clinical marker of glycemic control. Availability of CGM has made it easy to assess glycemic variability. CGM data reflects all the three components of variability. Standard Deviation (SD), mean amplitude and, coefficient of variation (CV – SD divided by mean) are used to quantify glycemic variability. Stable glucose levels are defined by a coefficient of variation less than 36% while CV more than 36% defined unstable glucose levels. Clinicians should look at glycemic variability also while interpreting CGM data as a key clinical marker of glycemic control **(Fig. 3)**.

Time in Range

As discussed earlier, time spent by an individual in the target glucose range is called Time in Range (TIR). TIR provides valuable information on current glycemic control, which cannot be derived from HbA1c.[12] TIR alone cannot be taken as a marker of good glycemic control; however, it effectively illustrates metrics for clinicians as well as researchers. The future studies must report TIR along with other parameters of glycemic control to better understand the glycemic variations and diabetes-related complications and outcome **(Fig. 4)**.

CGM in Clinical Practice

Patients with type 1 diabetes or type 2 diabetes on multiple daily insulin injections are required to frequently check their blood sugar levels as it is necessary for adjusting insulin regimens to optimize glycemic controls. A six- or seven-point SMBG often provides useful information on glucose patterns; however, there are still many limitations to the conventional SMBG. An rtCGM can be of great value in detecting and avoiding potentially dangerous hypoglycemia, in identifying unrecognized hypoglycemia. A CGM glucose rising or falling trend can alert the patient, and the patient can adjust the dose of insulin accordingly. CGM data when coupled with information on food intake, physical activity and insulin dose can help in discovering some glucose patterns, which will otherwise go unnoticed. The information can be used to make necessary changes in diet and insulin. However, use of CGM requires adequate training and education of the patient. Contact dermatitis may be a common side effect of CGM devices.

CGM Guidelines/Guidance

The most recent and updated guidance on use of CGM are given by American Diabetes Association (ADA).[13] ADA states that CGM devices are useful tools in adults with both type 1 and type 2 diabetes and should be considered in patients who are not meeting glycemic goals have hypoglycemic unawareness or had severe episodes of hypoglycemia. However, their proper use requires robust diabetes education, training, and support. ADA also recommends the use of CGM in all children and adolescents on insulin injection or insulin pumps to improve glycemic control. In pregnant women with diabetes ADA states that use of rtCGM can improve HbA1c, TIR, and neonatal outcomes. A position statement by EASD and ISPAD[14] have stated that use of CGM devices may be helpful in determining carbohydrate intake before, during, and after exercise as per the trends of the rate of rise and fall in glucose levels.

Conclusion

CGM is the future of diabetes monitoring. CGM data provides a lot of information on glycemia, including variability and rate of rise and fall of glucose levels. The data can help in improving glycemic control, reduce complications, and improve quality of life of a person living with diabetes. However, there are challenges like cost, standardization, reliability of data, ever changing technology. Nevertheless CGM finds a place in all the guidelines and recommendations, latest being provided by ADA. The year 2021 marks the centenary year for insulin, but at the same time it gives us an opportunity to realize that "How Diabetes Technology is assuming a greater role in diabetes care."

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CHAPTER

65 Role of 3Bs in Diabetes

Arthur Joseph Asirvatham, Adlyne Reena Asirvatham

Abstract

Understanding the pathophysiology of type 2 diabetes seems to be never ending, despite a leap of knowledge in the last decade. In addition to the ominous octet, newer pathophysiologic defects and disturbances are described to contribute to the development as well as progression of diabetes. Although β-cell failure and insulin resistance are the critical components in diabetes, brain, fat, and muscle influence both these core defects. Brain, Brown and Brawn—the 3 'B's have a considerable role to play in obesity and type 2 diabetes. Their major function is not limited to improving insulin sensitivity, but also in food intake regulation, glucose homeostasis, and also β-cell preservation. This novel concept would pave way for more research in therapeutic aspect by directly addressing the pathophysiological defects in type 2 diabetes rather than a guideline-based management.

Introduction

Obesity and type 2 diabetes are rampantly increasing in the developed as well as developing world. Weight gain occurs as a result of deregulated balance between calorie intake and calorie output. In order to achieve weight reduction, the focus has always been on the ways and means to increase the calorie expenditure. However, newer understanding on the physiology of calorie intake and its modulation in the management of metabolic dysfunction like obesity and type 2 diabetes has gained a lot of attention. Calorie intake and energy homeostasis revolves around Agouti-Related Peptide (AgRP), Brown Adipose Tissue (BAT) and skeletal muscle (SM) that form a circuit where hormonal and nutrient feedback from the periphery is signaled to the CNS.[1] In this topic, the new and important role of these 3 'B's—Brain, Brown, and Brawn in diabetes will be discussed.

3 'B's and their Role in Glucose Homeostasis

The knowledge and understanding about glucose homeostasis is increasing steeply and steadily. The role of brain especially hypothalamus and the arcuate nucleus (ARC) has been recognized as a key regulator of energy homeostasis, thus supporting the center driven control in regulation of food intake. Nevertheless, the brain integrates metabolic signals from peripheral tissues like liver, pancreas, adipose tissue, gut and skeletal muscle. Adipocytes in the brown fat also utilize glucose by UCP1-mediated thermogenesis as well as independent mechanisms thus contributing to glucose homeostasis.[2] This has been postulated to be one of the reasons behind the increasing prevalence of type 2 diabetes due to global warming. Thus, brain, brown fat, and brawn have a major role in glucose homeostasis and dysregulation of which contribute to obesity and type 2 diabetes.

Role of Brain in Diabetes

The role of brain in glucose homeostasis has been demonstrated by physiologist Claude Bernard in 1854 when he found glycosuria in a rabbit after puncture of the fourth ventricle. Ever since then in the last few decades, tremendous experiments prove the precise role

of brain and glucose sensing neurons in the hypothalamus. Glucose sensing neurons are of two types: Glucose-excited neurons in the Ventromedial Hypothalamus (VMH), Paraventricular Nucleus (PVN) and ARC that are stimulated by rise in extracellular glucose levels; Glucose-inhibited neurons in Lateral Hypothalamus (LH), PVN, and ARC that are activated by fall in glucose concentrations.

Brain in Feeding Control and Glucose Homeostasis

Neural circuits including AgRP neurons control appetite as well as glucose homeostasis. As a response to hunger, AgRP neurons induce eating and on the other hand, inhibit insulin-stimulated glucose uptake by SM. This effect of insulin resistance (IR) in the SM occurs due to the expression of muscle related genes in BAT. The effect of AgRP on the BAT and SM is shown in **Figure 1**. Acute regulation of AgRP plays the major role in feeding control and mice studies have shown that ablation of these neurons have resulted in cessation of hunger.[3] In addition to AgRP, Neuropeptide Y (NPY) an orexigenic peptide co-released by ARC and the neurotransmitter gamma-aminobutyric acid (GABA) also contribute in the food intake regulation. AgRP also plays a crucial role in glucose homeostasis apart from the feeding control. It has been demonstrated that suppression of hepatic glucose output by insulin occurs partially by inhibiting AgRP neurons in mice.[4] IR in obesity is also presumed to be due to obesity associated hypothalamic inflammation and consequently alteration of AgRP neuronal activity.[5]

Brain Integrates Peripheral Signals

Brain also puts together peripheral signals to regulate glucose metabolism. Hormonal input signals include insulin through hypothalamic insulin signaling pathway, leptin by leptin mediated regulation of glucose metabolism, long chain fatty acids through hypothalamic lipid sensing and more importantly glucose through glucose sensing. Glucose sensing mechanism in hypothalamus is better understood and is very similar to that in pancreatic β-cell. The sequence of events that occur in glucose-excited neurons following elevated plasma glucose is shown in **Figure 2**. On the contrary, the mechanism of glucose-inhibited neurons is unclear.

Brain and Effector Pathways

Besides the neuronal role and integration of peripheral signals, brain also has effector pathways to ensure glucose

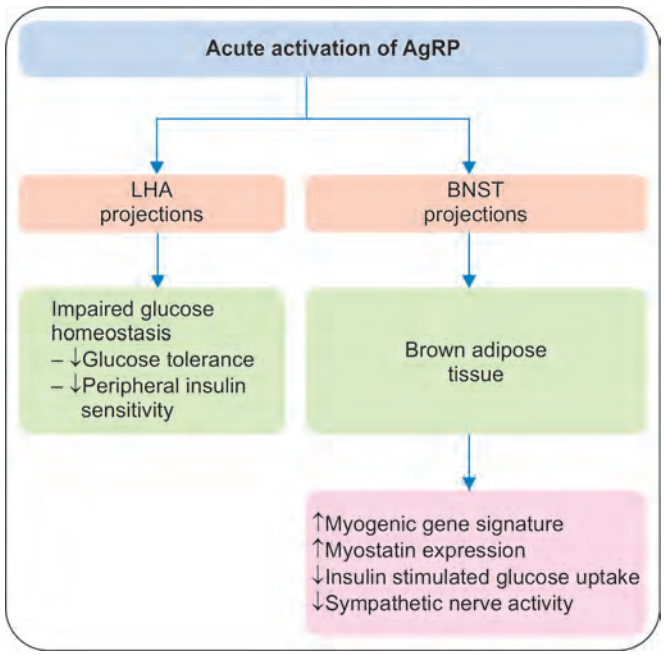

Fig. 1: Influence of AgRP on brain adipose tissue (BAT) and skeletal muscle (SM) during acute activation
LHA, lateral hypothalamus area; BNST, bed nucleus of the stria terminalis

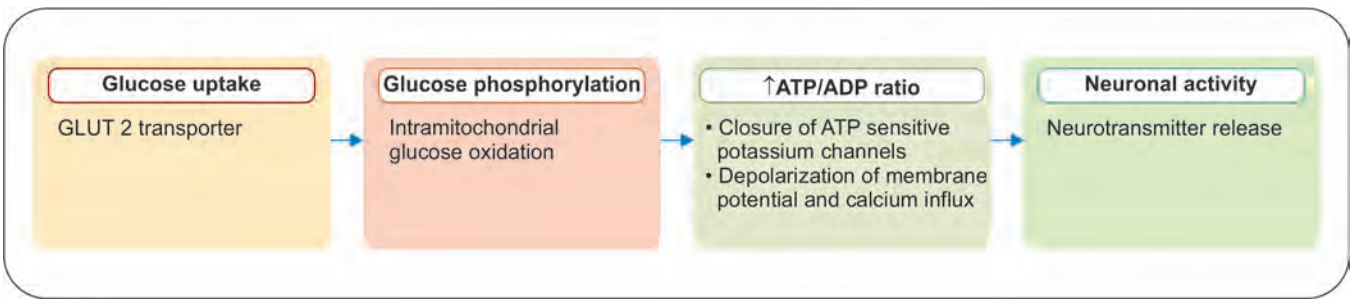

Fig. 2: Glucose sensing mechanism in hypothalamic glucose excited neurons

metabolism.[6] These pathways target organs as mentioned here.

- *Liver:* Insulin receptor in both liver and brain is required for the ability of insulin to effectively suppress hepatic glucose output. This has been proven in rodents where knockout of insulin receptor in brain sparing the liver did not completely produce hepatic glucose production (HGP) suppression.
- *Pancreas:* Autonomic nervous system controls the secretion of glucagon and insulin. Parasympathetic activity stimulates insulin and sympathetic nerves inhibit it while both stimulate glucagon secretion.
- *Skeletal muscle:* Leptin has shown to increase glucose uptake in skeletal muscle by translocation of GLUT4 glucose transporter. It also promotes glucose uptake via AMPK signaling pathway in SM through sympathetic nervous system.

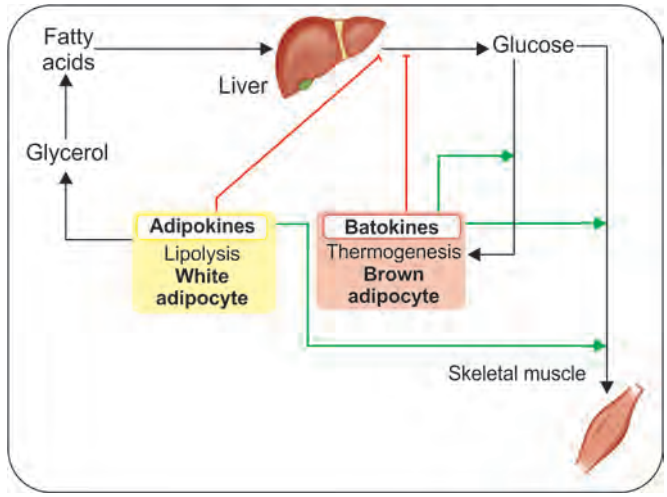

Fig. 3: Relationship between BAT and WAT and their role in systemic metabolic regulation

Role of Brown Fat in Diabetes

White adipose tissue (WAT) stores energy and is known for its association with metabolic disease. The role of BAT, which burns energy for thermogenesis, was unrecognized until few years ago due to underestimation of its existence in adults. Now, we know that the total amount of brown and/or beige fat is at least tenfold higher than previously calculated owing to studies with advanced PET scans.[7] Brown adipocytes regulate energy expenditure by their abundant and large mitochondria. Uncoupling Protein 1 (UCP1) is BAT specific protein located in the inner mitochondrial membrane, which when activated, generates heat instead of ATP and thus mediates BAT thermogenesis.

Glucose Uptake in BAT

Besides thermogenesis, BAT also plays a significant role in glucose homeostasis. At the cellular level, glucose uptake by BAT occurs through GLUT1 and GLUT4 contributing significantly to systemic glucose disposal. This glucose uptake and utilization is extremely responsive to β-adrenergic stimulation and insulin.[8] Cold induced stimulation of BAT has demonstrated improvement in glucose metabolism in type 2 diabetes.[9] Obesity attenuates GLUT1 translocation and thus glucose utilization in BAT. It has also been shown that 16.5% body weight reduction following chronic calorie restriction increased brown adipocytes in subcutaneous fat by 10%.[10] Furthermore, the fasting plasma glucose and fasting insulin levels improved.[9] The glucose uptake in BAT is also influenced by AgRP as discussed earlier.

Batokines and Glucose Metabolism

Batokines are the factors secreted exclusively by BAT in contrast to the adipokines secreted by WAT, which includes leptin, adiponectin, etc. These batokines regulate hepatic glucose output, hepatic lipogenesis in addition to glucose uptake and disposal by skeletal muscle.[11] The paracrine effect between BAT and WAT and the mechanisms by which they control systemic metabolic regulation are shown in **Figure 3**. Thus, brown and beige adipocytes have very good therapeutic potential in modulating glucose uptake, utilization, and glucose metabolism. Hence, several studies are on the way looking at increasing BAT size and function.

Role of Brawn in Diabetes

Function of skeletal muscle in glucose metabolism has been known for ages. IR has been the hallmark abnormality that is observed in SM. Several mechanisms have been hypothesized for IR including dysregulated GLUT4 translocation, insulin receptor downregulation, defective post-receptor signaling etc. Myokines are protein factors secreted by SM, which exerts its action on multiple tissues. Recently, suppression of adaptive glucose stimulated insulin secretion has also been found

to be an effect of these myokines on the pancreatic β-cell thus contributing even to the secretory defect of type 2 diabetes.[12]

Myostatin is another factor belonging to transforming growth factor-beta/bone morphogenetic protein (TGF-β/BMP) superfamily whose main role is inhibiting skeletal muscle growth. Myostatin inhibits skeletal muscle stem cell proliferation, differentiation and attenuates muscle fiber protein accretion and thereby result in decreased skeletal muscle mass. It also has a role in insulin stimulated glucose uptake as shown in animal studies. Myostatin knockout mice showed improved insulin sensitivity proving the impact of myostatin on liver and adipose tissue beyond SM. Myostatin mRNA levels were found to be increased in those with type 2 diabetes compared to controls.[13] Resistance training has shown to reduce myostatin levels by 20%.[14] This could possibly explain the benefit of inhibiting myostatin expression to achieve better lean body mass, enhanced insulin sensitivity, and improved glucose metabolism thus paving way for a potential beneficial target.

Recent studies prove the additional role of SM in improving β-cell mass and function that could also be regulated through myokines and protein factors. Exercise has shown to enhance β-cell viability to some extent through increased IL-6 release from SM that either act directly on β-cell[15,16] or indirectly by increasing GLP-1 secretion from L-cells and α-cells.[17] Other factors like Irisin are also released from SM that has been suggested to improve or protect β-cell mass and function.[18] On the contrary, muscle secretome could exert a negative effect on the β-cell mass and function. The myotubes and their secretory factors differ significantly between those with and without type 2 diabetes. Studies have proven that the myotubes in controls retained their ability to protect or augment glucose stimulated insulin secretion compared to those with type 2 diabetes.[12] This β-cell/SM communication and interaction remains to be understood further in type 2 diabetes.

Future Research

Despite several failures with BAT related therapies in the past, the future therapeutic targets seem promising. Pharmacological stimulation of BAT with BMP-7, FGF-21, protein regulator PGC-1α, etc. is being tried to produce favorable metabolic benefits. Even more interestingly, stimulation of precursor stem cells to differentiate into BAT is also being attempted. The ultimate challenge of BAT autotransplantation is currently under research. But whether increasing BAT mass be translated into augmented activity of BAT is questionable. Drugs to reduce myostatin activity like myostatin antagonist are in the pipeline.

Conclusion

The 3 'B's—Brain, Brown fat and Brawn play a significant role in food intake regulation, integrating metabolic cues from peripheral tissues, controlling glucose homeostasis, modulating IR, and protecting β-cell mass and function. Recent understanding of these circuits, the effectors and their cross talks, paves way for more research with possible therapeutic targets in metabolic diseases. Exercise, once thought to be an additional simple intervention to improve glucose uptake in SM, has been found to be more beneficial by reducing myostatin expression in SM and even preservation of β-cell mass and function. Novel therapies for diabetes and obesity are quite reassuring in the near future, until then easy modalities like exercise should be diligently practised for the more clearly proven benefits.

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CHAPTER

66 Sleep Disorders and Type 2 Diabetes

Umashankar Mishra, Abinash Hota

Abstract

Sleep is an essential component of human life. Its disorders are gateway to metabolic syndromes. Sleep disorders and type 2 diabetes mellitus (T2DM) are closely associated and they enhance disease severity of each other and their complications as well. Sleep disturbances along with T2DM accelerate the cardiovascular, neurological, ocular, neuroendocrine, and sexual complications increasing morbidity and mortality significantly. Also sleep disorder is an important reason for inadequate glycemic control and vice versa despite of treatment. Its incidence in T2DM is well documented and its treatment improves quality of life significantly.

Introduction

Sleep is a complex, active, and physiologic event constituting more than 30% of human lifetime. It has its pivotal importance in maintaining metabolic homeostasis, memory consolidation, and in restoration of psychic structure and function. Sleep follows a particular rhythm comprising non-rapid eye movement (NREM) sleep (N1, N2, N3) and rapid eye movement (REM) sleep, derangement of which affects body functions. Association of quantity[1] and quality[2] of sleep with metabolic syndromes has been clearly established. So, deprivation of sleep, which is a part and parcel of modern lifestyle, may be responsible for booming of metabolic syndrome at present era.[3]

Type 2 diabetes mellitus (T2DM), being the most prevalent noncommunicable disease, constitutes a significant health-care burden. United Nations General Assembly in 2006 declared T2DM to be the first noncommunicable disease that threatens the world health to the same magnitude as communicable diseases such as HIV and TB.[4] Sleep disorders and T2DM are two events of a vicious cycle. Patients with T2DM report a higher rate of insomnia, sleep fragmentation, poor sleep quality, excessive day time sleepiness, and excessive use of sleep medications. The reason of the sleep disturbance in T2DM may be due to the disease itself or its complications.

India, being the diabetic capital of the world, there should be awareness among the physicians for the assessment of sleep disorders in T2DM.

Sleep Disorders in T2DM

Comparing with nondiabetics, sleep disorders constitute a higher health-care problem among diabetics. The higher incidence of sleep disorders in T2DM is likely due to painful diabetic neuropathy, sleep breaks due to nocturia, night hypoglycemic, and hyperglycemic episodes. Restless Leg Syndromes (RLS) & Periodic Leg Movement Syndrome (PLMS) were found to be more prevalent in T2DM.[5] There can be associated autonomic neuropathy causing central sleep apnea in other breathing disorders. Depression occupies a significant proportion of health-related problems in diabetes that severely

affects sleep.[6] Also T2DM itself affects sleep quality by directly affecting neurobehavioral, neurotransmitter, and autonomic functions.[7]

The sleep complaints in T2DM are difficulty in initiating sleep (21.1%), difficulty in maintaining sleep (21.9%), and excessive daytime sleepiness (12.2%).[8] Sleep disorders like obstructive sleep apnea (OSA), insomnia, sleep deprivation, excessive sleepiness, restless leg syndrome (RLS), periodic limb movements (PLMS) are associated with T2DM. Amongst them OSA has a strong association with T2DM.[9]

Sleep Disorders Leading to T2DM

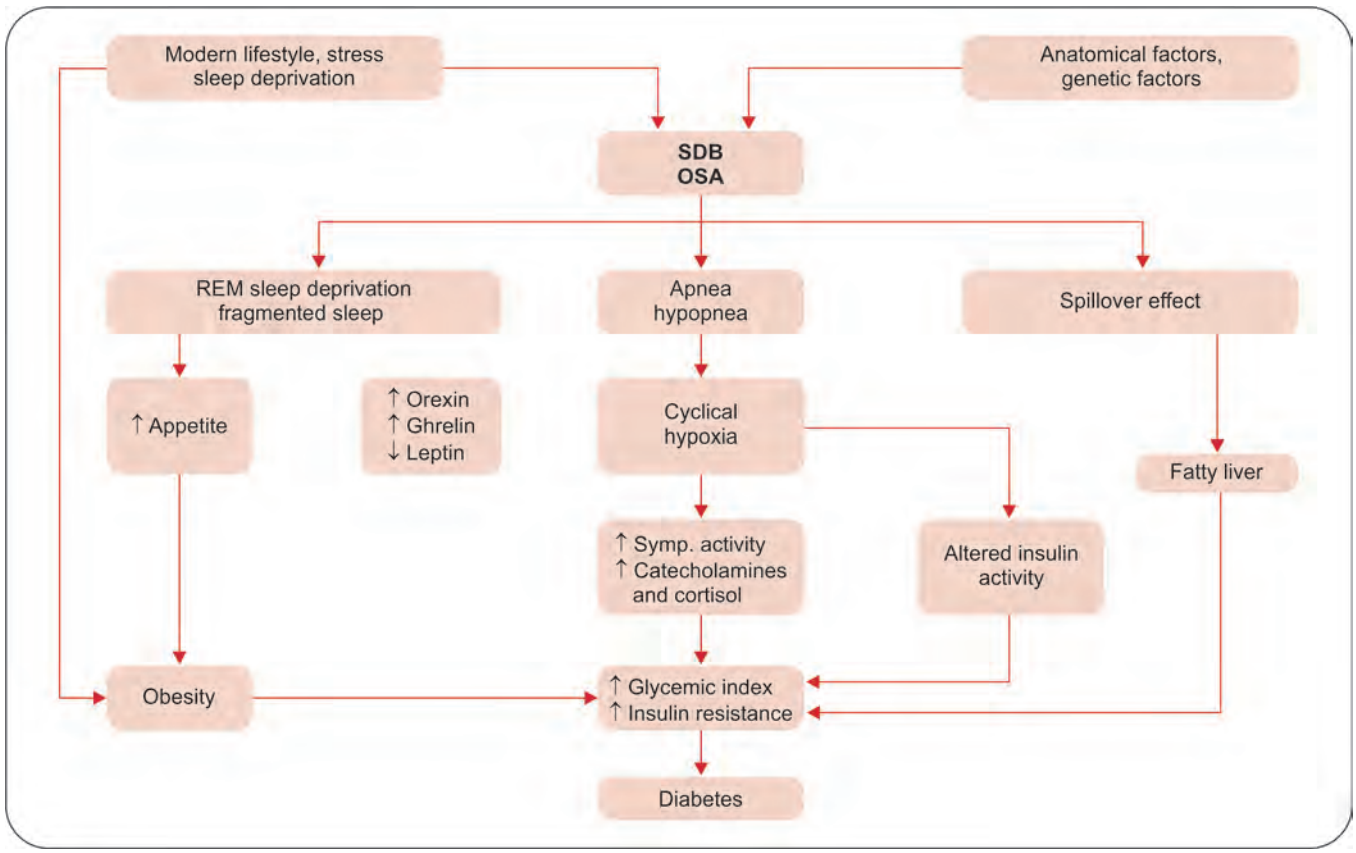
Among the sleep disorders, sleep disordered breathing (SDB), sleep deprivation, insomnia, excessive sleepiness, RLS dominantly affect glucose metabolism. A recent meta-analysis demonstrated that sleep disturbance is a significant risk factor for T2DM.[9] Difficulty in initiating sleep increased the risk of T2DM by 55%, while difficulty in maintaining sleep increased the risk by 74%. Likewise, the risk of development of T2DM in insufficient sleep (<6 hours) or excessive sleep (>9 hours) is comparably similar with the risk of T2DM in physical inactivity. This shows the importance of routine assessment of sleep disorder in T2DM.

The probable mechanisms of glycemic variability due to sleep disorders are summarized in the **Flowchart 1**.

Sleep Disorders and Neuroendocrine Control

REM sleep deprivation is common in OSA patients. Fragmented sleep and sleep deprivation decrease the neuroendocrine regulation over appetite. So, it leads to overfeeding causing hyperglycemia. The reason of overfeeding is thought to be associated with OREXIN hyperactivity in sleep deprived patient. Increased level of GHRELIN (hunger promoting hormone) and decreased level of leptin (satiety maintaining hormone) in the circulation of patients with sleep disorders were also found, which again supports the neuroendocrine theory.

Flowchart 1: Probable mechanisms of sleep disorders leading to development of type 2 DM



Sleep Deprivation Leading to Insulin Resistance

The presence of insulin resistance was demonstrated in sleep deprived patients.[10] Studies depicted that there is a clear association between sleep apnea and insulin resistance.[11] SDB and OSA are associated with cyclical hypoxia, which increases sympathetic and corticotropic effect. It increases level of catecholamines and cortisol in circulation causing "spill-over effect." It is thought to be the cause of increased visceral adiposity and insulin resistance in these patients.

Sympathetic Hyperactivity in Sleep Disorder

Repeated episodes of apnea and hypopnea during sleep in patients with OSA cause hypoxia, which increases sympathetic activity. Increased level of catecholamines itself cause dysregulation of glycemic status. So, if not associated with T2DM, these patients present with fasting hyperglycemia with normal postprandial oral glucose tolerance test (OGTT). So, only fasting hyperglycemia should raise a suspicion of sleep disorder.

Diabetes and Sleep Disordered Breathing

Prevalence

SDB is a spectrum of disorders consisting snoring, upper airway resistance syndrome and sleep apnea. Sleep apnea can be obstructive, central, or mixed. Higher incidence of SDB is clearly evident in T2DM and OSA is most common amongst them. The prevalence of SDB among T2DM can be as high as 58% and of OSA is 23%.[12] In Look AHEAD TRIAL (Action for Health In Diabetes), amongst the obese participants the prevalence of SDB reached up to 80%.[13] Though OSA is most common SDB among T2DM, but central type apnea are also reported, when associated with autonomic neuropathy.[14,15]

Clinical Features

OSA is characterized by collapse of the upper airway leading to deficient airflow despite of persistent respiratory effort. Though it usually occurs among obese, but nonobese, lean diabetics are also affected. Among the lean-diabetics anatomical factors of face and neck that promotes OSA include macroglossia, short neck, retruded chin or maxilla, neck circumference of more than 43 cm. So lean diabetics are to be screened for sleep disorders, as in India major proportion of diabetic patients are of low or normal body weight. Two prominent symptoms of OSA are habitual snoring and excessive day time sleepiness. Other symptoms are episodes of choking apnea, restlessness, diaphoresis, frequent change of posture during sleep, and difficulty in sleeping supine. Poor concentration, morning headache, mood swings, and irritability are commonly associated.

Complications

OSA independently increases the risk of developing insulin resistance, hypertension (HTN), and cardiovascular disease (CVD). Its causation can be defined by increased sympathetic activity, increased corticotropic action, altered lipid metabolism, hypoxia, oxidative stress, and systemic inflammation. Also T2DM has a clear association with CVD.

Hypothyroidism may be associated with OSA. Day time sleepiness and lethargy in obese patients with OSA can be confused with hypothyroid symptoms. So prescribing high doses of thyroxine without treating OSA can lead to higher mortality in CVD during sleep due to cardiac arrhythmia and cyclical hypoxemia.

Sexual dysfunction is a known consequence of OSA. In REM sleep, there occurs nocturnal penile and clitoral tumescence. So increased blood flow to these tissues possibly prevent excessive collagen formation maintaining their erectile function. So, REM sleep deprivation in OSA can be a possible explanation for it. Likewise, erectile dysfunction is a known complication of T2DM.

Cyclical hypoxemia during sleep in OSA has its deleterious effects on retina also. Sleep disorders in T2DM has been reported to play an etiological role in the development as well as progression of diabetic retinopathy.[16] Also there are repeated association of OSA with several eye disorders that is optic neuropathy, anterior ischemic optic neuropathy (AION), floppy eyelid syndrome, glaucoma, etc.[17] So, early treatment of OSA/SDB in T2DM may have a good retinal outcome.

Having above complications in common OSA/SDB can additively augment diabetic hazards. It can also be a cause of ineffective treatment of T2DM. Treatment of OSA with Continuous Positive Airway Pressure (CPAP) might correct the metabolic complications, but its effect over glycemic control is some-how mixed.[18] Treatment of OSA/SDB is of prime importance as it significantly improves quality of life and blood pressure control.[19]

Diagnosis and Management of Sleep Disorders

American Diabetes Association 2017 guideline recommends assessment of sleep pattern, sleep quality, duration, as part of comprehensive medical evaluation in persons with T2DM.[20] As reasons of sleep disruption in T2DM are multifactorial, so a detailed history and clinical evaluation is the primary tool toward diagnosis. Frequency of hypoglycemic and hyperglycemic episodes, frequency of nocturia, and associated causes are to be looked after. Proper neurological evaluation for peripheral neuropathy or associated autonomic neuropathy should be done. Association of depression should be given importance as its treatment is beneficial and diagnosis is easily overlooked. Keeping a sleep diary of past few weeks should be encouraged. However, when it's suspected for SDB/OSA, an overnight polysomnography should be done. Newer and more feasible technique like ACTIGRAPHY is also now widely available for detecting sleep disorders. Appropriate treatment of the sleep disorder requires finding out its cause and treating the same, some of which are enlisted in **Table 1**. A proper sleep discipline, sleep hygiene, sleep restrictions along with cognitive behavioural therapies, and relaxation therapies are required for primary insomnia and other refractory sleep disorders.

Recent Advances in Management of OSA

Looking into the progression of metabolic syndromes in untreated sleep disorders, there has been lots of studies for the treatment aspect, as well as the compliance of the patients toward it. As OSA is the most common SDB, there have been some new therapies specifically looking into the inconvenience of CPAP/BiPAP. In mild cases along with weight loss, positional therapy and oral appliances are advised. PROVENT therapy **(Fig. 1)** based

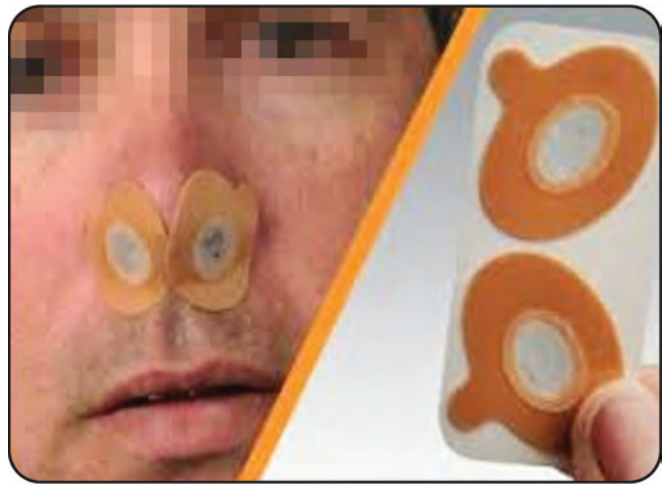


Fig. 1: PROVENT therapy

TABLE 1 Associated comorbidities for poor sleep in persons with diabetes and possible measures rectify them

Comorbidities	*Measures to rectify*
• Fluctuation in blood glucose • Restless legs syndrome & Periodic leg movement syndrome	• Optimum glycemic control avoiding hypoglycemia • Identifying and correcting iron deficiency, thyroid disease • Rule out RLS mimics • Dopamine agonists, dopamine precursors • Antiepileptics (gabapentin, pregabalin, carbamazepine) • Opiates in severe cases (oxycodone, methadone)
• Peripheral neuropathies	• Analgesics • Antidepressants (such as TCAs, SSRI) • GABAergic agents (gabapentin, pregabalin)
• Obstructive sleep apnea	• Weight loss, positional therapy • Oral appliances • Identification and treatment of upper airway obstruction • Nasal continuous positive airway pressure
• Depression	• Modafinil in res-OSA*[21] • Antidepressants and behavioral therapy

*Residual sleepiness in OSA despite of using CPAP; GABA, gamma-aminobutyric acid; SSRI, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants

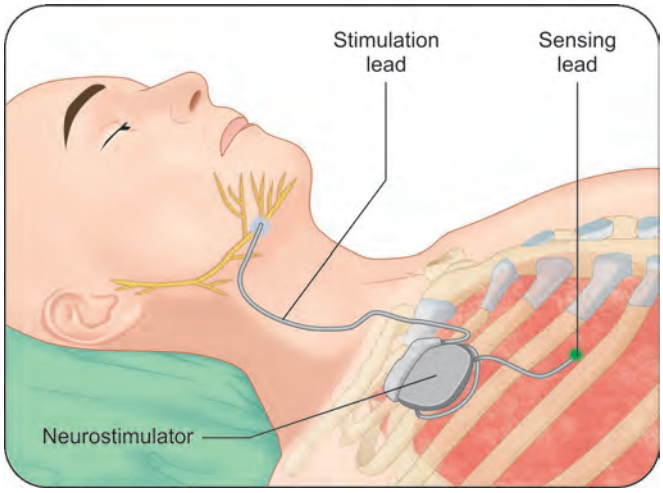


Fig. 2: Upper airway stimulation therapy

on nasal expiratory positive airway pressure (EPAP) is a new FDA approved therapy for mild to moderate OSA. Mini-CPAP consisting of battery powered micro-blowers, not requiring any hoses and masks, seems promising but still awaits FDA approval. Upper airway stimulation (UAS) therapy **(Fig. 2)** is an emerging option for refractory cases of moderate-severe OSA. Modafinil is found useful in OSA patients with residual sleepiness despite of using CPAP.[21]

Conclusion

Sleep disorders and T2DM are two events of a vicious cycle. So, ignoring sleep disorders not only leads to improper treatment of T2DM, but also helps in progression of its complications. OSA is no more considered to be a sleep disorder rather it's a gateway to metabolic syndrome. So, a routine assessment of sleep in T2DM should be done with a higher clinical suspicion in order to diagnose sleep disorders. Proper treatments of sleep disorder and its prevention by maintaining sleep hygiene should be enforced.

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CHAPTER

67 Current Status of Oral Agents in Treatment of Gestational Diabetes

AK Chauhan

Abstract

Gestational diabetes mellitus (GDM) is a serious complication of pregnancy, in which women without prior overt diabetes develop chronic hyperglycemia during gestation. Risk factors for GDM include overweight and obesity, advanced maternal age, and a family history of any form of diabetes. GDM can have an impact, not only on normal fetal development, and lead to birth complications, but also raises the risk of development of type 2 diabetes later in life. The rising prevalence of GDM globally and in India, in recent years, has placed the spotlight on better management strategies. Glycemic control has traditionally been based on a combination of diet and insulin therapy. More recent data has focused on the role of oral hypoglycemic agents, specifically metformin and glyburide.

Introduction

Gestational diabetes mellitus (GDM), is defined as "the type of glucose intolerance that develops in the second and third trimester of pregnancy, resulting in hyperglycemia of variable severity."[1] It is a severe and neglected threat to maternal and child health, with women experiencing multiple adverse pregnancy outcomes.[2] Approximately half of women with a history of GDM develop type 2 diabetes mellitus (T2DM) within 5–10 years after delivery[2] and the offspring are at increased risk for the development of obesity and T2DM early in life.[1]

There has been a steady rise in the prevalence of GDM. According to the 2019 data of the International Diabetes Federation (IDF), an estimated 223 million women between 20 and 79 years of age are living with diabetes. Twenty million or 16% of live births had some form of hyperglycemia in pregnancy and an estimated 84% were due to gestational diabetes.[2] A vast majority of cases of hyperglycemia in pregnancy occurs in low- and middle-income countries.[2]

It is important for women with diabetes in pregnancy or GDM to carefully control and monitor their blood glucose levels to reduce the risk of adverse pregnancy outcomes with the support of their health-care provider.

Etiological Factors for GDM

The rise in number of women with GDM has been attributed to increasing obesity prevalence and advancing maternal age.[1] Several risk factors, attributed to the development of GDM, are listed in **Table 1**.[1]

Pathophysiology of GDM

Normal physiology in pregnancy raises the risk of insulin resistance due to physiological increases in homeostatic hormones including cortisol, growth hormone, human placental lactogen, progesterone, and prolactin.[3] While there is a compensatory increase in the release of insulin of up to 250% in normal women,[3] in beta cells in women with GDM, are unable to compensate with sufficient insulin secretion due to pre-existing beta cell failure.[4]

TABLE 1 Modifiable and non-modifiable risk factors for GDM

Modifiable factors	*Non-modifiable factors*
High pre-pregnant BMI	Advanced maternal age
Poor dietary quality	Personal history of GDM or prediabetes
Sedentary lifestyle	Family history of diabetes
Vitamin D deficiency	Ethnicity (Asian, Hispanic, Native American, and African American)
PCOS	Maternal history of low birth weight
High total bile acid in the first trimester	Low stature Twin pregnancy Genetic susceptibility

PCOS, polycystic ovary syndrome

When insulin secretion does not increase sufficiently to counterbalance the insulin-resistant state of the later trimesters, maternal glucose intolerance leading to GDM occurs. β-cell secretory impairment is an important aspect of GDM, which is probably a pre-existing one, and thereby confers a high risk of overt diabetes post-pregnancy.[4]

Insulin mediated suppression of lipolysis is reduced contributing to increases in free fatty acids and severe insulin resistance in late gestation. There is a reduction in glucose transporter type 4 (GLUT4) translocation and decreased insulin uptake. Adiponectin levels decline and excess lipolysis and inflammation precipitates severe insulin resistance in liver, muscle, and adipose tissue.[3]

Management of GDM

The primary goal of therapy is aimed at lowering the risk of adverse perinatal outcomes, by achieving euglycemia.[4] Plasma glucose threshold goals for fasting and postprandial plasma glucose have been provided in the guidelines of the American Congress of Obstetricians and Gynecologists and the American Diabetes Association.[5] Consensus evidence-based guidelines for management of GDM in India are also available.[6]

Initial treatment of GDM includes medical nutrition therapy and moderate physical activity.[7] However, half of the women may not achieve established glucose goals with diet modifications alone and will require pharmacologic therapy.[5]

Traditionally insulin has been the mainstay of therapy for GDM as it is not known to cross the placenta. However, use of insulin in GDM comes with many challenges, the need for patient education and poor compliance, being the most common.[6] Insulin is also required to be administered as multiple-daily injections, with up to 70% risk of hypoglycemia in women, sometime during their pregnancy.[5]

Oral Antidiabetic Agents

Oral antidiabetic agents are a suitable alternative due to the lower risk of hypoglycemia, and the ease of taking the medications, without need for self-injections,[5] In addition, the pathophysiology of GDM also indicates the use of oral antidiabetic agents. The use of oral agents in pregnancy, however, involves the balancing of risk of hyperglycemia with potential medication side effects, transplacental passage and teratogenicity, and the long-term effects of the medication on the child.[5]

Among the oral antidiabetic agents, the biguanide, metformin, and the sulfonylurea, glyburide are the two well-studied agents in pregnancy. There is significant data on pharmacokinetics in pregnancy, placental transfer, and maternal and neonatal outcomes when compared to insulin use in women with GDM.[8]

Metformin

Metformin is a biguanide, "insulin sensitizer" and its mechanism of action in controlling hyperglycemia is still a topic of research. Metformin is known to inhibit gluconeogenesis, suppress hepatic glucose output, and increase intestinal glucose absorption. It is also known to stimulate glucose uptake in the liver and peripheral tissues.[5] The most widely accepted model of the anti-hyperglycemic action of metformin is the suppression of hepatic gluconeogenesis as a result of mitochondrial inhibition, via 5' AMP-activated protein kinase (AMPK). AMPK is also believed to play a key role in long-term effects of metformin by improving lipid metabolism and mitochondrial function in the liver.[9]

Metformin-Pharmacokinetics

Metformin is absorbed from the duodenum and jejunum within about 6 hours of ingestion. It has an absolute oral bioavailability of 40–60%. The drug is rapidly distributed following absorption and does not bind to plasma protein. No metabolites or conjugates of metformin have been identified. The parent drug is excreted unchanged through

the kidneys and in bile, with a half-life of about 6 hours. About 30% of the drug is excreted directly through the feces.[3]

Placental Transfer of Metformin

Metformin freely and readily crosses the placenta. Metformin is rapidly transferred across the placenta with a simultaneous decline in maternal metformin levels and increases in fetal levels in pregnant women.[8] Placental concentrations of metformin can reach at least 50% of circulating maternal levels.[3] Metformin, however, does not cross through cell membranes by passive diffusion and metformin transfer was found to be dose dependent.[8]

Effectiveness of Metformin in GDM

Metformin has been used for decades in early pregnancy in women with polycystic ovarian syndrome (PCOS). Prepregnancy metformin helps in restoring normal ovulation and improving conception. Continuing to take it through the first trimester lowers the risk of spontaneous abortion.[5]

The Metformin in Gestational Diabetes Trial (MiG) by Rowan et al., published in the New England Journal of Medicine in 2008, was the first randomized trial comparing use of metformin and insulin for treatment of GDM.[10] A total of 751 women with GDM at 20–33 weeks of gestation were initiated treatment with metformin (with supplemental insulin if required) or insulin. Of the 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. Metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin. Metformin was preferred over insulin, with more women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 27.2%, $P<0.001$).[10]

Subsequent studies have found metformin to be an acceptable alternative to insulin, to effectively achieve glycemic control in normal or slightly overweight women or those with mildly elevated fasting glucose values.

In the 2-year follow-up of offspring in the MiG-TOFU study group, no adverse outcomes above baseline risk were seen in infants born of women randomized to metformin or insulin during pregnancy. No differences were observed in central fat measures, total fat mass or percentage body fat for the infants in the metformin group. However, compared with the insulin group, the metformin group had larger upper arm circumferences, bigger biceps and subscapular skin folds, and a more favorable pattern of fat distribution suggesting a potential protective effect against later development of insulin resistance in the offspring.[11] In 2018, the MiG-TOFU study group published the longest offspring follow-up study for metformin exposure at 7 and 9 years at two individual study sites. Metformin or insulin for GDM was associated with similar offspring total and abdominal body fat percent and metabolic measures at 7–9 years.[12]

Safety in Pregnancy and Lactation

Since metformin does not stimulate secretion of insulin, it does not cause maternal hypoglycemic episodes as seen with insulin. No congenital anomalies, or teratogenic effects have been reported in the over two decades of its use in the preconception and early pregnancy period.[13]

Gastrointestinal side effects, including diarrhea, flatulence, nausea, and vomiting, affect 5–15% of women. The potential side effect of lactic acidosis, can be avoided by gradually increasing dose. This side effect has not been reported in neonates. Metformin is classified as FDA Pregnancy Category B.[5]

It is safe to breastfeed if metformin is to be continued after delivery, as levels of metformin in maternal milk are low. There are no reports of developmental or growth problems in infants of mothers using metformin while breastfeeding.[5]

Metformin Dose

Metformin is available in 500, 850, and 1,000 mg regular and extended-release tablets. The currently recommended starting dose is 500–800 mg/day, with a maximum daily dose of 2,500 mg/day, in divided dosing.[5]

Glyburide

Glyburide (also known as glibenclamide) is a second-generation sulfonylurea, which increases insulin secretion and sensitivity in peripheral tissues and reduces hepatic insulin clearance by binding to pancreatic beta-cell ATP-calcium channel receptors.[5]

Glyburide-Pharmacokinetics

Glyburide is well-absorbed with oral administration and is metabolized by the liver. It reaches peak concentration

in approximately 3 hours and has a half-life of 8 hours. Glyburide decreases circulating glucose by approximately 20% and is most effective in patients who are normal weight or slightly overweight.[14]

Placental Transfer

Hebert et al. reported that there is significant placental transfer of glyburide with fetal cord blood levels that were 70% of maternal serum levels.[15]

Effectiveness of Glyburide in GDM

Glyburide was the first oral antidiabetic agent to be tested in GDM. Effectiveness of Glyburide in GDM versus standard-of-care insulin was tested and published by Langer et al. in the New England Journal of Medicine, in 2000.[16] A total of 404 women with singleton pregnancies and gestational diabetes that required treatment were randomly assigned between 11 and 33 weeks of gestation to receive glyburide or insulin according to an intensified treatment protocol. Glyburide was equivalent to insulin in achieving glycemic control. Important neonatal outcomes were similar between glyburide and insulin-treated women included large for gestational age, macrosomia more than 4,000 g, hypoglycemia, neonatal intensive care unit admission, and fetal anomalies.[16] Subsequent meta-analysis of 9 studies, including 745 glyburide-treated and 637 insulin-treated showed similar results.[15]

It has, however, been seen that 4–21% of women with GDM may not achieve adequate glycemic control with glyburide. The characteristics of women who failed glyburide therapy included older women, multiparous, and more likely to be diagnosed at less than 25 weeks of pregnancy, with higher fasting glucose values. It has been suggested that such women may represent a group with undiagnosed T2DM and should probably not to be treated with glyburide as primary therapy.[16]

Safety in Pregnancy and Lactation

Glyburide is known to cross the placenta, and umbilical cord concentration may reach as much as 70% of maternal

TABLE 2 Comparison of glyburide and metformin in GDM

	Glyburide	***Metformin***
Mechanism of action	Increase insulin secretion, reduce hepatic insulin clearance	Increase insulin sensitivity, stimulate insulin uptake
Peak concentration	3 h	4 h
Half-life	8 h	2–5 h
Action and hypoglycemia	Action can directly cause maternal hypoglycemia	Action does not directly cause maternal hypoglycemia
Proof of efficacy	Glyburide=insulin in achieving glycemic control Failure rate: 4–21%	Metformin=insulin in achieving glycemic control Failure rate up to 46%
	Metformin failure rate may be twice glyburide failure rate Neonatal hypoglycemia similar for each Metformin associated with lower maternal weight gain	
Maternal safety-hypoglycemia	Symptomatic hypoglycemia in 1–5%	Symptomatic hypoglycemia in 0–10%, despite mechanism of action
Maternal safety-other side effects	GI, dermatologic side effects, rare elevation in liver function tests	GI side effects, rare lactic acidosis avoided with gradual dose increase
Fetal safety	Placental transfer demonstrated No known congenital anomalies	Placental transfer demonstrated No known congenital anomalies
Lactation safety	Levels in breast milk likely negligible Do not recommend breastfeeding avoidance or discarding breastmilk if glyburide indicated postpartum	Maternal milk levels negligible, 0.5% of maternal dose Do not recommend breastfeeding avoidance or discarding breastmilk if metformin indicated postpartum

concentration.[17] No congenital anomalies have been found with the use of glyburide in pregnancy. It has been placed in FDA Pregnancy Category C.[5]

In a comparative study, women using insulin experienced 4.1 asymptomatic hypoglycemic episodes whereas those taking glyburide experienced 2.1. Further, insulin-related episodes were more frequently severe at less than 40 mg/dL and predominantly nocturnal, unlike the glyburide episodes which occurred equally between day and night.[18]

Gastrointestinal symptoms including mild nausea, heartburn, or feeling full, dermatologic effects including mild itching or skin rash, and elevated liver function tests were common, but more manageable.[5]

If glyburide is initiated to manage GDM, it should be discontinued after delivery. In case there is a need to continue, levels of glyburides in maternal breast milk are negligible and undetectable in infant blood with a 5-mg daily dose.[5]

Dosing

The currently recommend starting dose of glyburide is 2.5 or 5 mg daily or twice daily, with a maximum daily dose of 20 mg, in twice daily dosing.

Glyburide or Metformin?

Glyburide and metformin have been compared in GDM. In one study by Moore and colleagues' women randomized to metformin were more than twice as likely to fail oral hypoglycemic therapy, compared with glyburide,[19] while another study reported similar failure rates for metformin and glyburide.[20] **Table 2** details the differences between metformin and glyburide in GDM.

Conclusion

Glyburide and metformin have emerged as potential oral antidiabetic agents for GDM by virtue of their efficacy and safety, over insulin and can benefit women who prefer oral medication over multiple daily insulin injections. With increasing prevalence of GDM, oral antidiabetic agents may be treatments to be considered. However, there is a paucity of long-term offspring safety data, which could be the reason why most professional societies still recommend insulin as the sole first-line option for treatment of GDM.

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CHAPTER

68

Diabetes in Young: Challenges

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Abstract

Diabetes mellitus (DM) is one of the most prevalent non-communicable diseases that lead to a significant morbidity and mortality. Worldwide, the pandemic of DM was 9.3% of global population in 2019 and projected to increase to more than 10% by 2030. In India, the estimated number of people living with diabetes was 77 million in 2019 and will reach to 101 and 134 million by 2030 and 2045, respectively. The prevalence of diabetes in children and adolescents is increasing worldwide, with profound implications on the long-term health of individuals. Young-onset type 2 diabetes also affects more individuals of working age, accentuating the adverse societal effects of the disease. The diagnosis and management of diabetes in youth presents several unique challenges. Although type 1 diabetes is more common among children and adolescents, the incidence of type 2 diabetes in youth is also on the rise, particularly among certain ethnic groups. The management of diabetes in children and adolescents is challenging in some cases due to age-specific issues and the more aggressive nature of the disease.

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic and its prevalence is continuously increasing. Initially it was considered as a disease of elderly population, but in current scenario it is equally seen in young population. Early appearance of this disease is associated with long-term major complications like microvascular and macrovascular complications. T2DM is most common type of diabetes and it is an estimation that by 2025, ~7.7% world's population will be affected with T2DM.[1] Under 40 years of age its prevalence is now increasing and early exposure will be having more complications in later part of life.[2-4] The development of T2DM at early age leads to serious health problem due to prolonged exposure to adverse risk factors like hyperglycemia and other components of the metabolic syndrome. And that is why it has become a major public health concern. Major concerns of T2DM in young adults are firstly it will be very aggressive as it develops at very young age and leads to various complications; secondly there is not long-term outcome studies are available to evaluate T2DM impact on young adults and lastly it certainly affects socioeconomic health of society.[5] This review article aims to explore the magnitude of the evolving problem and challenges physicians face in managing T2DM in younger adults.

Global Scenario of Diabetes Mellitus

Globally, 463 million population is living with diabetes mellitus, wherein china has the highest number of DM population, followed by India, which has 77 million diabetic population. From the current DM population, it is anticipated that by 2045, with the growth of 51%, globally total DM population will be 629 million; wherein currently 75% are from working-age between 30–55 years.[1,6] It is estimation that currently 5.8–6.4 years of life are lost in diabetes at the age of 50 years,[1] which can

TABLE 1 Prevalence estimates of Type 2 diabetes in adolescents and youth from the USA and UK studies

Study	*Prevalence of T2DM*	*Age group (years)*	*Year assessed*	*Source*
The SEARCH study (USA)	0.34/1000	<19	2001	Cross-sectional actie surveillance and case ascertainment
The SEARCH study (USA)	0.46/1000	<19	2009	As above
Ehtisham (UK)	0.21/100,000	<16	2000	Cross-sectional questionnaire survey of pediatric diabetes centers
Hsia (UK)	1.9/100,000	<18	2005	Retrospective cohort study: analysis of antidiabetic prescription for children from GP data
Royal College of Pediatrics and Child Health (UK)	3/100,000	<18	2009	Cross-sectional survey by secondary care clinicians in England

T2DM: Type 2 diabetes mellitus

lead to adverse social and economic complications.[6] For instance reported incidence varies from 0–330/100,000 person years depending on the age, gender, geography, and ethnicity of the study population and geographical region **(Table 1)**.[5] Globally many prevalence studies on T2DM are available but focusing on young T2DM patients is still waiting.

Challenges in Diagnosis of Diabetes in Young Patients

Insulin resistance is a pathological hallmark of T2DM and it is commonly associated with other conditions like obesity, polycystic ovarian disease (PCOD), and non alcoholic fatty liver disease (NALFD). These all metabolic conditions are overlapping with each other. In young people with T2DM is frequently associated with conditions like obesity and other cardiovascular risk factors such as hypertension, dyslipidemia, and nephropathy, which appear quite prevalent at the time of diagnosis and probably estimate abnormal glucose metabolism. Many times, patients will not have any symptoms of T2DM and it is detected incidentally, while in some case it may present with overt symptoms of T2DM like extreme weight loss, urinary tract infections, frequent urination, thirst or hunger, etc.[7,8] Differential diagnosis between T1DM and T2DM is very challenging as previous one is commonly associated with young age group of patients. And incorrect diagnosis of both diseases will cause adverse complications in patients. Incorrectly diagnosing T2DM in a young patient with T1DM could be life threatening if the situation is managed with oral diabetes medication rather than insulin. Likewise, misdiagnosing T1DM as T2DM can result in unnecessary life-long treatment with insulin, when alternative glucose lowering therapies may be more appropriate. Through biochemical test it can be differentiated, where in persistently high serum insulin and C peptide concentration is characteristic of T2DM and would be unusual in T1DM. However, at initial phase of diagnosis, these biochemical features are overlapping and may lead to misdiagnosis as well **(Table 2)**.[9,10]

Challenges in Management of Diabetes in Youngs

In T2DM, long-term evaluation and treatment is very challenging among many patients. Especially in young adults, to achieve target HbA1c and reduce blood sugar is difficult compared to adults. Even in 5 years of follow-up with therapy, young population find difficulties to achieve target with lesser complications. It is concerning to note that the proportion of young T2DM patients with suboptimal glycemic control was as high as 57% in the primary care setting in the UK.[5]

Proper Education

Appropriate education and life style modification certainly delay new onset of DM and also reduces severity of complications. But young T2DM patients have more depression and T2DM related stress, and they are failed to follow on regular guideline recommendations.

Glucose Lowering Therapy

In the management of T2DM along with glycemic control and HbA1c level <6.5% is an utmost important goal but along with that appropriate lifestyle modification, weight control is also required to get desired medication

TABLE 2 Differentiating features of different types of DM

	T1DM	*T2DM*	*MODY*
Prevalence (among young people with diabetes)	>90%	<10% (Japan 60–80%)	1–3%
Clinical features			
Onset	Usually acute onset	Usually insidious onset	Variable
Osmotic symptoms (polyuria, polydipsia, weight loss)	Prononounced	Often asymptomatic but can present with severe symptoms in some cases	Variable
Ketosis	Almost always present	Usually absent (except Afro-Caribbean origin)	Common in neonatal forms, rare in others
Body habitus	Usually not obese	Often osese	Usually not obsese
Signs of insulin resistance	Rare	Often present	Rare
Association with other autoimmune disorders	Yes	No	No
Family history in parents	2–4%	80%	90%
Diagnositic aid biomarkers			
Antibodies	ICA, Anti-GAD, ICA 512-positive	Negative	Negative
C-peptide	Negative	Positive	Noral range
C-peptide/reatinine ratio	Low	High	Normal
Treatment			
	Insulin	Oral hypoglycemic agents	Variable from diet to sulphonylurea to insulin

effect.[11] Physical exercise like aerobic activity, alone or in combination with diet, can reduce weight, body lipid level, elevated blood pressure and also helps to maintain healthy mental status as well.[12] For pharmacological management approach, metformin is the most appropriate starting point for any age group with T2DM. Results of the TODAY study suggest that monotherapy with metformin was associated with durable glycemic control in children and adolescents.[13] Apart from this in young age group patients, currently, many newer oral anti-diabetic agents are recommended which not only control sugar level but also reduce cardiovascular mortality as well like sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1), dipeptidyl peptidase-4 (DPP-4) inhibitors. Metformin is always considered as first-line therapy until any contraindications, but after metformin or along with metformin if the patient has any marked CV risk factor then SGLT2 inhibitors, GLP-1 analogues are preferred agents. Treatment with these agents may increase the cost of therapy but proper counselling of patient may improve adherence to this therapy. In alternative cases, along with metformin other agents like sulfonylureas, meglitinides, thiazolidinediones, α-Glucosidase inhibitors, DPP-4 inhibitors are preferred options. In case of uncontrolled sugar level after dual oral antidiabetic drugs, or HbA1c level is more than 9% or T1DM; insulin injections and its analogues are preferred option to manage DM.[14] Bariatric surgery has emerged as a viable treatment option in young individuals with type 2 diabetes and evidence has shown that it is safe and effective in obese adolescents.[15]

Conclusion

Type 2 DM is going to be epidemic in younger adults and they are on high risk for development of diabetes-related complications such as nephropathy and CVD at early in the disease process with high mortality at a relatively young age. However, there are many gaps and lack of evidence for intervention to either optimize glycemic control or to address CV risk factors also results in non-standardized treatment and inevitable variations in standards of care in a young population. There is a need for sufficient scientific data and focused guideline-based approach for management of DM in young population for having a balanced socioeconomic condition in future.

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CHAPTER

69 Management of Postprandial Hyperglycemia

Dinesh Sharma, Jugal Kishor Sharma

Abstract

Diabetes is increasing all over the world, so are its complications. There is much evidence that postprandial hyperglycemia is a major contributing factor for atherosclerosis development, causing cardiovascular morbidity and mortality in diabetic patients. There are rapid and high blood glucose levels after meals in diabetic patients known as hyperglycemic spikes responsible for cardiovascular complications. Hyperglycemia generates free radicals, which lead to atherosclerosis formation by multiple mechanisms. Early recognition and treatment of postprandial hyperglycemia by pharmacological and non-pharmacological means can prevent cardiovascular complications.

Introduction

Diabetes mellitus (DM) is a metabolic disorder due to defects in insulin secretion, insulin action, or both, thereby causing hyperglycemia. Chronic hyperglycemia is associated with long-term damage and dysfunction of different organs such as the eyes, kidney, nerves, heart, and blood vessels. Many studies have shown that increased plasma glucose in the body is an independent risk factor for morbidity and mortality in diabetic patients due to cardiovascular complications. Isolated postprandial hyperglycemia (PPHG) blood sugar >140 mg/dL (7.8 mmol/L), with normal fasting sugar <110 mg/dL and normal HbA1c (<6.1) is associated with a twofold increase in cardiovascular deaths. Management of PPHG becomes necessary as increased fasting glucose level alone is not a risk factor to cause cardiovascular complications.[1,2] This is a well-established fact that controlling blood sugar levels (HbA1c <7.0%) can reduce the progression of diabetic complications.[3-5] The risk of cardiovascular disease can be prevented by proper control of postprandial glucose. Management of PPHG is more difficult than FPG because there are no standard guidelines and treatment practices among diabetologists and physicians. However, treatment modalities are now available to treat PPHG, such as AGI, Glinides, Short-acting SU, Insulin analogs, DPP4 inhibitors, and GLP-1 derivatives.

Diagnosis

ADA in 2013 defined PPHG as a 2-h plasma glucose level of more than 200 mg/dL (11.1 mmol/L) for diabetes and 140–199 mg/dL for IGT by oral glucose tolerance test. The glucose load is 75 gm glucose dissolved in water as per the recommendation of WHO.[6]

IDF defines PPHG as a plasma glucose concentration of 140 mg (7.8 mmol/L) or more after 1–2 hours of food ingestion.[7]

Current guidelines recommend self-monitoring of blood glucose (SMBG) for assessing plasma glucose levels in diabetic patients. The timing and frequency are individualized according to the treatment regime and glycemic control.[7] Some emerging technologies for evaluating postprandial glucose levels are CGM and plasma 1.5-anhydroglucitol (1.5AG).[8] CGM measures plasma glucose every 1–10 minutes by a sensor; this is

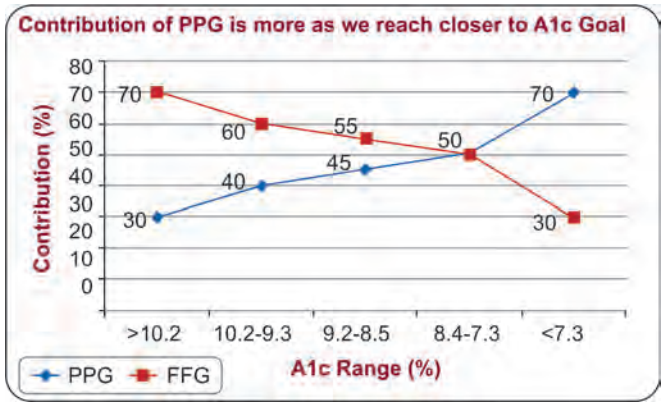


Fig. 1: As patients get closer to A1c goal, the need to manage PPG increases

transmitted to a storage device. 1.5AG is a natural dietary polyol that is the marker for postmeal hyperglycemia, but it is not readily available at this time.[9,10] HbA1c values can give many indications of PPG. Monnier et al. in 2003 demonstrated that contribution of PPG to glycemic load varies with the degree of glycemic control. In poorly controlled (HbA1c >10.2%), it was only 30% of the 24 hours. AUC, in better-controlled patients (HbA1c <7.3–8%), the contribution of PPG was 70–50%[11] **(Fig. 1)**. Flash glucose monitoring is a new noninvasive glucose monitoring launched by Abbott, using a sensor applied on the back of the arm, which measure and stores glucose values for 14 days. Compared to SMBG, which is painful and inconvenient, this is a safe, effective, and better alternative method.[12,13]

Epidemiology

PPHG is a frequent and under-diagnosed condition. Dickson et al. reported that Asian Indians had a marked increase in postprandial sugar after 75 gm of bread meal.[14] There is a direct relationship between CVDs and glycemic control in patients with type 2 DM (T2DM).[15] One study of 90 patients with T2DM demonstrated that isolated PPHG was seen in 24.4% of patients.[15] The mean HbA1c was a good indicator of IHD, as observed in the UKPDS study.[16] There was a ~10% increase in cardiovascular disease risk with each 1% increment in HbA1c. In the interventional version of UKPDS, intensive treatment with ~1% reduction in HbA1c leads to a 16% less MI incidence.[17] Many other studies such as Hoorn Study, Honolulu Heart study, Chicago Heart Study,[18] and DECODE study[19,20] have reported that postprandial glucose is a major CV risk indicator. This was confirmed by Coutinho et al.[21] and with pooled data of Whitehall Study, Paris Prospective Study, and Helsinki Policeman Study.[22] Diabetes Intervention Study favors PPHG as an independent risk factor for MI.[23] STOP-NIDDM data indicates acarbose for treatment for IGT can reduce 36% risk in progression to diabetes and 34% in the development of new hypertensive cases, and 49% in cardiovascular complications. A significant decrease in the progression of intima-media thickness was seen in a subgroup that is a surrogate for atherosclerosis.[24]

Pathophysiology

In nondiabetic individuals, the blood glucose levels begin to rise ~10 minutes after the start of a meal, with a peak at 60 minutes and returning to pre-prandial levels within 2–3 hours. Even after that, the absorption of ingested carbohydrates continues for 5–6 hours after a meal. PPHG depends on carbohydrate absorption, insulin, and glucagon secretion and their effect on glucose metabolism in peripheral tissue and the liver. In T2DM, peak insulin levels are delayed and insufficient to control PPG excursions, while in T1DM, peak insulin levels depend on the type of insulin injected as there is no endogenous insulin secretion. In diabetic patients, abnormalities in secretion of insulin and glucagon, hepatic glucose uptake, decreased hepatic glucose production, and peripheral glucose utilization lead to higher and prolonged PPG excursions than nondiabetics. Isolated PPHG doubles the risk of cardiovascular deaths,[16] and it is the earliest abnormality of glucose homeostasis in T2DM and further progress to fasting hyperglycemia.[25] During the meal, insulin is secreted in two phases. In the first phase, a small amount of insulin is secreted over approximately a 10-minute period, which controls postprandial glucose excursions. More sustained second phase insulin secretion occurs as plasma glucose levels increase and depend on the meal's glycemic load. The earliest manifestation of diabetes is the loss of first-phase insulin release, leading to increased PPG and free fatty acids, which delays second-phase insulin response **(Fig. 2)**. PPHG leads to increased lipid levels, triglycerides, and lipoprotein particles. This is known as postprandial dysmetabolism, which is a major risk factor for cardiovascular events.

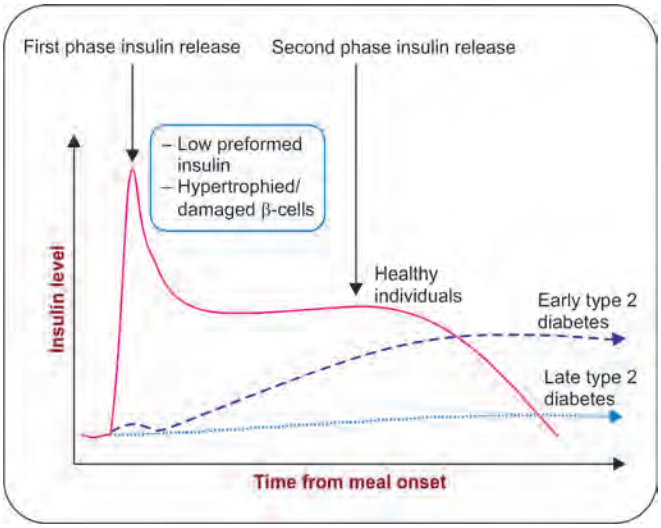


Fig. 2: Delay of first phase insulin in early type 2 DM

The main pathophysiological mechanism leading to cardiovascular damage is endothelial dysfunction, oxidative stress, and activation of inflammation, and coagulation mechanisms, thus facilitating lipoprotein particles' penetration into the arterial wall.[8] Hyperglycemia generates free radicals, promoting atherogenesis through peroxidation of LDL, fibrinogen oxidation leading to increased coagulation products, increased platelet activation by collagen,[26,27] and decreased production of nitric oxide.[23] Recent studies suggested that hyperglycemia causes an overproduction of superoxide by the mitochondrial electron-transport chain,[28] leading to an increase in NO generation due to endothelial NO synthase (eNOS) and inductively NO synthase (iNOS) uncoupled state, which leads to the formation of strong oxidant peroxynitrite, which damages DNA.[29] DNA damage stimulates activation of nuclear enzyme poly (ADP ribose) polymerase. This leads to depletion of the intracellular concentration of NAD+, decreases the rate of glycolysis, electron transport, ATP formation, and produces an ADP ribosylation of the GAPDH (glyceraldehyde-3-phosphate dehydrogenase).[29] All this results in acute endothelial dysfunction in diabetic blood vessels, which leads to the development of CVD[29] (**Flowchart 1**). Many direct and indirect evidence support this concept.

Management

Management of PPG includes non-pharmacological and pharmacological interventions. These are as follows.

Screening Tests

ADA recommendations for screening for PPG in all asymptotic patients who are overweight (BMI >25 kg/m^2) and have additional risk factors. Also, in other conditions such as IGT, high-risk CVD, GDM, Hypertension, Dyslipidemia, PCOD, Acanthosis nigricans, and first-degree relatives of people with diabetes. SMBG is important for detecting and treating PPHG, which is to be monitored in gestational diabetes and patients having high HbA1c and normal FBG.

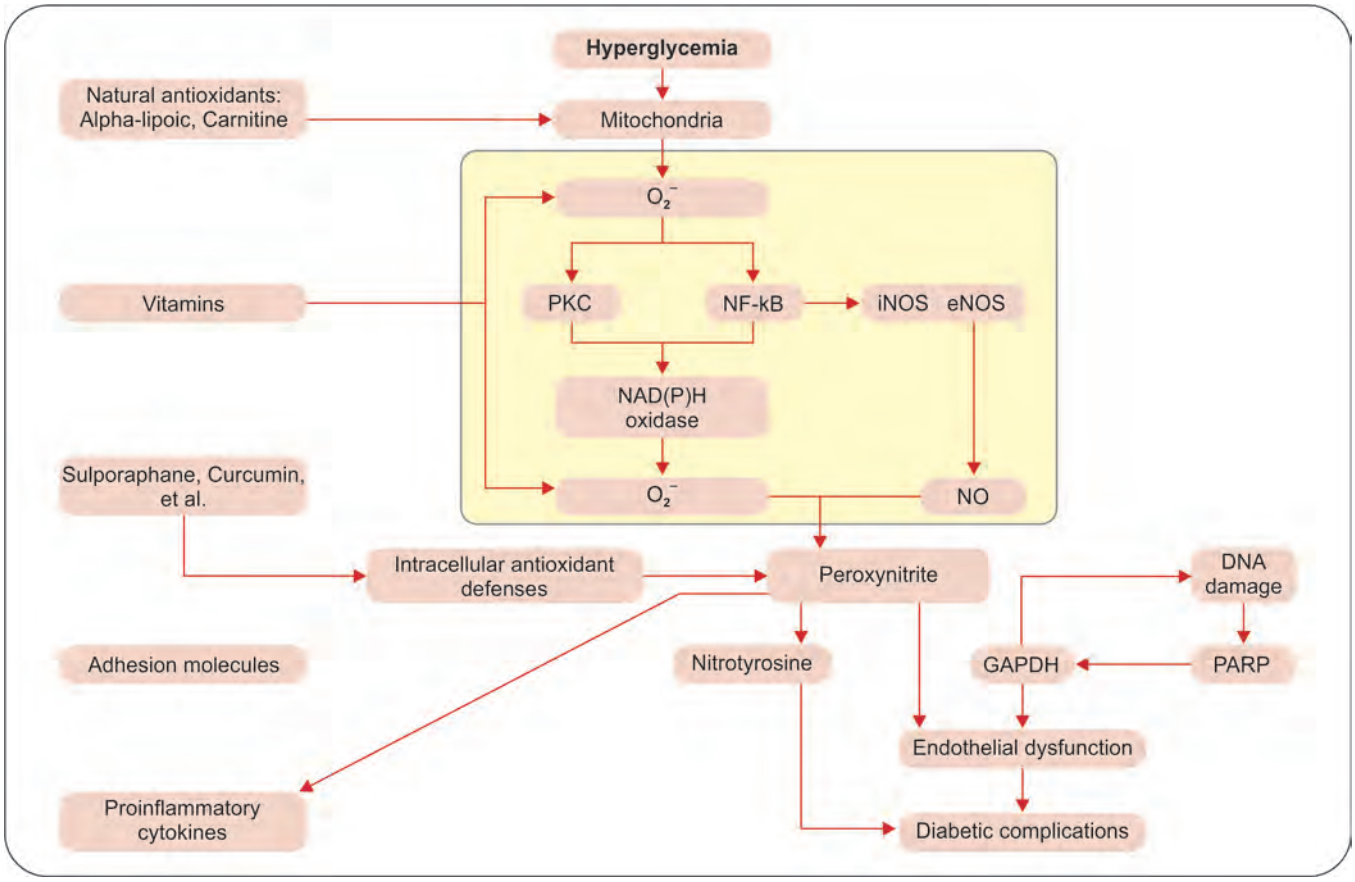
Non-pharmacological Therapy

In patients with IGT and T2DM with suboptimal glycemic control (HbA1c 7–8%), lifestyle modifications such as weight reduction, exercise, and dietary control can maintain normal glucose levels, thereby reducing the risk of development of diabetes.[30-32] Exercise helps in glycemic control by increasing insulin sensitization. Dietary modification for PPHG control depends on the type and quantity of carbohydrates taken. Foods with a high glycemic index (GI), such as rice, pasta, potatoes, white and brown bread, and breakfast cereals, have more glycemic load (GL), which is the product of carbohydrate content of the diet and its average GI. Low GI foods such as legumes, most of the fruits, which are slowly digested and absorbed, will cause less GL. The higher GL in the Indian diet causes more prandial glycemic excursions, increased incretin and glucosidase activity in the gut leading to high lipemic peaks resulting in CVS diseases. It is recommended that the diet should contain 45–65% carbohydrates of total calorie intake, food with a low GI, unsaturated fat, high fiber, fruits and vegetables, and pulses.

Pharmacotherapy

Pharmacotherapy is indicated when lifestyle modifications do not control the PPHG. Drugs that target PPHG may be given as monotherapy or in combination, which includes alpha-glucosidase inhibitors (AGI), Glinides, short-acting Sulfonylureas (SU), DPP-4 inhibitors, glucagon-like peptides (GLP-1) derivatives, and rapid-acting insulin.[33,34] SU and insulin sensitizers (metformin and thiazolidinediones) mainly affect fasting blood sugar; however, a combination of metformin and glyburide has shown a reduction in postprandial glucose excursion in some studies.[35]

Flowchart 1: Hyperglycemia



Meglitinides (Repaglinide and Nateglinide)

These are non-sulfonylurea insulin secretagogues that bind to islet beta cells at different sites than SU with different kinetics, which mainly affect early insulin release. They are recommended just before meals for early insulin release and a short half-life. Repaglinide is a new class of non-sulfonylurea secretagogues, which after oral administrations with meals, has rapid and short-lived insulinotropic action.[36] This is less hypoglycemic and weight neutral than SU. It is used as mono or combination therapy with metformin, insulins, and thiazolidinediones. Nateglinide is rapid-acting with a shorter duration of action than repaglinide.[37] It is less effective and causes less hypoglycemia than repaglinide.

Alpha-glucosidase Inhibitors (Acarbose, Miglitol, and Voglibose)

Inhibits glucosidase enzyme in the brush borders of the small intestine, which breaks down the disaccharides and more complex carbohydrates, thereby delaying the carbohydrate digestion, which reduces PPHG. Acarbose also increases the secretion of glucagon-like peptide (GLP-1). AGI causes abdominal pain, diarrhea, and flatulence.[38,39]

GLP-1 Analogs

It is an incretin hormone secreted by gut L cells into the circulation after meals, which lowers glucose by stimulating glucose dependent insulin secretion through activation of cyclic AMP dependent protein kinase in pancreatic Beta cells, inhibits glucagon secretion, delays gastric emptying, and induce satiety. Liraglutide and Exenatide are commercially available GLP-1 analogues. Subcutaneous injection of GLP-1 effectively reduces PPHG in people with T2DM with a low risk of hypoglycemia.

DPP-4 Inhibitors

Inhibits the DPP-4 enzyme causing degradation of GLP-1, which increases the active form of the hormone. This

stimulates glucose-dependent insulin secretion and suppresses glucagon release. DPP-4 inhibitors improve HbA1c by decreasing postprandial glucose without causing hypoglycemia. These are used as monotherapy or in combination with other oral hypoglycemia agents.

Insulin and Insulin Analogs

Injection of regular or long-acting insulin before meals will decrease postprandial glucose. Genetically engineered insulins are insulin analogues that are more beneficial than human insulin and cause less risk of hypoglycemia, improved physiological profile, and negligible weight gain. Rapidly acting insulin analogues effect is the same as normal insulin secretion, having faster absorption, shorter duration of action, and peaks about 1 hour after injection. These are insulin aspart, insulin lispro, and insulin glulisine.

Conclusion

PPHG alone can cause both microvascular and macrovascular complications in diabetic patients, thereby leading to cardiovascular morbidities and mortality. It is a better indicator of glycemic control than fasting blood glucose (FBS). Patients having normal fasting blood sugar and HbA1c, control on diet, exercise, and medical therapy may have uncontrolled PPHG. The main pathophysiology for PPHG is impaired early insulin secretion in diabetic patients. Early detection, optimal glycemic control, and treatment by effective medications can reduce diabetic complications. The emerging new treatment modalities such as meglitinides, AGI, GLP-1 agonists, insulin analogues, and DPP-4 inhibitors that target PPHG are now available to control PPHG, thereby preventing cardiovascular complications.

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CHAPTER

70 Sexual Dysfunctions in Diabetes Mellitus

Jugal Kishor Sharma, Dinesh Sharma, Sunil Sharma

Abstract

Diabetes mellitus is reaching near to pandemic state and causes many psychological and sexual problems other than retinopathy, neuropathy, nephropathy, and other macrovascular complications. Sexual dysfunction is one of the most common complications and most under diagnosed complications of diabetes mellitus. This is common in both male and female because of end organ damage and psychological stress caused by diabetes mellitus. Sexual dysfunction maybe an early sign of diabetes mellitus and can occur in any phase of sexual process. Male sexual dysfunctions include disorders of libido, ejaculatory problem, and erectile dysfunction. All these can cause significant problems and affect the quality of life. Erectile dysfunction is three times more common in diabetic patients than in non-diabetic. There is multifactorial pathology but the common is endothelial dysfunction and autonomic neuropathy. Sexual dysfunction in females is difficult to identify and there are limited studies on it but there can be many problems such as arousal, lubrication, and orgasmic dysfunction. Diabetic patients do not volunteer their problems, hence the health-care professionals should routinely question about the sexual problems because it can cause deleterious effect on relationship and quality of life of both the partners. Many treatment options are now available to manage the sexual problem in time.

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases in almost all countries; its increase is near to pandemic assumptions. As per the 2015 reports of the International Diabetic Association (IDA), more than 371 million people had diabetes in 2012; by 2040, the number of people with diabetes is expected to be 642 million.[1] It is a well-known fact that DM causes different medical, psychological, and sexual complications.[2] Both macrovascular (including CVD) and microvascular (including retinopathy, nephropathy, and neuropathy) complications are associated with complications of diabetes.[3] Sexual dysfunction (SD) is a common occurrence in diabetic patients in both men and women due to diabetes-induced end-organ damage and psychological stress.[4-7] In some instances, SD can be an early sign of DM.[8] SD can occur in any of sexual function phases: desire, arousal, plateau, orgasm, and resolution.[9]

Sexual Dysfunction in Men

Diabetes is a known risk factor for SD in men. Most common SD in men with diabetes is erectile dysfunction (ED). ED is three times more common in people with diabetes compared to non-diabetic men.[5,10] Factors responsible for ED in diabetes varies from psychological, physical, and social. Anxiety is an essential factor responsible for erectile disorder and premature ejaculation in diabetes. Low sexual satisfaction, sadness, low self-esteem, distress, and depression can express in persons suffering from SD. ED may be defined as the perpetual inability to attain or maintain penile erection for successful sexual intercourse causing the compromised quality of life in men.[11,12]

TABLE 1 The sexual health inventory for men (SHIM)

How do you rate your confidence that you could get and keep an erection?		Very high	High	Moderate	Low	Very low
		1	2	3	4	5
When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No. Sexual activity	Almost always or always	Most time (much more than half the time)	Sometime (about half the time)	A few times (much less than half the time)	Almost never or never
	0	1	2	3	4	5
During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered your partner?	Did not attempt intercourses	Almost always or always	Most time (much more than half the time)	Sometime (about half the time)	A few times (much less than half the time)	Almost never or never
	0	1	2	3	4	5
During sexual intercourses, how difficult was it to maintain your erection to completion of intercourse?	Did not attempt intercourses	Not difficult	Slightly difficult	Difficult	Very difficult	Extremely difficult
	0	1	2	3	4	5
When you attempted sexual intercourses, how often was it satisfactory for you?	Did not attempt intercourses	Almost always or always	Most time (much more than half the time)	Sometime (about half the time)	A few times (much less than half the time)	Almost never or never
	0	1	2	3	4	5

Incidence of ED is directly proportional to the age. By the year 2025, the worldwide prevalence of ED is expected to reach 322 million patients.[13]

Diagnosis of Male Sexual Dysfunction

Diagnosis of ED in a person can be made using standardized questionnaires involving his sexual activity. One such suitable questionnaire commonly used is the International Index of Erectile Function (IIEF)-5, which comprises items 5, 15, 4, 2, and 7 from the full-scale IIEF-15. A score of 21 or less suggests the possibility of ED.[14] Other scales used are the Sexual Functioning Questionnaire—male, Arizona Sexual Experience Questionnaire (ASEX), Male Sexual Health Questionnaire (MSHQ), and Premature Ejaculation Profile (PEP) **(Table 1)**. To work out your level of erectile function/dysfunction, add the numbers are corresponding to questions 1-5. The Sexual Health Inventory for Men further classifies erectile dysfunction as 1–7 severe, 8–11 moderate, 12–16 mild to moderate, and 17–21 mild ED.

Sexual Dysfunction in Women

The link between SD and diabetes is well established in men. However, among women, the data to support this association is lagging despite a significantly higher prevalence of female sexual dysfunction (FSD) in women who have diabetes as compared with women without diabetes.[15,16] As per the American Foundation of Urological Diseases (AFUD), female sexual dysfunction (FSD) comprises four components:

- Hypoactive sexual desire disorder (HSDD; reduced frequency of sexual intercourse, aversion to intercourse)
- Female arousal disorder (FAD; inability to achieve arousal)
- Female orgasmic disorder (FOD; inability to achieve orgasm)
- Sexual pain disorder (SPD; dyspareunia).

Also decreased sexual desire, lack of sexual satisfaction, decreased vaginal lubrication, and orgasmic dysfunction have been documented in a few studies conducted in women suffering from DM.[17] Anxiety and depression in women lead to difficulty in arousal, orgasm, and achieving pleasure.[18] Furthermore, SD interferes in cordial relationship with the partner. It increases emotional stress, and in the absence of regular communication, it may end up with divorce due to less marital satisfaction, difficulty in resolving problems and decreased self-care behavior, which may result in poor glycemic control.[19] FSD is caused

by disturbances in psychophysiological factors and alters the sexual response cycle in the female, which consist of disorders of sexual desire, arousal, pain, and orgasm.

Diagnosis of Female Sexual Dysfunction

In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) combines sexual desire and arousal disorders into the "female sexual interest/arousal disorder" category, whereas vaginismus and dyspareunia together constitute "Genito-pelvic pain/penetration disorder" category. A woman suffering from these symptoms for a minimum of 6 months fits into the criteria for making a diagnosis. For distinguishing transient sexual difficulties from more persistent SD, severity criteria are used.

The Diagnostic tools used to diagnose SD in females are:

Female Sexual Functioning Index: It consists of 19 questions with six domains, desire (2 questions), arousal (4 questions), lubrication (4 questions), orgasm, satisfaction and pain (3 questions each). Sexual activity of the last 4 weeks is evaluated, and a score of less than 26.55 confirms SD.

Arizona Sexual Experience Questionnaire (ASEX): It consists of 5 components scale with five domains—sex drive, arousal, lubrication, orgasm, and satisfaction following orgasm. It evaluates the sexual activity of last week, including the consulting day. A total ASEX score of ≥19, anyone component with a score of ≥5, or any three components with a score of ≥4 suggests SD.

Sexual Functioning Questionnaire (SFQ): 28 items with six domains—Desire, Arousal, Orgasm, Pain, Enjoyment, and Partner relationship.

Female Sexual Distress Scale-Revised (FSDS-R): 13 items, and one domain included is distress about sexual life. Sexual Interest and Desire Inventory (SIDI)—15 items for Hypoactive Sexual Desire Disorder Domain.

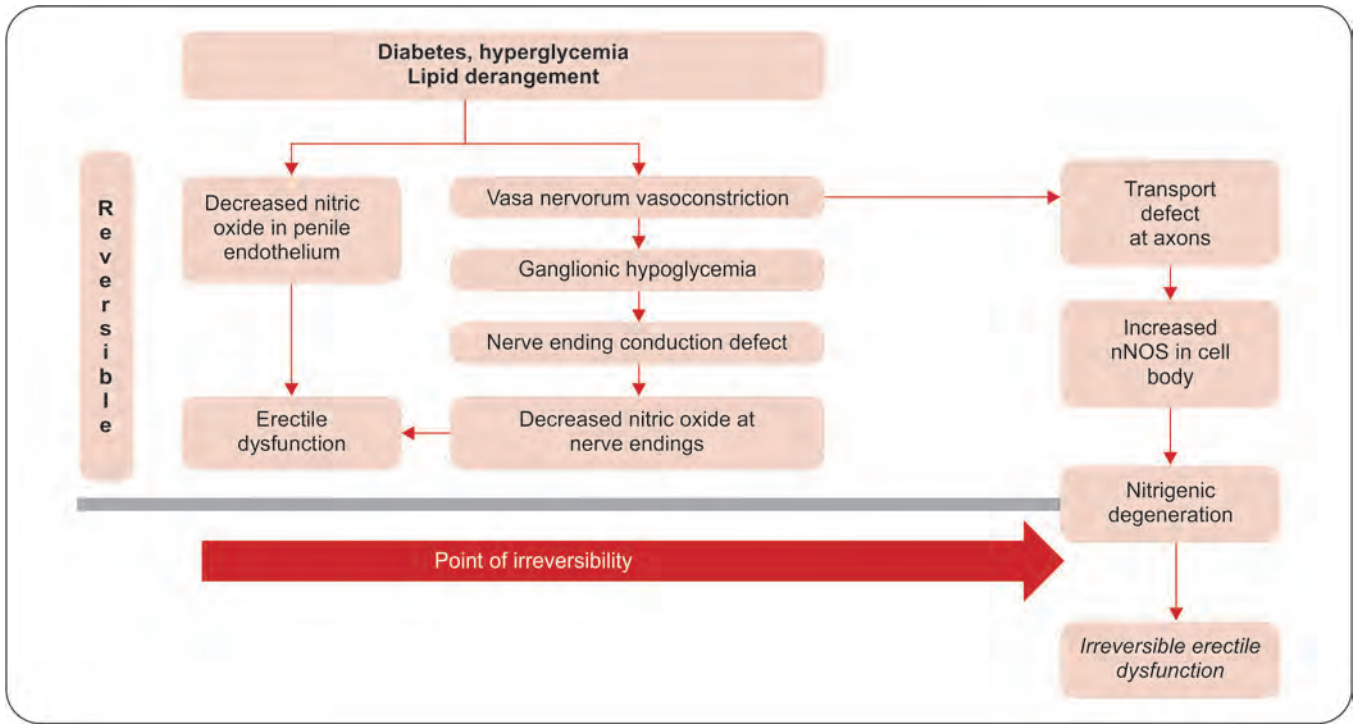
Pathophysiology

Pathophysiology of ED in diabetes is manifold which develops gradually. Usually, psychological and biological factors work together resulting in an erection.[20] In an average person, psychological arousal results in parasympathetic stimulation leading to nitric oxide (NO) release from local endothelial cells. NO release causes smooth muscle and vascular relaxation resulting in increased arterial flow in penile corpora cavernosa. This increased blood flow hampers venous return by causing compression of penile venules, which maintains the penile erection. The mechanism of ED in diabetic patients is the result of vasculopathy, neuropathy, insulin resistance, visceral adiposity, and hypogonadism. Vasculopathy is the result of endothelial dysfunction, macroangiopathy and microangiopathy. Macrovascular complications of diabetes lead to atherosclerotic damage in blood vessels causing decreased blood flow to the penis.[21] Microvascular complications impair distal circulation leading to ischemic damage, autonomic and peripheral neuropathy. This results in impairment of sensory impulse from the penis to reflex erectile center thereby inhibiting parasympathetic activity necessary for smooth muscle relaxation of corpus cavernosum. Norepinephrine and acetylcholine positive fibers in the corpus cavernosum are reduced in people with diabetes which impairs muscle relaxation. Endothelial dysfunction in diabetes is caused by decreased nitric oxide bioavailability, which impairs relaxation of the vascular smooth muscle of corpora cavernosa.[22] Accumulation of advanced glycation end products, increased free radicals levels, decreased bioavailability of NO are few causative factors in endothelial dysfunction, which leads to increased vasoconstriction due to imbalance between vasoconstriction and relaxation.[23]

Around 25% of diabetic males have low testosterone levels with low luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Testosterone is necessary for the erectile function. It regulates smooth muscle relaxation, the endothelial function of corpora cavernosa.[24] It regulates the timing of erection, sexual desire, and maintains the penile erection during sex. Overweight and obese diabetic males having insulin resistance and visceral adiposity have proinflammatory state leading to decrease the bioavailability of NO causing ED.

SD in diabetic female includes loss of sexual desire, arousal, lubrication difficulties, dyspareunia, and loss of orgasm.[25] Diabetes causes vascular and nerve dysfunctions, which impair sexual response by causing functional and structural changes in female genitalia. Vascular abnormalities causing atherosclerosis and endothelial dysfunctions are responsible for reduced clitoris engorgement and vaginal lubrication, which attenuates arousal and causes dyspareunia during coitus.

Flowchart 1: Flowchart of pathophysiology of erectile dysfunction



Diabetic neuropathy also alters normal transduction of sexual stimuli and initiating a sexual response.[26] FSD maybe because of imbalance in hormonal levels in diabetic females. Some epidemiological studies suggest an association between sexual problems in diabetic females and levels of estrogens, androgens, and sex hormone-binding globulin. Many endocrinal dysfunctions of thyroid, hypothalamic-pituitary, polycystic ovarian syndrome also contribute to this problem in such females[27] **(Flowchart 1 and Fig. 1)**.

Management

There are many treatment modalities for SDs in both males and females, which include:

Lifestyle modification: Regular exercise, weight reduction, blood glucose monitoring, thereby maintaining a reasonable glycemic control, control of hypertension, cessation of alcohol intake, smoking cigarette, and avoiding drugs which cause ED will help and lowers the risk of developing SD. The effect of lifestyle modification on ED in diabetic patients is modest.[28]

Phosphodiesterase type 5 inhibitors (PDE5I): PDE5I revolutionized the treatment of ED, this class of oral agents are the treatment of choice. FDA approved sildenafil, vardenafil, tadalafil, and avanafil for the treatment of ED. The action of PDE5I depends on the NO/cGMP pathway. Sexual stimulation causes the release of NO from cavernous nerves and endothelial cells. By multiple mechanisms, cGMP causes penile smooth muscle relaxation, which is deactivated by PDE5 found in the penis.[29] PDE5I prevents the deactivation of cGMP, resulting in persistently elevated levels of cGMP, which in turns maintain continued smooth muscle relaxation of the penis. The release of NO is mediated by neuronal and endothelial NO Synthase (NOS). Diabetic patients develop neuropathy and endothelial dysfunction, which blunts the efficacy of PDE5I. That is why the effect of PDE5I is better in non-diabetics than diabetic patients. These drugs are to be taken 1–2 hours before intercourse, and their effectiveness require sexual stimulation. Side effects are headaches, light-headedness, flushing and dizziness. These are contraindicated in patients taking nitrates IHD, CHF, HOCM, and hypertension. Another oral drug

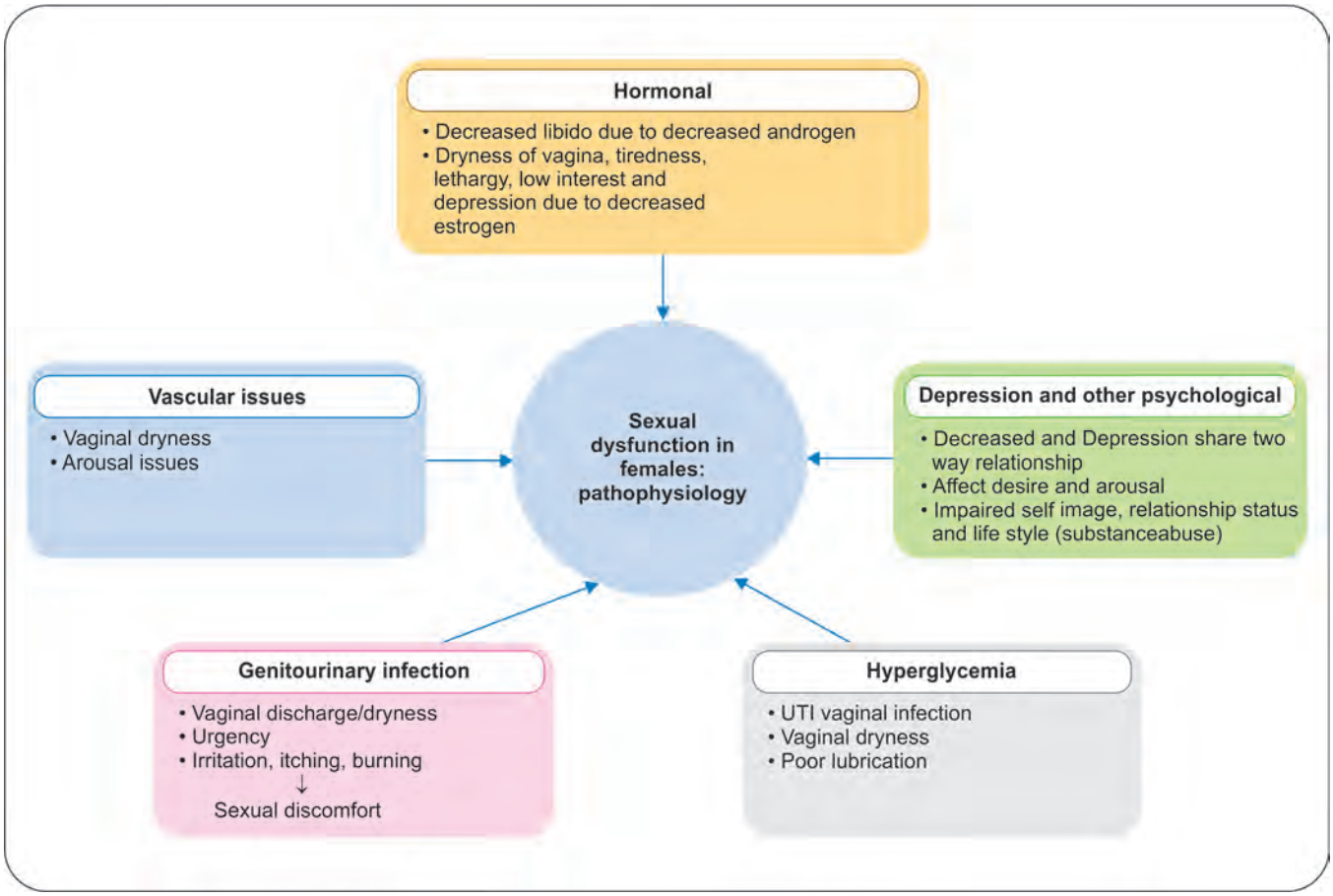


Fig. 1: Sexual dysfunction in females: Pathophysiology

is alpha2 adrenergic receptor blocker Yohimbine, which increases cholinergic and decreases adrenergic tone. It stimulates the midbrain and increases libido; this is more effective in psychogenic ED and less effective in diabetics.

Other treatment modalities (in those patients who are non-responders to oral treatment):

Vasodilators: Directly administered to the penile erectile tissue. These are papaverine, phentolamine and Prostaglandin E-1 (PgE1).[30] These are used in combinations; only PgE1 is approved by the FDA. PgE1 and papaverine may be injected Intracavernosal in the shaft of the penis with sterile techniques and under supervision of urologist 10–15 minutes before intercourse. Prostaglandins are also used as intraurethral suppository Medicated Urethral Suppository for Erections (MUSE). Side effects are pain, priapism, urethral burning, and irritation of partner's mucous membranes.

Mechanical therapy such as Vacuum Erection Devices (VED): It is used in non-responders of injections and urethral suppository. Vacuum pressure increases arterial inflow, and occlusive tension rings decrease venous outflow from penile corpus cavernosa. The penis is placed in a cylinder, a vacuum is created by a pump, which increases blood flow in the penis than a tension ring is applied at the base of the penis, and the erection lasts till the ring is removed.

Penile prostheses are the best substitutes for ED in persons who have diabetes if other modalities fail and give dissatisfaction. Prosthetic surgery is irreversible because it causes permanent alteration of corporal tissue, and thus, the physiological erection is not possible. Many materials, flaps, grafts have been tried, and most recent is hollow silicon cylinders inflated with saline or semi-rigid roads. The prosthesis has the highest satisfaction rate among all modalities for the management of ED, around 95% as

demonstrated by two large studies. A future version of prosthesis will be remote control devices similar to the garage door opener. The complication of surgical implant is the risk of infection.

Testosterone therapy: Persons having low testosterone and suffering from hypogonadism such as decreased libido, decreased energy, depression, fatigue, weight gain, anxiety may get benefitted with this therapy.

Future therapies can be gene therapy, penile low-intensity shock wave lithotripsy, which consists of 1,500 shocks twice weekly for 3–6 weeks to stimulate neovascularization to corporal bodies to improve penile blood flow and endothelial function. Some are NO-releasing polymers injected in cavernosa, which may improve ED.

Conclusion

SD in diabetes is an under-discussed, unrecognized, and usually untreated complication. It equally affects both the partners and is one of the treatable diabetic complications. This is due to vascular, neurological, and hormonal disturbances caused by diabetes. Sexual problems in diabetes include ED, sexual desire and ejaculatory dysfunction in males and many sexual problems in the female. Awareness about sexual problems is now increasing among diabetic patients. Many treatment options are now available such as oral medications, injectable drugs, vacuum devices, and inflatable prostheses. Controlling diabetes, discussing sexual problems, and management in time may improve sexual life in diabetic patients.

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CHAPTER

71 CVOT Trials in T2D—What do they Mean for Clinical Practice?

V Palaniappen

Abstract

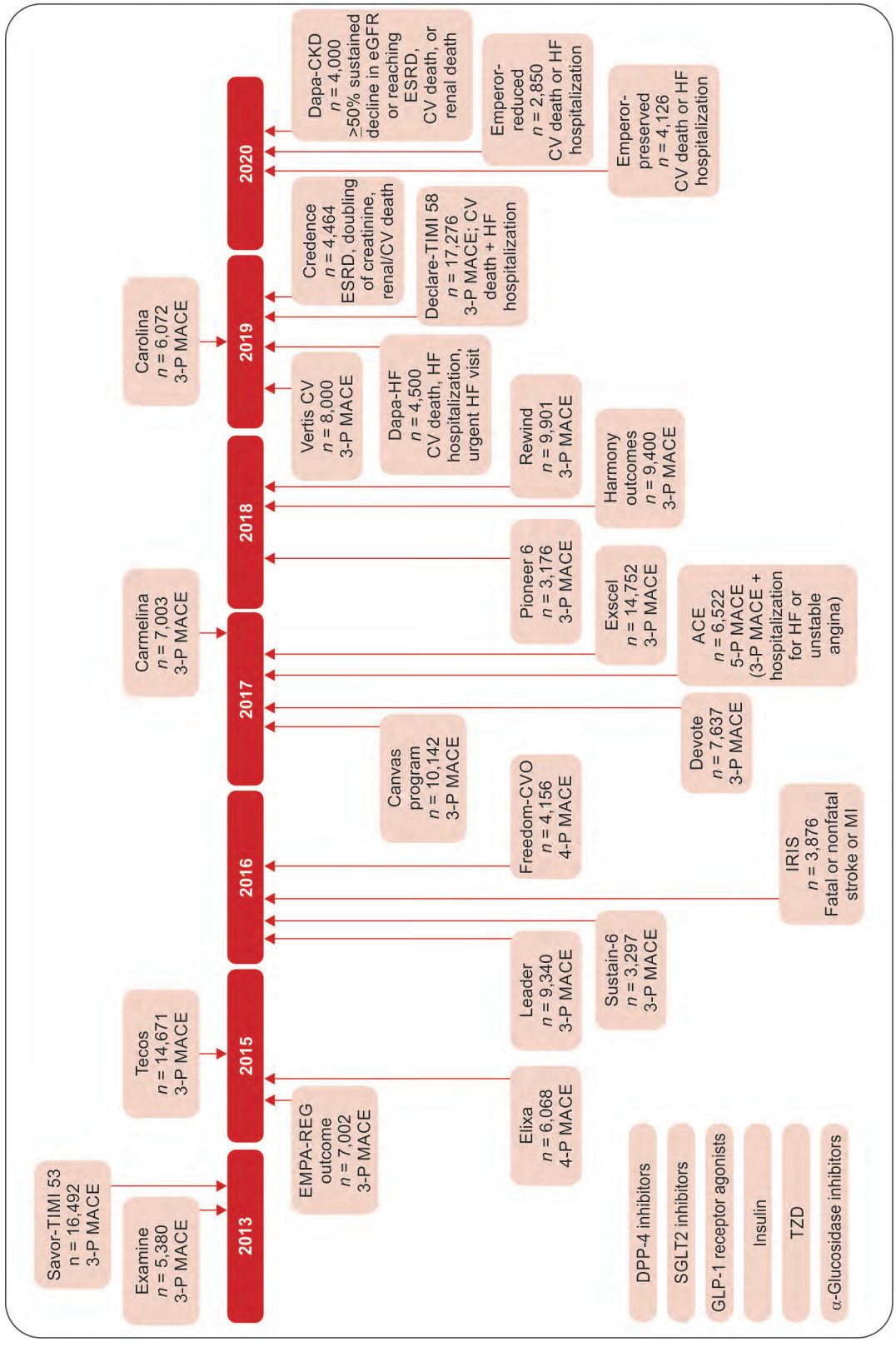
Nowadays good move is without CVOT trail and FDA approval no antihyperglycemic drugs can enter the market. EMPA REG outcome trail and LEADER trail had shown superiority and beneficial effects on CV safety in type 2 diabetics. SGLT2 inhibitors have shown to decrease the progression on renal dysfunction in long standing diabetics. All SGLT2i had shown significant reduction in hospitalization for heart failure.

Introduction

Patients with type 2 diabetes mellitus in general are more prone for atherosclerosis induced vascular disease like myocardial infarction and cerebrovascular accident with a tenfold increased risk. The is also increased risk of heart failure in diabetic patients. As diabetic patients are started on long-term oral hypoglycemic agents, the drugs should have a detrimental effect on cardiovascular safety. FDA imposed that "every newer antihyperglycemic agent have to undergo a CV safety trial" when there was a controversial results of rosiglitazone trial, which increased the risk of myocardial infarction and deaths due to CV disease. In cardiovascular outcome trial (CVOT) design, the newer glucose-lowering drug is added to standard of care (SoC) treatments in patients at high risk of CV events, and compared with SoC alone or added to an active comparator. The primary outcome is known as the 3-point MACE (major adverse cardiovascular events) which includes any CV death, nonfatal MI and nonfatal stroke and 4-point MACE which includes composite- or add hospitalization for unstable angina (HUA). Few of the studies has also included heart failure and renal protection effects. As per the guidance, CVOTs comparing an antihyperglycemic agent with a comparator must demonstrate that the upper bound of a two-sided 95% CI is <1.8. Few of the newer antihyperglycemic agents have also showed beneficial effects on CVD beyond glycemic control. The current chapter will elaborate on the various trials done in CV safety in type 2 diabetes mellitus. The first trial (SAVOUR-TIMI)was started in 2003 and many trials have been completed since then. It is done in DPP4 inhibitors, GLP-1 analogues, sodium-glucose cotransporter 2 (SGLT2) inhibitors, insulin analogues. **(Flowchart 1)**.

DPP4 Inhibitors

SAVOUR-TIMI involving Saxagliptin and EXAMINE trial that involved Alogliptin, Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes (TECOS), CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA), and CARdiovascular Safety & Clinical outcoME with LINAgliptin (CARMELINA). SAVOUR-TIMI showed a non-inferiority in CV safety compared to the placebo but there was an observation of increased hospitalization due to heart failure. EXAMINE trial also showed the rates of major composite events were not increased with alogliptin as compared with placebo in a follow-up to 40 months.



Flowchart 1: Approved CVOT trails between 2013 and 2020

Alogliptin neither increased CV morbidity or mortality, nor worsened preexisting heart failure, including in those patients with a very recent acute coronary syndrome, after a median duration treatment of 18 months. CAROLINA is first in kind head-to-head comparison between a SU and a gliptin (linagliptin) in high CV risk patients which showed a non-inferior risk of a composite CV outcome. CARMELINA trial showed that across all GFR, there is no increase in CV and renal events.

SGLT2 Inhibitors

There are four SGLT2 inhibitor trials with a composite 3-point MACE is the primary end point; in two, a composite renal outcome is the primary end point; and in three, a composite of HF outcomes and CV death is the primary end point in people with established HF. These include CANVAS, CREDENCE (ongoing), EMPA-REG outcome, EMPA-CKD, DAPA-HF, EMPEROR trials.

CANVAS

Canagliflozin compared with placebo was associated with a lower frequency of adverse cardiovascular events. Canagliflozin was also associated with a lower rate of progression of albuminuria; however, amputation occurred more frequently.

EMPA-REG Outcome

This trial was an event driven trial in CVOT trials that has shown a superiority in CV events by. Further it appears to have a salutary effects on renal outcome including the need for renal replacement therapy. It also reduced heart failures an hospitalizations for heart failure. The patients were receiving 10 and 25 mg of empagliflozin and the results include in the empagliflozin group there were significantly lower rates of death from cardiovascular causes (3.7%, vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7% and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7% and 8.3%, respectively; 32% relative risk reduction).

DAPA-HF

In patients with type 2 diabetes, inhibitors of SGLT2 reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. This was shown by the DAPA-HF (dapagliflozin heart failure) trial among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo.

With all these trials showing major CV benefits, ADA 2020 recommends in type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor can be added after metformin therapy.

GLP-1 Analogues

The CV safety is been studied in eight trial involving GLP-1 analogues out of which four trials have been completed.

ELIXIR

The first trial ELIXIR where lixisenatide was studied in patients with recent acute coronary syndrome (ACS) where it had a noninferiority in 4-point MACE, but showing no superiority in CV outcome.

LEADER Trial

Liraglutide was employed in this double blind trial where the rate of death from any cause was lower in the liraglutide group [381 patients (8.2%)] than in the placebo group [447 (9.6%)] (hazard ratio, 0.85; 95% CI, 0.74–0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events.

SUSTAIN-6

This trial involved long acting semaglutide with weekly injection of 0.5–1 mg which has a favorable effect on 3-point MACE with a significant decrease in nonfatal stroke, nonsignificant decrease in nonfatal MI with no trend on CV deaths or all cause mortality.

EXSCEL Trial

This was performed in a usual-care setting among patients with type 2 diabetes with or without previous CVD. It was

shown to have noninferiority in 3-point MACE, but not superiority, of once-weekly treatment with 2 mg of the long-acting extended-release exenatide (HR 0.91 [95% CI 0.83–1.00], P=0.06).

REWIND Trial

Once-weekly dulaglutide administered via subcutaneous injection is superior to placebo in improving glycemic control and reducing CV events in patients with type 2 diabetes and higher CV risk. There was also a significant reduction in nonfatal strokes. In addition, the drug had a moderate effect on the composite renal outcome, and reduced new macroalbuminuria in this patient population.

Insulin

Two major trials were done with both the Basal insulin namely glargine and degludec. Increased fasting blood glucose is an independent risk factor for adverse cardiovascular outcome in patients with long-term diabetes. Control of fasting blood glucose less than 100 mg% by basal insulin has shown a clear cardiovascular benefit.

ORIGIN

This a 6.2-year study where glargine was used to control the fasting blood glucose, the therapy with basal insulin glargine had a neutral effect on cardiovascular outcomes and cancers. Limitations of the study are that metformin was ultimately used by 47% of the insulin-glargine group. Evidence that metformin is cardioprotective raises the possibility that any cardiovascular harm of insulin may have been mitigated by metformin.

DEVOTE

The risk of hypoglycemia was more with glargine compared with degludec insulin once daily. This trial was done comparing the CV outcome of glargine and degludec insulin which showed the noninferiority, if degludec on CV events compared to glargine with lesser hypoglycemic events.

The ADA guidelines have been revised regarding the second drug after metformin after CVOT trial outcomes individualizing the patients' associated CV risk factors. SGLT2 inhibitors and GLP-1 analogues have become the choice after metformin therapy with CV risk.

BOX 1 Changes to consensus recommendations

We previously recommended that, in the setting of type 2 diabetes, established CVD was a compelling indication for treatment with a GLP-1 receptor agonist or SGLT2 inhibitor. We now further suggest the following:

General consideration

- In appropriate high-risk individuals with established type 2 diabetes, the decisio to treat with a GLP-1 receptor agonist or SGLT2 inhibitor to reduce MACE, hHF, CV death or CKD progression should be considered independently of baseline HbA_{1c} or individualised HbA_{1c} target.
- Providers should engage in shared decision making around initial combination therapy in new-onset cases of type 2 diabetes

GLP-1 receptor agonist recommendations

- For patients with type 2 diabetes and established atherosclerotic CV disease (such as those with prior myocardial infarction, ischemic strok, unstable angina and ECG changes, myocardial ischemia on imaging or stress test, or revascularisation of coronary, carotid or peripheral arteries) where MACE is the gravest threat, the level of evidence for MACE benefit is greatest for GLP-1 receptor agonists
- To reduce risk of MACE, GLP-1 receptor agonists can also be considered in patients with type 2 diabetes without established CVD with indicators of high risk, specifically, patients aged 55 years or older with coronary, carotid or lower extremely artery stenosis >50%, left ventricular hypertrophy, eGFR < 60 mL/min $(173\ m)^2$ or albuminuria

SGLT2 inhbitor recommendations

- For patients with or without established atherosclerotic CVD, but with HFrEF (EF <45%) or CKD (eGFR) 30 to ≤60 mL/min $(1.73)^2$ or UACR >30 mg/g, particularly UACR >300 mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors
- SGLT2 inhibitors are recommended in patients with type 2 diabetes and HF, particularly those with HFrEF, to reduce hHF, MACE and CV death
- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, MACE and CV death in patients with type 2 diabetes with CKD
- Patients with foot ulcers or at high risk for amputation should only be treated with SGLT2 inhibitors after careful shared decision making around risk and benefits with comprehensive education or foot care and amputation prevention

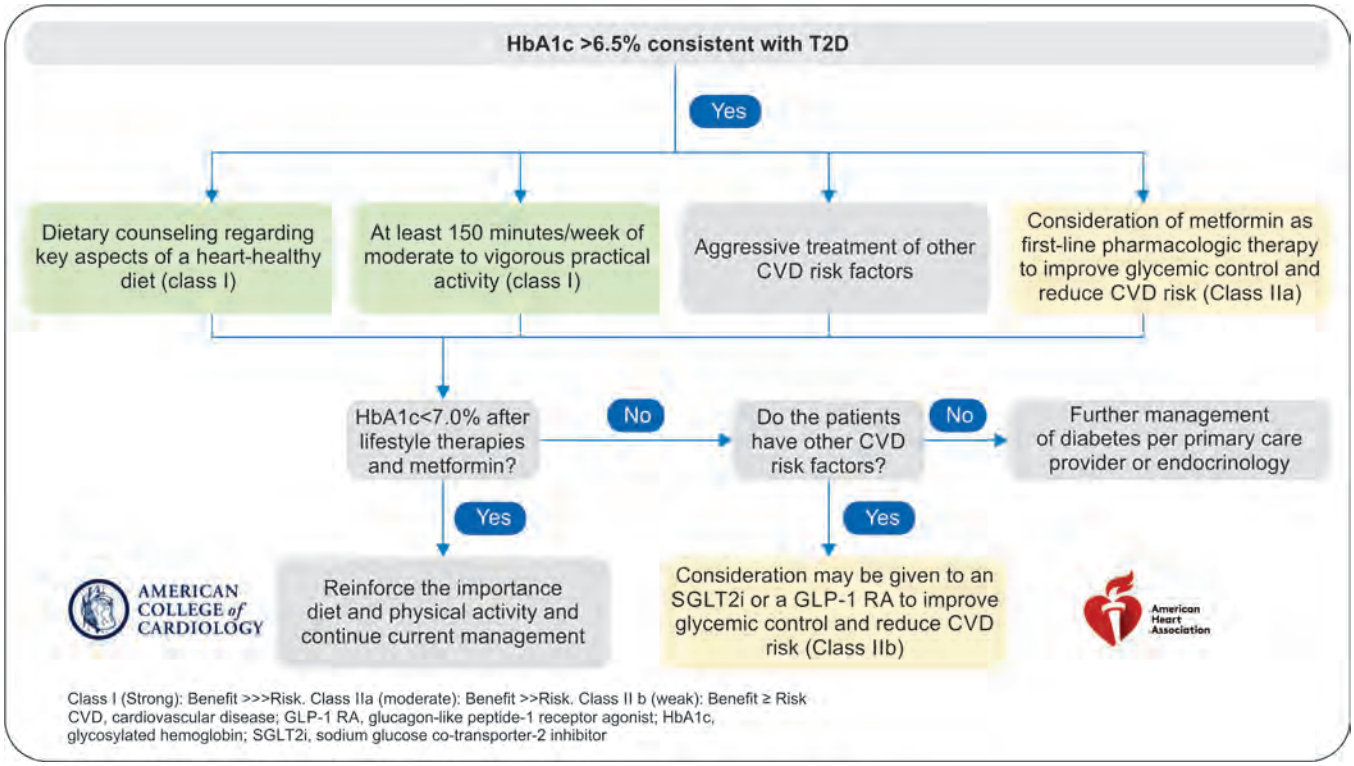
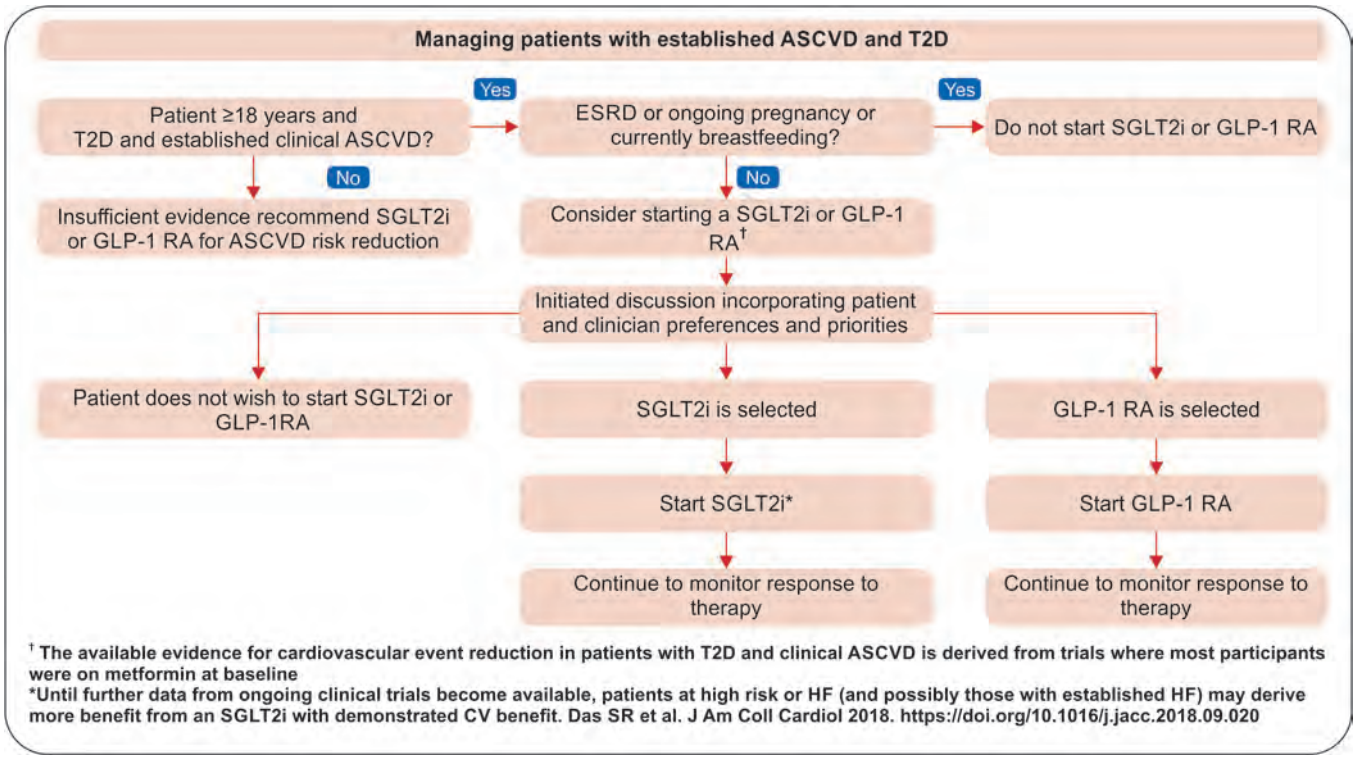


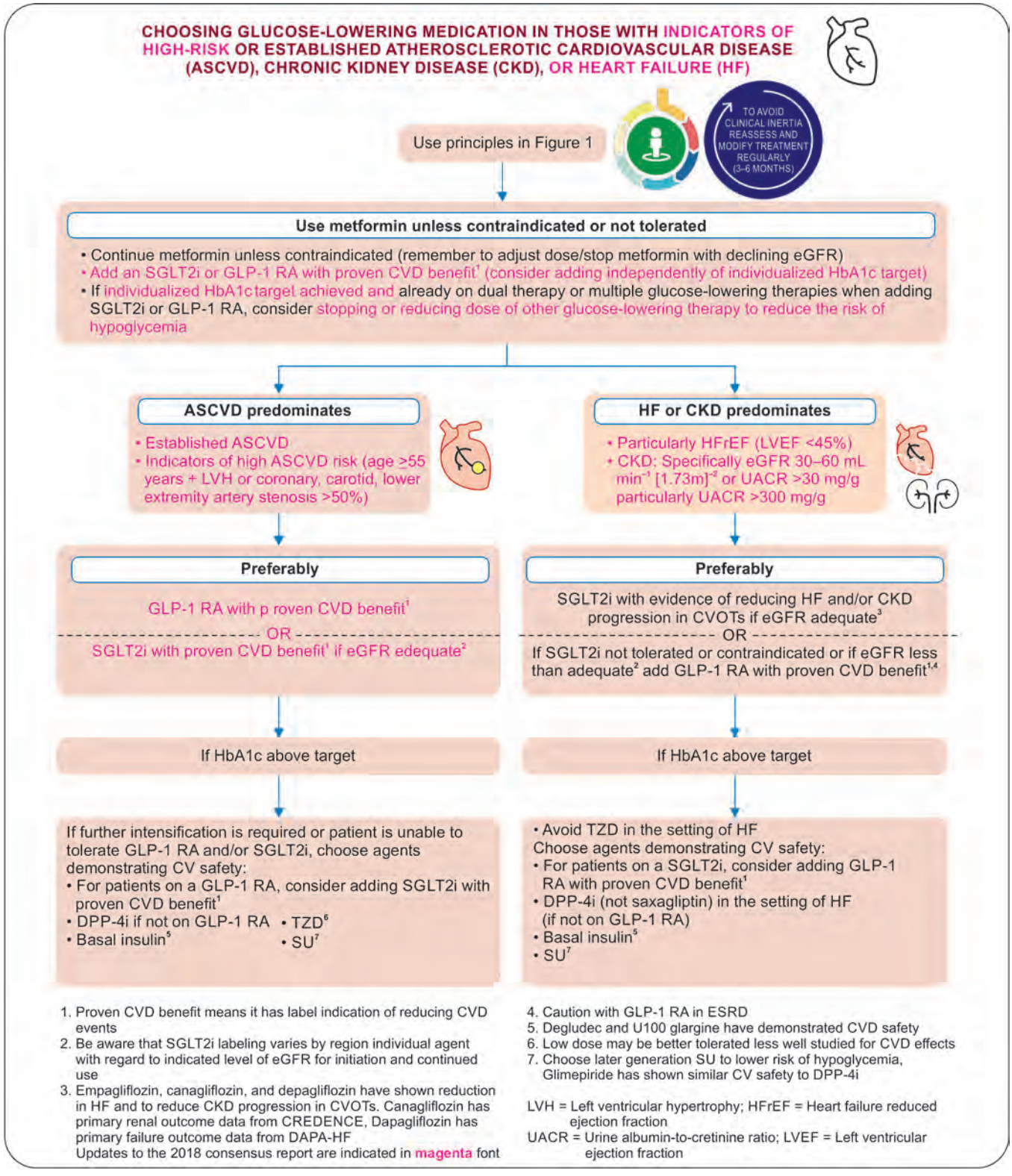
Fig. 1: Treatment of T2D for primary prevention of CVD

Flowchart 2: Managing patients with established ASCVD and T2D



† The available evidence for cardiovascular event reduction in patients with T2D and clinical ASCVD is derived from trials where most participants were on metformin at baseline
*Until further data from ongoing clinical trials become available, patients at high risk or HF (and possibly those with established HF) may derive more benefit from an SGLT2i with demonstrated CV benefit. Das SR et al. J Am Coll Cardiol 2018. https://doi.org/10.1016/j.jacc.2018.09.020

Flowchart 3: Choosing glucose lowering medication in those with indicators of high risk or established ASCVD, CKD, or HF



A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) has been shown in **Box 1**.

The treatment of diabetes for primary prevention of CVD is given in the **Figure 1**.

Managing patients with established ASCVD and T2D have been shown in the **Flowchart 2**.

Choosing glucose lowering medication in those with indicators of high risk or established ASCVD, CKD, or HF have been shown in the **Flowchart 3**.

Conclusion

- The CVOT trials, after the usage of rosiglitazone which had a detrimental effects on CV outcome.
- FDA has given a CV safety trial for all newer antihyperglycemic drug.
- Few of the studies showed a superiority in decreasing the deaths due to CV events and has a beneficial effects on CV outcome. These include EMPA-REG OUTCOME trial and LEADER trial which had shown clear beneficial effects on CV safety in type 2 diabetic adult patients and with this favorable outcome combined ADA and EASD has given clear guideline about the place after metformin therapy in diabetic population.
- SGLT2 inhibitors have shown to decrease the progression on renal dysfunction in long standing diabetes.
- DAPA-HF had shown that there is a significant decrease in hospitalization and deaths due to heart failure in long standing diabetes with heart failure with decreased ejection fraction when dapagliflozin is employed.

Suggested Readings

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CHAPTER

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Diabetic Fatigue Syndrome

Puneet Saxena, Deepak Chadha, Rishika Goyal

Abstract

Fatigue occurring in diabetes is a multispectrum disorder with etiology touching many horizons ranging from glycemia related and endocrinal/iatrogenic to nutritional and lifestyle factors. In this article we tried to illustrate fatigue in general and from neurological standpoint alongside enumerating the etiology of fatigue in diabetes with further mentioning the pathogenesis behind causation of fatigue in diabetes and ways to diagnose and manage the problem. The recognition and timely management of fatigue in diabetes is of paramount importance as it hinders with the self management tasks of diabetes on part of the patient. The diabetes self management is the cornerstone in management guidelines of diabetes in current scenario. The major aim of this literature is to highlight the topic of diabetic fatigue syndrome and engrave the path for more focused studies on this subject in the near future.

Introduction

Diabetes mellitus is a major public health threat with a global prevalence that has expanded enormously over past decades and is affecting approximately 6% of total world's adult population.[1] Among those affected, there are frequent symptoms of fatigue including decrease ambulation, frailty, generalized muscle weakness, and loss of independence thereby regarding fatigue as one of the omnipresent but distressing complaint and is a strong predictor of functional limitations, disability, and increasing mortality. The fatigue in diabetes has a multifactorial causation and is not just only limited to poor glycemic control. Currently there is paucity of focused studies on diabetes fatigue syndrome describing the severity of problem thereby highlighting the need for further clarification over this neglected, but extremely important aspect of diabetes care.

What is Fatigue (In General)?

Fatigue is a subjective sensation with no measurable signs and is defined as physical or mental exhaustion leading to decrease the quality of life. There is no proper standardized quantification of measurement of fatigue thereby explaining the position of no proper defining criteria till now. Hence, fatigue is mainly identified on subjective grounds or decrement in physical performance.[2] The causation of fatigue touches multiple horizons that range from physiological to psychological and pathological disease states.[3,4] At the onset fatigue can occur in normal daily activities where it is regarded as the protective mechanism that signals the body's requirement of rest. This kind of fatigue is mainly acute in onset and relives off by taking adequate rest whereas on the other side of spectrum is chronic fatigue that is majorly associated with multiple disease states like diabetes, malignancies, fibromyalgias, and even chronic pulmonary obstructive disorders. It typically does not relieve on rest and is initiated by mild to moderate level of activity.[5,6]

The physiological mechanism behind fatigue broadly classifies fatigue into main types: peripheral and central fatigue. In peripheral fatigue, the underlying pathogenesis is attributed largely to the neuromuscular transmission

defect, muscular metabolic defects, or rarely to circulatory failure states.[7] In this type, patient complains of physical fatigue where he is unable to sustain adequate force during exertional activities. On the other side, in central fatigue there is failure of initiation of attentional tasks (mental fatigue) and physical activities requiring self motivation (physical fatigue) in the absence of any obvious motor weakness or neurological deficit.[8] The central fatigue can be of short duration as evident by normal individuals after loss of sleep, following stress, in females during menstruation and also after episodes of viral illness or persistence of central fatigue mainly seen in central disorders like Parkinsonism.

Fatigue can even be psychological in origin as is evident in clinical depression, stress, and burnout states.

Fatigue in Diabetes: Etiopathogenesis

The fatigue in diabetes is multifactorial in origin and is largely attributed to physiological, psychological, and lifestyle factors pertaining to diabetes as explained in **Flowchart 1**.

Physiological Factors

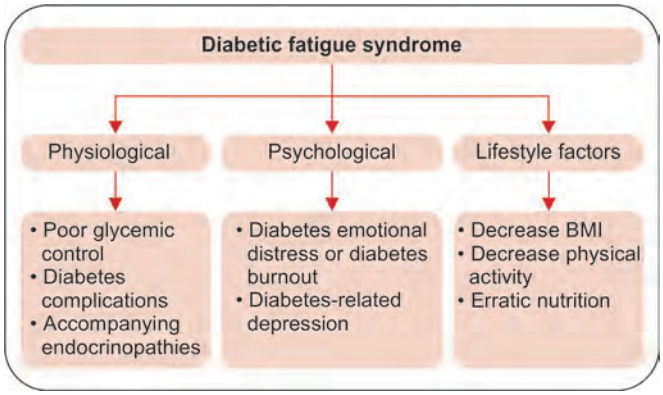
The physiological factors responsible for causation of diabetic fatigue syndrome (DFS) are mainly discussed under three subheadings like:

- Poor glycemic control
- Presence of diabetes-related complications
- Concomitant other endocrinopathies.

Poor Glycemic Control in Diabetes

- As evidenced by number of studies in the literature acute episodes of hyperglycemia are frequently associated with fatigue along with alteration in the mood states and decreased cognition.[9] This association is notably seen with fasting plasma glucose levels rather than HbA1c thereby corroborating the strong relation between fatigue and acute rather than chronic hyperglycemia.[10]
- Similarly acute episodes of hypoglycemia are also linked up with bouts of fatigue as evident by one of the controlled study conducted among type 1 diabetics.[11]
- There are fewer data available to establish linkage between chronic hyperglycemia and its contribution to fatigue, but still no association has been found between HbA1c and fatigue symptoms. The excursions of HbA1c are linked up with sleepiness, but not with fatigue.[12]
- There is also a strong association between symptoms of fatigue and glucose variability that is defined as fluctuations in glucose levels occurring over minutes to hours that are not revealed by single measurement of blood glucose or even by HbA1c. The frequency and magnitude of glucose variability is more marked in type 1 diabetics who are under the effects of exogenous insulin than in type 2 diabetics. The exogenous insulin is more responsible for alteration in the levels of counter regulatory hormones like glucagon or nor-epinephrine thereby responsible for more frequent episodes of hypoglycemia.[13] Among type 2 diabetics, the glucose fluctuations occurring during post prandial phase are frequently associated with bouts of fatigue.

Flowchart 1: Etiopathogenesis of fatigue in diabetic fatigue syndrome



Diabetes-related Complications

- There are many notable chronic complications of diabetes that are frequently associated with fatigue.
- Peripheral vascular diseases often present in diabetic patients and causes deep aching pain in the calves owing to perfusion defects in the lower extremities among diabetics and such patients frequently report fatigue.
- Similarly, neuropathic pain in hands and feet of diabetic patients with concomitant dysesthetic sensations also are linked up with onset of fatigue.[14]
- The leading cause of end stage renal disease is diabetes. This form of chronic kidney disease is largely linked with anemia that directly attributes to causation of increased fatigue.[15]

Other Accompanying Endocrinopathies

Patients with type 1 diabetes are prone to develop other concomitant endocrinopathies like hypothyroidism, hypogonadism, Cushing syndrome, and Addison's disease. These conditions if left untreated may further worsen DFS.

Psychological Factors

It encompasses two main states namely:

- Diabetes emotional distress
- Diabetes-related depressive symptom complex.

Diabetes Emotional Distress

- It also known as diabetes burnout phase is a state of psychological disturbances that arises while managing and living with diabetes.[16,17] There are many factors that directly or indirectly responsible for DFS in diabetes emotional distress.
- Stress of living with diabetes causes depletion of energy and fatigue with disruption of sense of well-being.
- The increase burden of self management of disease especially in type 1 diabetics with self adjustment of insulin dosages associated with sense of psychological or emotional fatigue apart from improve physiological blood levels.
- Also in diabetes burnout phase, the patient feels cynicism, emotional fatigue, and sense of detachment from recommendations of health-care providers when patient experience negative results during the course of self management of diabetes. The sense of ineffectiveness prevails during this phase.[18]

Diabetes-related Depression

- Diabetics are more likely to suffer from depression than general population.
- The elevated depressive symptoms further likely contribute to sense of physical and mental fatigueness.[19,20]

Lifestyle Factors

There are several factors linked up with DFS like the following:

Increased BMI

It has been found that type 2 diabetic patients are majorly overweight and obese that are two independent factors causing fatigue. There is increased level of proinflammatory cytokine production that plays a major role in the pathogenesis of fatigue.[21] This increased production of proinflammatory cytokines storm further causes oxidative stress and initiate apoptotic pathways in the central neural circuits that contribute to symptom complex of fatigue.[22]

Reduced Level of Physical Activity

- Regular physical activity especially vigorous exertion helps in building up of muscle mass, increases substrates usage for energy production, improves aerobic exercise capacity, decreases lactic acid production at the cellular level, and finally improves mood. Therefore, physical activity and exhibition of fatigue symptoms exhibit inverse relationship with increase activity; there occurs little or no fatigue at all.[23,24]
- Moreover physical activity helps in rejuvenation of mood and alleviation of multiple somatic symptoms like depression.

Erratic Nutritional Factors

Increase calorie consumption can precipitate excursions of glycemia that further play a role in fatigue. Even excessive dietary restriction causing very low calorie consumption leads to protein energy malnutrition and starvation ketosis that can precipitate DFS.

Miscellaneous Causes

Common medical conditions associated with DFS are:

- Multiple vitamin deficiencies, especially low vitamin D levels and vitamin D deficiencies are markedly notable in diabetic patients that are further associated with fatigue, depressive symptoms, and low quality of life. The prolonged muscle weakness associated with musculoskeltal pains is associated with vitamin D deficiency.
- Anemia in diabetes is also one of the medical conditions in causation of DFS as being described previously. Apart from being the stigmata of chronic kidney disease, anemia is also evident in patients with excessive blood loss or with worm infestations.

Approach to Patient with DFS

As the pathogenesis of DFS touches multiple horizons so the clinical approach in patients with DFS is not

TABLE 1 Common causes of fatigue in a person with diabetes

Disorders associated with endocrine dysfunction
• *Related to glycemic variations:* – High fasting plasma glucose – High postprandial surges with normal fasting – Recurrent episode of hypoglycemia – Glycemic variability
• *Presence of complications of diabetes:* – Nephropathy – Peripheral arterial disorders – Neuropathy
• *Presence of other endocrinopathies:* – Hypothyroidism – Hypogonadism – Polycystic ovarian syndrome – Cushing syndrome – Addison's disease
• *Association with drugs:* – Statins – Beta blockers – Corticosteroid use
Disorders associated with non-endocrine dysfunction
• *Lifestyle factors:* – Reduced BMI – Decreased level of physical activity – Erratic nutrition
• *Psychology-related to diabetes:* – Diabetes emotional distress – Diabetes depression syndrome

only centered on poor glycemic variability but should thoroughly follow hierarchy of responsible factors that need to be evaluated before labeling patient with DFS. All of the major causes are tabulated in **Table 1**.

- The initial assessment begins with lifestyle-related factors followed by endocrinal assessment. The evaluation of daily routine of patient with special emphasis on exercise habits, pattern, and quality of sleep, dietary habits. If the patient is having more sedentary lifestyle then motivation to be given for increase physical activities in the form of aerobic exercise or joining a game or simply doing cycling.
- For the assessment of glycemic control and presence of chronic diabetic complications, the search begins with thorough history and physical examination of the patient.
- When the symptoms of fatigue occur characteristically in the early morning and are associated with headache, sweating and relives on taking breakfast simply suggests hypoglycemia as the cause of fatigue.
- The appearance of pallor in patient with long standing diabetes accompanied by symptoms of breathlessness on exertion signifies prompt investigations for nephropathy and hypothyroidism. When symptoms of fatigue accompany breathlessness along with inability to do exercise suggest decrease cardiac reserve in the form of heart failure.
- The prominence of symptoms of pain in the calves while walking along with neuropathic symptoms suggests development of diabetic neuropathy responsible for DFS. When fatigue is accompanied by symptoms of weakness of proximal muscles then ruling out vitamin D deficiency is important, similarly if patient complains of bony pain and tenderness then osteomalacia or hypoparathyroidism are mare notable to exist.
- When fatigue occurs with symptoms of sexual dysfunction or loss of libido may suggest menopause, andropause, or even hypogonadism.
- Before labeling patient to be psychiatric, thorough evaluation for diabetes emotional distress and diabetes-related depression should be sought for.
- Drugs like centrally acting anti-hypertensives, diuretics, statins, and beta blockers also causes fatigue and are considered iatrogenic causes of fatigue.

Subjective Evaluation of Fatigue

There are multiple questionnaires for evaluation of fatigue as well like:

- Avlund Fatigue Scale
- The 36 Item Short Form Health Survey
- Sleep Quality Scales Like Pittsburg Sleeping Quality Index
- Multidimensional Sleep Inventory

What Fatigue does to Diabetic Patients?

The major drawback of fatigue is that it completely affects the self-rated health and quality of life in a very negative sense, and therefore is taking a huge toll over the diabetic patients.[25] The patient characteristically present with decreased physical functioning and inability to manage the daily routines of life. The most dreaded effect of fatigue in patients with diabetes is that fatigue acts as a strong barrier in patient's health promoting behaviors like

participation in self-care regimens of diabetes, following a regular exercise plan, and participation in healthy eating habits.[26] Thereby fatigue remains a challenging problem to manage on the part of health-care providers. The lack of standardized definition and paucity of diagnostic criteria makes the management part more difficult.[27]

Important Differentials of DFS

Differentiating DFS from Chronic Fatigue Syndrome

Chronic fatigue syndrome (CFS) is UNEXPLAINED and PERSISTENT fatigue that is not due to any exertional activity and not relieved by taking rest but leads to significant limitation of activity. There are few cardinal hallmarks of CFS that must be present for at least a period of 6 or more months like:

- Myalgias
- Multiple joint pains with no underlying inflammatory signs
- Impair attention span
- Headaches
- Unfresh even after sleep

The most important point differentiating CFS from DFS is that CFS is a diagnosis of exclusion and indeed requires a thorough evaluation of underlying mental status of the patient in terms of mood, personality, intellectual functions, and memory. Apart from psychological factors, there are also many biological factors responsible for causation of CFS like:

- Genetic factors.
- Immune etiologies like increase in number of natural killer cells CD16/CD3 causing abnormal cytotoxicity of natural killer cells and increase in immune activation markers.
- Infectious causes linked up with CFS are infectious mononucleosis, glandular fever, parvovirus B19, nipah virus human herpesvirus 4-6-7, and borna virus disease.

Hence, diagnosis of CFS requires a holistic bio-psychological approach.

Fibromyalgia

Fibromyalgia syndrome denotes symptom complex of chronic pain, muscle fatigue, de arranged sleep, and many functional symptoms. The underlying mechanism for causation is based on oxidative stress and modified inflammatory response with baseline predisposition attributed to genetics as well. The diagnostic criteria defined by American College of Rheumatology states at least 3-month duration of pain both above and below the waist along with presence of 11 out of 18 possible tender points that are not explained by other disorders.

Management of DFS

There are many aspects of management scheme.

Improving Lifestyle Factors

Counseling and constant motivating the patient for:

- Initiating physical activity regimen in the form of playing outdoor games, aerobic activity like jogging, cycling and swimming. The patient should be motivated to do at least 150 minutes of moderate activity per week.
- Indulging in eating healthy diet.
- Participating in meditation for stress control.
- Good sleep pattern.

Maintenance of Euglycemia

The health-care providers should assess the condition of the patient in totality and initiate the drug regimens for complete and effective control of glycemia. There should also be optimization of other endocrinal and medical aspect of patient like correction of thyroid status if concomitant hypothyroidism ensues, correction of hormonal deficits in a patient with hypogonadism.

Mitigation of Diabetes Distress

As diabetes is a self-managing disease, so distress occurs when patient is unable to cope with the demands of life with diabetes that further makes the patient incapacitating in managing and monitoring the disease as well.

This psychological aspect can be overcome by:

- Utilization of external support
- Enhancing coping skills on the part of patient
- Enhancing self perception of the patient
- Making the patient to understand to minimize the discomfort of change.

Pharmacological Intervention

There are no practical prospective studies available for addressing fatigue in diabetes, but there is a list of drugs

TABLE 2 Drugs important in treatment of DFS

SSRI:
• Fluoxetine
• Paroxetine
• Sertraline
SNRI:
• Duloxetine
• Venlafaxine
• Desvenlafaxine
Atypical antidepressants:
• Milnacipran
Stimulants:
• Modafinil
• Methylphenidate

available based on experience of clinician in regards to treatment of depression and presence of fatigue in other conditions like CFS, fibromyalgia, or HIV as mentioned in **Table 2**.

Conclusion

Fatigue is very common and neglected problem for the people living with diabetes and its causation is indeed multifactorial interplay of physiological, psychological, and lifestyle-related factors. The poor self management of diabetes is both the causative factor and net result of DFS. Therefore, regular screening of fatigue along with other complications of diabetes is of paramount importance to prevent or retard the course of DFS. Lastly, to improve the quality of life and obtaining a good control of diabetes, early detection and management of DFS are very essential.

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CHAPTER

73 Clinical Implications and Management of Glycemic Variability in Diabetes

Ashutosh Chaturvedi, Girish Mathur, Divyansh Mathur, Mihika Sinha

Abstract

Poor glycemic control is a major risk factor for long-term micro- and macrovascular complications of diabetes. In the day-to-day practice clinicians frequently encounter patients with high dysglycemic patterns. Measuring Glycated hemoglobin A1c (HbA1c) does not take into account the fluctuations in blood glucose levels. The intraday and interday swing in blood glucose levels including episodes of hyper- and hypoglycemia is known as glycemic variability (GV). GV can be due lifestyle related causes, pharmacological causes, biomedical related causes. It is now strongly suggested that diabetes management strategies should include minimizing GV and must focus on decreasing the postprandial glycemic excursions along with HbA1c levels to lower the risk for long-term complications.

Introduction

Diabetes mellitus (DM) is now a rapidly growing global epidemic with type 2 diabetes mellitus (T2DM) accounting for over 90% of cases. As per estimated by International Diabetes Federation (IDF), worldwide every 1 in 10 people or 592 million individuals will suffer from diabetes by the year 2035.[1] Poor glycemic control is a major risk factor for long-term micro- and macrovascular complications of diabetes. This poor blood glucose control in diabetes results due to both acute glucose fluctuations and chronic hyperglycemia over time. Thus, the main aim of diabetes management is to decrease the risk of diabetes complications by optimizing blood glucose levels and minimizing blood glucose variability and episodes of hypoglycemia. Glycated hemoglobin A1c (HbA1c) is considered the gold standard for assessment of glycemic control in diabetic patients, but it does not take into account the fluctuations in blood glucose levels This intraday and interday swing in blood glucose levels including episodes of hyper- and hypoglycemia is known as glycemic variability (GV). Studies suggest that GV contributes to diabetes-related complications[2] and also impacts patient's psychological well-being and quality of life (QoL).[3] Newer therapeutic strategies like glucagon like peptide-1 (GLP-1) analogs and dihydropeptidyl peptidase-IV (DPP-IV) inhibitors targeting multiple pathophysiological mechanisms are most promising in control of HbA1c and decreasing GV. It is important today to understand the clinical implications of GV and its management in diabetic patients.

Glycemic Variability: A Rising Concept

In the day-to-day practice clinicians frequently encounter patients with high dysglycemic patterns. Few individuals have extreme fluctuations in glucose levels during a particular day, while others present with variable blood sugar readings from day to day. GV may be associated with symptomatic hypoglycemia, impaired QoL, failure to titrate doses of anti-diabetic drugs, unwanted chronic complications and subsequently increased cost of treatment.[4] Thus, it has become a challenge for good diabetes care. Two important pathophysiologic

mechanisms proposed for the development of various micro- and macrovascular complications in diabetes are excessive advanced glycation end products (AGE's) and activation of oxidative stress. Lowering of hyperglycemic excursions that leads to reduction in GV also decreases the oxidative stress markers.[5] Studies also suggest that fluctuating glucose levels that produce harmful effects on endothelial function and oxidative stress may be more damaging for the cardiovascular system than is chronic sustained hyperglycemia.[6] Traditionally, diabetes management plans mainly targeted to decrease the triad of fasting and postprandial blood glucose and HbA1c. Nowadays GV and QoL have been added to the known components and these five elements are collectively termed as "glycemic pentad." The need was felt because even studies like DCCT, UKPDS, and ADVANCE trials failed to show any benefits of intensive treatment to retard the development of various chronic complications of diabetes.[7-9] In recent studies it was observed that HbA1c is not sufficient to justify all the uncertainties of diabetes complications and that GV might be a better indicator of glycemic control than HbA1c.[10]

Causes of Glycemic Variability

GV can be broadly classified under three main categories:

- lifestyle related causes
- pharmacological causes, and
- biomedical related causes **(Table 1)**.

Before evaluating the etiology of GV in a particular patient *Spurious or Fictitious GV* must be excluded, which can be due to wrong technique of self monitoring of blood glucose (SMBG) being used. It is important to assess the instrument and strips used, method of pricking the finger, how the instrument is being used and results are being read and recorded. Everything must be in order. Venous blood glucose estimation can be simultaneously ordered to check and confirm GV. It is now well known that continuous glucose monitoring systems (CGMS) and ambulatory glucose monitoring (flash) much more accurately confirm GV.[11]

TABLE 1 Causes of glycemic variability

Cause	*Type of variation*	*Example*
Lifestyle related	Diet	• Composition of diet • Diet pattern • Quality of diet
	Physical activity	• Exercise timing • Exercise duration • Intensity of exercise
	Management of stress	• Psychological stress • Sleep cycle issues • Social environment
Pharmacological	Type of preparation	• Long acting/ultra long acating insulin • Immediate release/ controlled or sustained release tablets
	Type of regimen	• Human insulin/ analong insulin • Premixed/bolus insullin
	Drug delivery related	• Site of injection • Injection at hypo-perfused or euperfused site • Gap between drug/ injection and meal
	Drug interactions related	• Rifampicin increases metabolism of sulfonylureas (SUs) • Azoles inhibit the metabolism of pioglitazone and SUs
Biomedical	Neuroendocrine causes	• Pancreatic exocrine deficiency • Glucagon deficiency • Hypoglycemia unawareness
	Gastrointestinal causes	• Malabsorption syndrome • Diabetic gastroparesis

Source: Kalra S, et al. Managing glycemic variability: clinical approach. JPMA. 2019;69(2):274-6.

Lifestyle-related GV

After confirmation of GV, first of all variability in lifestyle needs to be excluded. This can be due to either variation in diet, physical activity, or management of stress in life. Proper history taken from the patient reveals the variation in the composition, pattern, or quality of food taken, sleep pattern and timing, duration or intensity of physical activity/exercise, psychological or social stress. All these day-to-day variations in lifestyle can lead to fluctuations in glycemic levels.

Pharmacological GV

The GV can also arise due to variation in the selection of drug regimens, drug formulations, and manner and method of drug delivery. For a particular patient's glucophenotype the selected drug regimens, drug formulations, and manner and method of drug delivery may not be appropriate.[12] For example, for a person having severe hyperglycemia prescribing a basal insulin and using human insulins which have higher coefficients of variability as compared to analogue insulins which have lower. The physician, therefore, should be well-versed with the pharmacokinetics and pharmacodynamics of the each anti-diabetic drugs and various insulin regimes while prescribing them.

Biomedical Causes of GV

When the lifestyle related and pharmacological etiologies are ruled out, it is important to look for the biomedical causes of GV. Biomedical causes can be gastrointestinal, neuroendocrine or drug-drug interactions related. Disorders of absorption and motility result in a nutrient-insulin mismatch that leads to variable changes in the absorption of nutrients. Neuroendocrine reasons include endocrine and exocrine disorders of various glands of body and of the autonomic nervous system (resulting in hypoglycemia unawareness) that leads to GV through different mechanisms. Another type of biomedical cause is the drug-drug interaction occurring when new drugs are prescribed to treat the secondary illness like anti-fungal drugs (fluconazole and ketoconazole) to treat mycoses, anti-tubercular drugs (rifampin) for treating tuberculosis, and anti-seizure drugs (phenobarbital) for any neuropsychiatric illnesses.[13]

Measurement of GV

With the development of increasing interest in the clinical implications of GV in diabetes, a lot of methods and metrics has been described for assessment of GV which is at times really confusing for both physicians and patients. For those clinicians who want to apply GV in their routine clinical practice, unavailability of a uniformly accepted standard method of measurement of GV is a real challenging issue. Among all these methods the four most clinically relevant and commonly used methods are coefficient of variation (CV or % CV), standard deviation (SD), interquartile range (IQR), and mean amplitude of glycemic excursions (MAGE).

Most of the physicians commonly use SD to measure GV, but still it has been pointed out that SD is not regularly distributed around the mean glucose; therefore, the IQR, which is also strongly correlated with SD, can be used as a preferred method to measure GV. IQR is a part of the proposed international standard or uniform one-page glucose profile report [Ambulatory Glucose Profile (AGP)] and can be easily recognized on a standard day or 24-hour glucose profile plot and can be actually clinically relevant in decision-making for the clinician and patient.[14] For the purpose of research work, the coefficient of variation (CV or % CV) is still the preferred GV metric which is least influenced by fluctuations in mean glucose level or HbA1c. MAGE is an another long-used measure of GV which is defined as the average of all blood glucose excursions (up or down) that are of a magnitude greater than 1 SD of all glucose measures.[15] Different aspects of GV parameters which are commonly used in research and clinical practice are summarized in **Table 2**.

Timing of Glucose Excursions

It is the clinically most important metrics that give us the time which the patient spends within, above, and below the target blood glucose range. With the increasing availability of CGMS in recent years, such time-related GV metrics have become more well-known. Time in targeted blood glucose range (TIR) provides useful information on the level of glycemic control although it gives an incomplete picture of overall glycemic control. Clinically, assessment of TIR can help patients to know better than over the time how hypoglycemia or hyperglycemia improves with treatment.

Clinical Implications of GV

GV and Microvascular Complications of Diabetes

Due to the lack of consensus on the most reliable method of assessment of GV, ambivalent conclusions have been made from the studies examining the relationship between GV and development of complications of diabetes till now. In epidemiological studies while GV was an independent predictor of the prevalence of peripheral neuropathy,[16] while mean blood glucose (MBG) was significantly associated with the development of diabetic retinopathy but not with that of nephropathy.[17]

TABLE 2 Summary of GV metrics[15]

GV metric	*Definition*	*Advantages*	*Clinical implications of GV metric*
SD	The amount of variation or mean dispersion of all glucose readings in a set of data	Widely used, straight forward and easy to calculate	• Provides a measure of inter- or intraday GV depending on frequency of blood glucose measurements • Does not take into account the number of glycemic swings
% CV	It is the corrected measure of dispersion in relation to the mean blood glucose	It is useful in two or more gourps with different glucose tolerance	• Probably the best research metric to compare GV over time or between data stets • Does not consider the number of glycemic swings
IQR	It consists of values 25% above and 25% below the median	Likely the best method to visualize GV around the median glucose curve	It is easier to spot and give attention what time of day has the most GV by plotting the IQR around the median glucose curve
MAGE	It is the average amplitude of glucose excursions that are more than 1 SD	Most commonly used in literature and reflects both upward and downward glucose fluctuations	• Can be aplied to SMBG or CGMS data as well • Reflects intraday GV but it excludes minor fluctuations and is dependent on sampling frequency
CONGA (Continuous overall net glycemic action)	It is the standard deviation of the differences of glucose readings for a defined period of hours	It can capture smaller glycemic swings over shorter time intervals	• It measures intraday GC and is specifically developed for CGMS • Provides measures of short- or long-time intervals but requires software for calculation
MODD (Mean of dialy differences)	It is the mean absolute difference between blood glucose values derived from SMBG data at the same time on consecutive days	It shows the consistency and stability of day-to-day blood glucose patterns	It is measure of interday GV but it is affected by different daily lifestyle patterns

GV and Hypoglycemia

Cox et al. proposed GV as a better measure of predictor of future severe hypoglycemia than HbA1c.[18] The association of risk of hypoglycemia was found to be as much related to glucose variability as to the mean glucose value in the diabetes outcomes in veterans study (DOVES).[19] Limiting glycemic excursions along with maintaining the MBG and HbA1c in target range can be a key factor in achieving glycemic control.

GV and Cardiovascular Disease Risk

In patients with DMT2 and acute myocardial infarction, increased risk of mortality was observed in patients with increased visit-to-visit GV.[20]

Kilpatrick et al. showed that pre- and postprandial blood glucose, MBG were significantly related to cardiovascular disease risk but there was no association between HbA1c and glucose variability.[21]

GV and QoL

Increased frequency of fluctuations in blood glucose with hypoglycemia and hyperglycemic excursions can lead to mood changes, depression and poor QoL. High GV was shown to be associated with low QoL than HbA1c and 24-hour average blood glucose.[22]

Management of Glycemic Variability in Diabetes

Glycemic management of diabetes should focus on achieving near euglycemia without episodes of hypoglycemia; hence, reducing the risk for complications. It is now strongly suggested that diabetes management strategies should include minimizing GV and must focus on decreasing the postprandial glycemic excursions along with HbA1c levels to lower the risk for long-term complications.[10]

For improving the glycemic control management can be strategized into four possible categories of treatment which can be called as 4Ts:

- *Targets:* Setting the individualized glycemic goals carefully.
- *Team approach:* Use of team care along with self management training to patient and sharing the process of decision-making.
- *Therapeutics development:* Developing new oral and injectable anti-diabetic drugs.
- *Technology:* Application of new technologies in management like continuous glucose monitors, smartphone apps for tracking glucose, insulin pumps, tools for remote communication between the patient and team.

Lifestyle Measures

It is well known that weight loss through dietary restrictions and exercise are capable of decreasing blood glucose levels and improving the insulin sensitivity thus delaying the progression from impaired glucose tolerance (IGT) to diabetes. In a study it was shown that a diet based on whole cereals, legumes, vegetables, and fruits and rich in dietary fiber led to reduction in postprandial glycemic (PPG) excursions subsequently reducing GV.[23]

Oral Hypoglycemic Agents

Minimizing the PPG excursions is an important aspect of overall glycemic management, and a major barrier to optimal control of diabetes. Selection of diabetes medications and blood glucose goals must be beneficial for the individual, simultaneously reducing the risks of hypoglycemia. Sulfonylureas have been shown to be associated with significant GV, and can lead to an increase hypoglycemic episodes and mortality. Rationally glimepiride must cause less GV than glibenclamide because of the insulin-releasing activity which is high with glibenclamide and lowest with glimeperide.[24] In a study controlled-release glipizide combined with acarbose was found to be more effective in decreasing MAGE than controlled-release glipizide monotherapy.[25]

The DPP-4 inhibitors secrete insulin and suppress glucagon in a glucose-dependent manner, controlling postprandial glucose excursions as well as reducing the overall hyperglycemia without increasing the risk of hypoglycemic episodes. As compared to glimepiride and pioglitazone, sitagliptin, and vildagliptin significantly reduced GV in patients with type 2 diabetes not sufficiently controlled on metformin monotherapy.[26]

Prandial and Basal Insulins

Newer rapid prandial insulin analogs closely mimic the normal physiological insulin response to meals. Rapid acting insulin analogs such as insulin lispro, aspart, and glulisine better reduce the GV by reducing the periods of acute hyperglycemia, with lower rates of hypoglycemia than regular human insulin. In metformin-treated patients, as compared to insulin glargine alone, a premixed basal insulin glargine and rapid-acting insulin lispro was shown to result in reduced GV.[27] In type 1 diabetics, continuous subcutaneous insulin infusion (CSII) was considered as alternative when glycemic targets were not achieved with use of multiple dose insulin regimen in type 1 diabetic patients.

GLP-1 Analogs

When added to background therapy of oral antidiabetic drugs or high-dose basal-bolus insulin therapy, glucagon-like peptide-1 (GLP-1) receptor agonists like exenatide, liraglutide and lixisenatide have shown remarkable decrease in GV in the comparative studies. Heine et al.[28] compared the efficacy of insulin glargine (once-daily) or the GLP-1 agonist exenatide (twice daily) in suboptimally controlled type 2 diabetes. It was found that glargine lowered fasting glucose levels to a greater degree than exenatide, while exenatide decreased postprandial variability to a greater extent than glargine. HbA1c lowering was same in both groups but exenatide decreased glycemic excursions by almost 50% in the end when compared with baseline.

Conclusion

GV is a physiological phenomenon that contributes to increased mean blood glucose levels and also plays a key role in the development of chronic diabetes complications. Newer technologies in the field of diabetes education, monitoring, and therapy, especially in type 1 DM, have made it easier to identify GV as a promising target for betterment of overall diabetes management. By using CGMS, it is now possible to detect glucose fluctuations and relate their dynamics to relevant clinical implications. By carefully using SMBG and available

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newer pharmacologic agents to avoid hyperglycemia and decrease hypoglycemic episodes, the burden of complications, disability, and mortality events associated with diabetes can be significantly reduced. However, due to lack of consensus for a standard metric and also difficulty in measuring GV, it remains a challenge for the clinicians to find out the most optimal approach for managing diabetes.

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CHAPTER

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Stem Cell Therapy in Diabetes

Sandeep K Mathur, Anshul Kumar

Abstract

Achievement of normoglycemia and a life free of insulin or oral anti-diabetic drugs has always been the goal of diabetes research and management. Stem cell therapy is the closest that we have ever got to the achievement of the above-mentioned goals. Here, in this chapter we aim to summarize the latest advancements in the use of stem cell therapy as a treatment modality in diabetes.

Introduction

Diabetes mellitus is a major pandemic that has been plaguing humanity since long and is growing tremendously with each passing year and is responsible for causing roughly four million deaths each year.[1] The trends for diabetes prevalence and incidence are particularly worrisome in developing countries.[2] Diabetes, which touched 230 million marks in 2008, is expected to affect over 300 million worldwide by the year 2025.[3]

Curative approach to diabetes that would make the administration of drugs such as insulin secretagogues, insulin sensitizers, or insulin itself redundant has long been sought. Pancreatic (whole organ) transplantation or islet transplantation following the Edmonton protocol has shown to be quite successful in achieving this "endeavor" of curing diabetes, primarily Type 1 Diabetes (T1D).[4] However, the main pitfall has been the lack of donors and the requirement of lifelong immunosuppression and thus, limits the application and benefit of this approach to only a few candidates.

Stem cell therapy heralds a promising new era in the management and possibly curative modality of advanced diabetes. Particular concerns regarding the type of stem cell, the transplantation procedure, and the long-term effects remain to be seen.[5-7] Several animal trials have shown the potential advantages of using stem cells for treating diabetes mellitus. However, given the numerous hurdles in the procedure and the ethical questions attached, human trials are still few and far between.

In this chapter, we briefly aim to review the treatment approach, the advances, the complexities, and the future directions in the treatment of both T1D and T2D using stem cell therapy as this might prove to be the one therapeutic approach that humanity has been searching.

What is a Stem Cell?

Stem cells are cells that can differentiate into a large number of cells; they are undifferentiated or partially differentiated cells. They are the first cells to form in the body and a particular cell lineage and tissue. They have the unique ability to proliferate without the loss of differentiation potential. They can broadly be classified into five different types:

- *Totipotent stem cells:* Also called omnipotent stem cells, they can differentiate into any embryonic or extraembryonic tissue, e.g., Totipotent cell from a zygote.

- *Pluripotent stem cells:* They can divide and differentiate into any of the three germ layers, i.e., ectoderm, mesoderm, or endoderm, e.g., Embryonic stem cells.
- *Multipotent stem cells:* These cells can multiply and give rise to a specific type of cells, e.g., Mesenchymal stem cells can differentiate into the osteoblastic lineage, myocyte lineage, adipocyte cell lineage, or chondrocyte lineage.
- *Oligopotent stem cells:* They are like the multipotent stem cells but are further limited in their capacity to differentiate, e.g., Hematopoietic stem cells are of mesodermal origin and can differentiate into all types of blood cells.
- *Unipotent stem cells:* These have the potential to differentiate into a single lineage of cells, e.g., Muscle stem cells.[8]

Pancreatic Islet Cell and Its Development

The human pancreas has dual functions: exocrine as well as endocrine. The exocrine part secretes various digestive enzymes. In contrast, the endocrine part is involved in the secretion of hormones that regulate body metabolism. The endocrine portion is organized into islets. These islets are composed of a variety of cells with each cell serving a different function; α cells, which secrete glucagon, β cells that secrete insulin, δ cells secrete somatostatin, ε cells secrete ghrelin while PP cells secrete pancreatic polypeptide. The chief action of all these various hormones is to maintain glucose homeostasis.[9] It is primarily the dysfunction of the β cells that leads to diabetes mellitus in T1D; there is autoimmune destruction of the β cell, and in T2D, there is β cell dysfunction combined with end-organ insulin resistance, but in both cases, the result is the same dysglycemia.

The development of stem cell-based therapy for diabetes requires the knowledge of underlying transcription factors that control the underlying islet cell differentiation process. However, this has been difficult owing to the relative unavailability of fetal endocrine tissue, and most of our knowledge of the development of endocrine pancreas comes from rodent experiments. Nevertheless, the development of islets in both rodents and humans is similar, and several generalizations can be made.

The human endodermal tissue becomes dedicated to pancreatic development before the evagination of dorsal and ventral pancreatic buds.[10] These buds contain multipotent pancreatic progenitor cells (MPCs), which under the influence of several transcription factors, get committed to endocrine or exocrine fates. After committing, these endocrine progenitors further differentiate and mature under the influence of lineage-specific transcription factors.

Here, we briefly discuss the transcription factors with involvement in β-cell development. The various stages in β-cell development and the different transcription factors expressed during that stage are shown in **Figure1**.

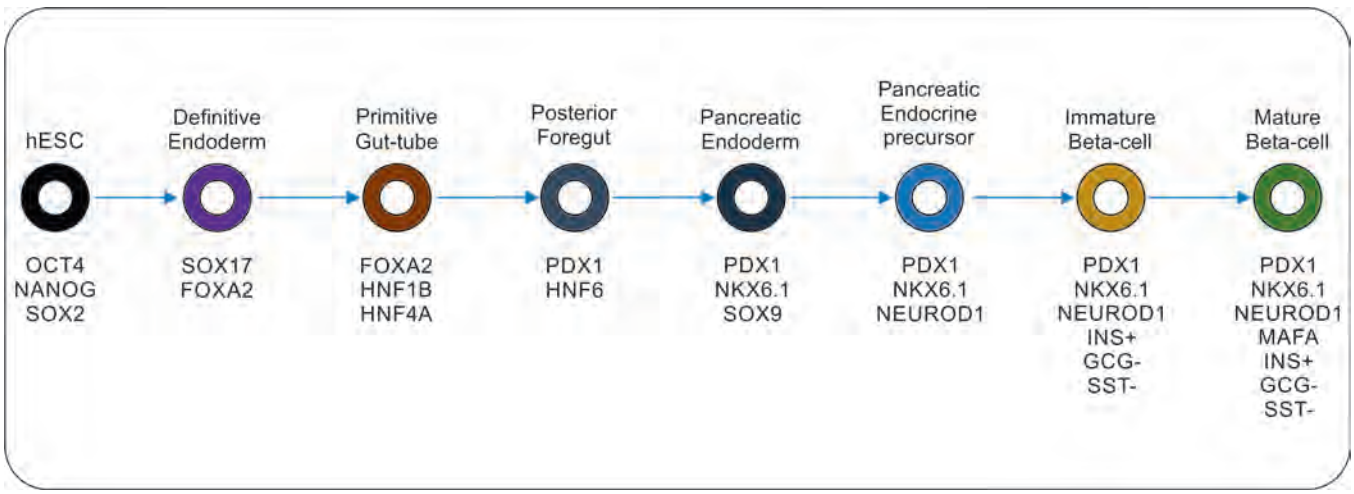

Fig. 1: Schematic representation of progression from hESC to mature beta-cell. The various stages and the different transcription factors expressed are shown

Transcription Factors Involved in Early Stages of Development

- *FOXA2:* This is an early transcription factor and is consistently expressed from week four onward,[11-14] as shown in several fetal pancreas studies.
- *SOX 17:* This high mobility group box gene is seen before 4 weeks but disappears within 1-week. Studies in mice have shown that its early expression is required for endoderm formation the continued expression represses pancreatic fate.[15]
- *Hepatocyte nuclear factor (HNF6):* This transcription factor is consistently found to be expressed from weeks 7–21 of the human pancreatic development.[12,13] INN rodents, it has been shown to have broad development until just before birth when it becomes restricted to alpha and acinar cells.
- *Hepatocyte nuclear factor 1 homeobox b (HNF1b):* In humans, it is expressed as early as 7 weeks and persists throughout pancreatic development.[16,17] Its heterozygous loss of function mutation leads to MODY 5.
- *PDX1:* It is also known as insulin promoter factor 1 (IPF1). It is present throughout the development, with high levels of expression limited to β cells only later in development and in adults.[11,12] Homozygous inactivating mutations of PDX1/IPF1 result in pancreatic agenesis (MODY4).
- *Pancreas transcription factor 1A (PTF1A):* It is barely detectable in the human pancreas until mid-gestation, perhaps owing to its enriched expression in the acinar cells at that time point. One study has identified a mutation in the PTF1a enhancer region leading to pancreatic agenesis.[18]
- *GATA binding protein 4 (GATA4):* These transcription factors are also expressed in the early development stages, and the late expression is limited to the mature acinar cells.[11]
- *SOX9:* It is found in PDX1+ cells in the early human pancreas by about 4 weeks and is then excluded from the pancreas development.[11,19]
- *Homeobox protein NK-6 homolog (NKX6.1):* This is expressed in the developing human pancreas after 4 weeks once SOX17 is excluded from the development.[11] Then by 14–16 weeks, its expression becomes restricted to β cells.[11,19] In adult pancreas, NKX6.1 is a key β cell identity factor and has severely reduced expression in human T2D islets.[20,21]
- *Motor neuron and pancreas homeobox 1 (MNX1):* In humans, its expression is found as early as 7 weeks and, then its expression decreases by 14–16 weeks of gestation.[12,13] Patient with a homozygous mutation in the DNA binding homeodomain of MNX1 presented with permanent neonatal diabetes.[22,23]

Multipotent pancreatic progenitor cells: These cells of developing pancreas are characterized by the continued expression of FOXA2, PDX1, SOX9, NKX6.1, and GATA4.[10] These cells are further destined to form the ductal endocrine and the exocrine components of the pancreas. The various transcription factors expressed at this stage include:

- *GATA6:* It is considered to be very important in the development of human pancreas with mutations in GATA 6 leading to pancreatic agenesis.[24,25]

Transcription Factors Involved in the Production of Islet Endocrine Cell Lineages

- *Neurogenin 3 (NGN3):* With the loss of SOX 9, as mentioned earlier, the expression of NGN3 initiates pancreatic endocrine commitment.[26] Its first expression is seen around 8 weeks, peaks around 11 weeks, and then declines to low levels by 19 weeks.[26] A case of permanent neonatal diabetes carrying a null mutation in NGN3 with low C-peptide levels has been reported.[27]
- *Regulatory factor X 6 (RFX6):* As demonstrated by quantitative real-time PCR, the expression of RFX6 is limited to the adult human pancreatic islets and autosomal recessive mutations have been found to result in rare cases of neonatal diabetes with the absence of insulin, somatostatin and glucagon secreting cells in the islets.
- *Paired box gene 4 (PAX4):* Its expression is evident by 9 weeks of gestational age,[13] and its mutation has been associated with MODY9.
- *GLIS family zinc finger 3 (GLIS3):* Patients with an autosomal recessive mutation at this locus have been associated with inherited forms of diabetes and congenital hypothyroidism.[28-30]
- *MAFB:* In humans, MAFB expression increases 7–21 weeks and after that continued expression is seen in adult α and β cells.[13,31]

Endocrine Cell Differentiation and Maturation

In humans, pancreatic hormone expression is first evident at about 8 weeks of gestation, with insulin being the first islet hormone to be formed; this is followed by the appearance of glucagon at around 9 weeks of gestation.[13,32,33]

Transcription Factors Involved in β-cell Differentiation

- *NKX2.2:* It is first seen around 8 weeks in the developing α and β cells with increased expression around 14–16 weeks.[11]
- *Insulin gene enhancer protein ISL-1 (ISL1):* It is also known as ISLET 1 and is thought to be essential for the development of the pancreas in humans.[33] A nonsense mutation in ISL1 seen in a Japanese diabetic patient points toward the potential role of ISL1 in pancreatic β cell development.[33]
- *NEUROD1:* It is first expressed at 15 weeks and is found in all islet cell types.[11-13] Heterozygous NEUROD1 mutation has been found associated with MODY 6 and neonatal diabetes as well (autosomal recessive).[34,35]
- *PAX6:* Its expression is seen around 14–16 weeks and persists in all cells throughout adulthood.[12] Single nucleotide polymorphism at PAX6 has been reported to result in decreased insulin sensitivity and response.[36]
- *MAFA:* In humans, MAFA is nearly undetectable in the human pancreas from 7–21 weeks, after which it is almost exclusively seen to express in human pancreatic β cells.[13,31] Decreased expression of MAFA in human pancreatic β cells has been proposed as a sign of dysfunctional cells.[21]

The sequence of development and expression of the various transcription factors is of immense importance in the proper development of the pancreas, and as noted above, any deviation resulting from mutation can result in pancreatic agenesis or diabetes mellitus.

Stem Cell-derived Treatment for Diabetes

The advances made in recent years in the field of stem cell research have opened up avenues toward newer approaches in treating both T1D and T2D. These advances have led us one step closer to finding the cure for diabetes and is now a real and achievable goal.

Significant progress in the generation of β cells from human stem cells has been made in the last decade, and the defining strategy is to emulate the development pathway closely from pluripotency to β cell.[21,37] Efforts have also been made to generate β cells that are capable of producing glucose stimulated Insulin secretion (GSIS).[38-42]

We shall review in brief the current state of generating human embryonic stem cell (hESC) derived pancreatic islet cells.

Stem Cell Niche Optimization for Islet Structure Generation

In vivo, the β cells do not occur in isolation. However, they are parts of intricate 3-dimensional islets composed of numerous cells, as noted earlier, whose products exert a variety of autocrine and paracrine effects on each other. As opposed to rodent islets where there is homologous cell-cell contact with a core of β cells surrounded the other types of islet cells,[43,44] the human islet has heterologous cell-cell contact with all the islet cell types found intermingled with one another.[45] This arrangement has several implications, for example, the homologous contact in rodents facilitates synchronous and simultaneous insulin secretion from islet β cells, while in humans, and there is an asynchronous release of insulin.[45] Recent data from cell sorting and sequencing also suggests the existence of distinct β cell types in human islet cells.[46]

Another critical interaction occurring in the islet cells is the interaction with non-endocrine cells, including mesenchymal, neuronal, perivascular, and endothelial cells.[47-49] The developing islet recruits several endothelial cells by the secretion of VEGF-A.[50] These endothelial cells help form the basement membrane, which a critical modulator of β-cell function, growth, and survival.[48,51-53] This intricate relationship between the β cells and the surrounding non-endocrine cells only strengthens the fact emulating the native β-cell niche will help improve the survival and function of hESC derived β cells in vitro.

Various efforts have been made to engineer the islet structure into "pseudo-islets" in vitro.[54] Several studies have shown enhanced functionality of these reaggregated "pseudo-islets" in vitro or in vivo after transplantation. Penko et al.[55] also showed improved GSIS with reaggregated "pseudo islets" with endothelial cells compared to pseudo-islets composed of β cells alone.

To summarize, more work is needed to determine the optimal islet microarchitecture that will attain the

maximum functionality and survival. One available option is the generation of niche cells themselves from the hESC or from induced pluripotent stem cells (iPSC). Another challenge is that pseudo-islets generation relies on the property of endocrine and non-endocrine to align themselves; this can perhaps be solved using 3-D printing techniques of islet tissue, allowing us to enforce the desired islet structure. The use of microfluidic devices, the so-called "organ on a chip" approach, may provide further sophistication and optimization of function.

Transplant Site

The site chose for the transplant also has a significant bearing on the survival as well as the functionality of the transplant, for example, in case of the engrafted islets stem-cell-derived or otherwise via infusion through the portal vein often require multiple infusions.[56] Another factor which is of significant importance is that the islets infused into the portal vein are not retrievable, and this is of concern for the clinical translation of trials using hESC-derived β cells until it has been indisputably proven that the cells have developed into mature human islet cells and all the possibility of neoplastic transformation has been ruled out completely. While, at the present stage of development, the risk of development of the transplant into a teratoma cannot be ignored, but the optimization and the generation of fully differentiated islet and β cells can negate this concern.

Learning from the information gained from solid organ and islet cell transplant, it is evident that a more optimal site for the transplant is required. Several investigators are evaluating subcutaneous and intramuscular sites for islet transplantation to increase engraftment and also allow for removal of the graft in case of tissue dysfunction or transformation.[57,58] Successful pancreatic transplant in T2D patients suggests that given an unlimited source of β cells and may provide a benefit in a vast majority of T2D patients.[59]

Immune Modulation in β-cell Replacement Therapy

Alloimmune and autoimmune systems remain significant barriers to the more widespread application of cell replacement therapies for curative treatment in T1D as well as T2D. Lifelong treatment with immunosuppressive drugs offers a solution to this problem but is riddled with its new problems like side effects and toxicities.

Engineered Stem Cell-derived β-cell to Protect against Immune Rejection

One of the major unresolved issues with the stem cell-derived islet cells is the task of evading the immune system and preventing rejection. Immune rejection is an even bigger issue in T1D where the immune cells are already primed to attack self β cells and, therefore, more likely to attack the stem cell-derived β cells. Furthermore, an allogeneic immune response to the stem cell-derived islets poses another obstacle in both T1D and T2D recipients.

Stem cell technology offers unique solutions to engineer the β cells to evade the immune system. The development of revolutionary gene-editing tools like CRISPR/Cas 9 system[60] provides the possibility to dismantle MHCs in the hESCs and thereby to prevent the presentation of alloantigens. This strategy would also work against autoimmune-mediated β-cell destruction in T1D patients. T cell-mediated recognition of the MHC molecules is the root cause behind alloimmunity. At the same time, in T1D patients, autoimmunity against transplanted β cells is dependent upon MHC class 1 expression on islet cells.[61] Thus, the strategy of using the CRISPR/Cas9 technique to dismantle MHC 1 and 2 can lead to a reduction of the immune rejection process of the transplanted β cells.

The abolition of HLA expression can abate the alloimmune as well as an autoimmune reaction. However, still, the islet autoantigens from the graft can be presented by the host antigen-presenting cells (APCs), thereby activating the autoreactive T cells leading to islet injury and rejection. Control of NFκB activation by overexpressing A20 and suppressing STAT1 activation by overexpressing SOCS 1 may prove effective in controlling inflammatory cascade against the β cells.[62-64] Additionally, using other immunomodulatory approaches like enhancing immune checkpoints via forced expression of PDL1, it may also be used for the protection of β cells against autoreactive T cells.

Also, to be considered are NK cells, which can be activated against the HLA ablated stem cell-derived β cells[65] Class1 HLA are major ligands for NK inhibitory receptors. So, complete ablation of Clas1 HLA expression

on stem cell-derived Islet cells may make them vulnerable to NK mediated killing. HLA-e and G are less Hla A, B, and C and can be expressed in islet endocrine cells;[66] these molecules have a strong inhibitory effect on NK cells. By retaining HLA-E and G alleles intact while deleting HLA-A, B, and C, it might be possible to inhibit NK cells while keeping a reduction in T cell responses.

Cell Encapsulation Strategies

Despite earnest efforts to develop immune tolerant β cells through genetic manipulations as discussed earlier or other methods, there is still a high likelihood of autoimmune and alloimmune reactions against the transplanted stem cell-derived islet cells.

We could also use another approach by utilizing a semi-permeable membrane/capsule to deliver the transplanted β cells, which would protect the cells against immune derived reactions while at the same time allowing the transfer of sufficient mass of insulin secretions. This encapsulation strategy would also serve to protect the patient against any stem cell-derived β-cell oncogenic transformation. This idea of encapsulation has been a pipe dream for many years. However, the development of an optimal device remains an elusive dream as the semi-permeable membranes that protect the cells against the immune reactions are not sufficiently permeable to the nutrients needed for the viability of the cells.

The use of a suitable device membrane as a physical barrier between the recipient and hESC-derived β cells could potentially enable the use of these therapies while eliminating the use of immunosuppressants. An idle encapsulation device would be one which provides blood supply for sustenance, biocompatible, immunoprotective, allow secreted insulin to pass, contain any tumorigenic transformation.

Encapsulation Strategies in Clinics

Microencapsulation based strategy is perhaps the only device that has made any headway in clinics; it uses microcapsules made from alginate, 300–400 microns in diameter, which are used to encapsulate allogeneic islets. These were delivered intraperitoneally and reduced insulin requirements.[67-71] One of the significant limitations to these devices has been the lack of oxygen one company Beta-O2 developed the bAir device, this device exogenous oxygen to the transplanted tissue. The device consists of a compartment, which contains islets that are encapsulated within an alginate hydrogel slab, which is adjacent to a gas chamber where cells obtain oxygen by diffusion through a gas-permeable membrane.[72] This device contains ports to allow for daily refilling of oxygen. A single case report on the device usage reported islet survival with a modest reduction in insulin requirement for 10 months.[73]

Two devices, the "theracyte" device and the "sernos" cell pouch,[74] aim to revascularize a subcutaneous site before implantation of the device, and this increased vascularization is aimed at improving the survival of the cells.

Microfabricated Devices

The use of microfabricated silicon membranes can lead to the achievement of high precision control over pore sizes, as shown by nanoporous biocapsules[75,76] and nanogland.[77-80] The resultant pore size control could potentially allow separating soluble inflammatory mediators and also provide immunoprotection while allowing insulin secretion. The surface of the silicon membranes can further be selectively grafted with biocompatible polymer thin films to ensure functional performance over extended periods.

Conclusion

We stand at the cusp of technology where history can be made; the use of hESC derived islet cells to cure diabetes is no longer a distant dream but a tangible reality. The use of cutting edge technology like CRISPR/Cas9 to modulate the immune response, the use of 3-D printers to design and fabricate islet cells, use of microencapsulation devices hopefully in the near future will bring forth the dream of humanity of finding a cure for diabetes.

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CHAPTER

75 GLP Analogs versus SGLT2 Inhibitors in Diabetic Patients with Cardiovascular Disease

Udai Lal

Abstract

Complications of type 2 diabetes are broadly classified as macrovascular and microvascular. This spectrum usually encompasses conditions like chronic renal disease, heart failure, and atherosclerotic heart disease. While the older classes of anti-diabetic agents have demonstrated benefit in terms of microvascular outcomes, newer anti diabetic agents like SGLT2 inhibitors and GLP1RAs have gone one step ahead to demonstrate macrovascular benefits. Both these classes have demonstrated CV safety in CV outcome trials. GLP1RAs demonstrate CV benefits mainly due to reduced atherosclerosis. On the other hand, benefits of SGLT2i are derived due to reduction of heart failure. These benefits of both classes are attributed to mechanisms independent of glucose control. Based on the benefits demonstrated in the CV outcome trials, recent global guidelines like the ADA guidelines have favored the use of these drugs in diabetes patients with renal and cardiovascular risk.

Introduction

Type 2 diabetes is a metabolic disorder that affects nearly 10% of the global population. Its prevalence is predicted to increase in the coming years. It is now established that a long-standing diabetes patient would be at increased risk of macro- and microvascular complications. Cardiovascular (CV) disease is a leading cause of mortality in patients with diabetes. It is up to 2–4 times more common in patients with diabetes as compared to the ones without. The older agents that control hyperglycemia like the sulfonylurea, metformin, meglitinides, thiazolidinediones, and dipeptidyl peptidase inhibitors have shown improvements in microvascular outcomes. However, they fall short in reducing the morbidity and mortality associated with macrovascular disease. This vacuum is addressed by the newer antidiabetic classes, Sodium Glucose Cotransport-2 inhibitors (SGLT2i), and Glucagon like peptide 1 analogs (GLP analogs). These molecules have demonstrated cardioprotection and were associated with reduced CV outcomes in the cardiovascular outcome trials (CVOTs). The recent American Diabetes Association (ADA) guidelines recommend these newer classes in type 2 diabetes patients with chronic kidney disease (CKD) and CV disease after monotherapy with metformin, which remains the mainstay.[1]

This review dissects the data available with SGLT2i and GLP analogs in terms of CV protection and throws light on the proposed mechanism for these benefits.

CVOTs with SGLT2i

In the EMPA REG CVOT, 7020 subjects were treated for a duration of 3.1 years. The composite primary CV outcome was lower in subjects receiving empagliflozin. Death from CV causes, deaths from any cause and heart failure hospitalization was significantly lower in empagliflozin arm compared to placebo. There was no difference between groups in the rate of stroke and myocardial infarction (MI).[2]

In the CANVAS trial program (CANVAS plus CANVAS Renal) with canagliflozin, 10142 type 2 diabetes subjects at high risk for CV disease were followed up for a duration of 188.2 weeks. Subjects on canagliflozin had significantly low risk of non-fatal stroke, non-fatal MI and death from CV causes compared to those on placebo. However, there was an increased risk of amputations. CANVAS Renal was designed to detect the effects of canagliflozin on albuminuria. Subjects on canagliflozin had less frequent albuminuria progression. These effects of canagliflozin were more prominent in CANVAS Renal as compared to CANVAS.[3]

In the CREDENCE trial, type 2 diabetes patients with albuminuria and CKD with a GFR of 30–90 mL/min/1.73 sqm body surface area received either placebo or 100 mg of canagliflozin. At a follow-up of 2.6 years, CV events and risk of renal failure were lower in patients on Canagliflozin as compared to placebo.[4]

In the DECLARE TIMI CVOT with dapagliflozin, 17160 subjects were followed for a duration of 4.2 years. With respect to major adverse CV events, dapagliflozin met the criteria for non inferiority to placebo arm. Heart failure hospitalization rate or CV death rate was lower in dapagliflozin arm. This was due to the lower rate of heart failure hospitalizations.[5]

CV Benefits of SGLT2i

There are numerous mechanisms proposed to explain the beneficial effects of SGLT2i on heart. They may improve bioenergetics and cardiac metabolism due increased ketone production. Ketones are more efficient source of myocardial energy as compared to fatty acids. Ketones improve myocardial oxygen efficiency as it requires lesser oxygen for metabolism. Thus, it increases the efficiency of cardiac function.

Furthermore, SGLT2i causes hemoconcentration, thereby improving the oxygen delivery to tissues. Hemoconcentration and shift in the metabolic myocardial substrate have a synergistic effect. Natriuresis and osmotic diuresis reduce blood pressure (BP) and arterial stiffness resulting in favorable conditions for ventricular loading.

Investigations are underway to determine the effects of SGLT2i on cytokine production and modification of cardiac fibrosis.

SGLT2i in addition to CV diseases, reduce progression of albuminuria and nephropathy. The possible explanation of these benefits is due to reinstatement of the tubuloglomerular feedback. Reduction of intrarenal hypoxia has also been proposed as a mechanism for the beneficial effect on renal system.[6]

CV Outcome Trials with GLP Analogs

ELIXA CV outcome trial with lixisenatide was the first of the CVOT among GLP analogs. It was conducted in subjects with acute coronary syndrome (ACS) within 6 months of screening. 6068 subjects were followed up for 25 months. The study concluded that lixisenatide did not significantly change the rate of major CV outcomes in subjects with type 2 diabetes and recent ACS.[7]

Liraglutide in the LEADER CVOT was compared with placebo. The study had 9340 subjects with CV condition or CV risk factor who were followed up for 3.5 years. The primary composite outcome was significantly lower in the patients receiving liraglutide. In addition, secondary endpoints like death from CV causes and death from any cause were significantly lower in the liraglutide group.[8]

SUSTAIN 6 CVOT compared semaglutide versus placebo in type 2 diabetes subjects with CKD, CHF, pre-existing CV disease, or at least 1 risk factor for CV disease. 3297 subjects were enrolled and followed up for 2.1 years. Non-fatal stroke, non-fatal MI, and CV death rate were significantly lower in subjects receiving semaglutide versus placebo.[9]

The EXSCEL CVOT with once weekly exenatide showed no difference in major CV events incidence as compared to placebo.[10]

Albiglutide in HARMONY CVOT demonstrated its superiority over placebo in terms of major CV events.[11]

Composite CV outcome and non-fatal stroke were lower with dulaglutide in the REWIND CVOT when compared to placebo.[12]

CV risk profile of semaglutide (oral) was non inferior to placebo as shown in PIONEER 6 CVOT.[13]

To summarize, on one hand dulaglutide, albiglutide, subcutaneous semaglutide, and liraglutide demonstrated significant benefit in lowering the composite CV outcomes; oral semaglutide, weekly exenatide, and lixisenatide demonstrated non inferiority.[14]

GLP Analogs: Beneficial Effects on Cardiovascular System

Glycemic Control

GLP analogs are effective in reducing A1c. In addition to lowering A1c, they reduce glycemic variability (GV)

thereby reducing oxidative stress. This reduction of GV may explain its beneficial effects in CV disease.[15,16]

Hypertension

Dysglycemia and hypertension significantly raise the risk of stroke, heart failure, and MI. Data from trials have shown GLP analogs to reduce BP values. However, the mechanism behind the BP lowering is not clearly understood. Studies have shown that the fall in BP happens early (within 2 weeks of GLP analog initiation). Several potential mechanisms have been suggested. GLP1 receptor activation in renal system and arteries resulting in vasodilation and improved endothelial function might explain this effect. It is also hypothesized that the lowering of BP may be GLP receptor independent due to nitric oxide-mediated vasodilation.[16]

Dyslipidemia

Risks of CV episodes are much higher in patients with elevated low density lipoprotein (LDL) levels and diabetes. Even though the mechanisms are unclear, clinical trials have shown GLP analogs improve dyslipidemia. While, improvement of dysglycemia itself improves lipid profile due to reduction in hepatic synthesis of triglycerides and improved insulin sensitivity, reduction in triglycerides may also be due to reduced apolipoprotein B48 secretion mediated by intestinal mucosal GLP 1 receptors.[16]

Weight

It is a well-known fact that obesity is associated with both CV disease and type 2 diabetes. GLP analogs cause modest weight loss in addition to glycemic control thereby improving patient's quality of life and functional activity.[16]

Other Benefits

In a preclinical study, liraglutide, a GLP analog improved endothelial function by inhibiting expression of vascular adhesion molecule and plasminogen activator inhibitor 1.[17]

Studies have demonstrated cardioprotective effect of liraglutide. In patients who underwent coronary angioplasty, smaller infarct size along with lower levels of high sensitivity C reactive protein, and superior myocardial salvage index were seen in liraglutide arm compared to placebo.[18]

Effects of GLP Analogs/SGLT2i in Patients at Increased CV Risk

A network analysis published recently showed that as compared to patients on placebo, GLP analogs reduced incidence of stroke. Among the GLP analogs, odds were lower with dulaglutide and semaglutide administered subcutaneously.[19]

SGLT2i reduced heart failure related hospitalization. This was seen with all the 3 SGLT2i (dapagliflozin, canagliflozin and empagliflozin).[19]

The all cause mortality was reduced by extended release exenatide, liraglutide, dapagliflozin, and oral semaglutide. Liraglutide, empagliflozin, and oral semaglutide have lesser odds of death from CV cause compared to extended release exenatide, sulphonylureas, dulaglutide, pioglitazone, dapagliflozin, DPP4 inhibitors, and canagliflozin.[19]

Impact of CVOTs on Guidelines

In the 2017 guidelines, ADA recommended to begin with metformin monotherapy and add any one of the non-insulin agents for dual therapy.[20] However, these recommendations dramatically changed in the next 2 years to include GLP analogs/SGLT2i as add on to metformin in type 2 diabetes patients with atherosclerotic cardiovascular disease (ASCVD) or CKD.[21]

In addition, the European Society of Cardiology now recommends GLP analogs/SGLT2i should be considered as the first choice ahead of metformin in type 2 diabetes patients with high risk for CV disease or known CV disease.[22]

Exploring Uses/Potential Uses of SGLT2i

Obesity is an established risk factor for type 2 diabetes development. SGLT2i in addition to improving hyperglycemia, induces weight loss thereby targeting the pathogenesis of type 2 diabetes. Patients on SGLT2i excrete about 60–80 g of carbohydrates per day. As mentioned, the recent ADA/EASD guideline recommends these classes of drugs are for patients with type 2 diabetes with heart failure or CKD and those with established or high risk of ASCVD.

In addition, in patients without type 2 diabetes who have heart failure with reduced ejection fraction,

dapagliflozin has showed improved CV outcomes. This suggests that dapagliflozin may be used as a heart failure drug irrespective of whether the patient has diabetes or not. Furthermore, trials exploring its role in heart failure patients with preserved ejection fraction or CKD patients without type 2 diabetes are underway. SGLT2i are even being tried in type 1 diabetes concomitant to insulin therapy due to its insulin independent mode of action.[23]

Conclusion

Due to the results of CVOTs and the recommendations of international bodies,[24] SGLT2i and GLP analogs are preferred agents in diabetes patients with established CV disease and risk factor for CV disease. A physician can choose either of the therapies in case of atherosclerotic CV disease. However, in the presence of comorbid conditions like renal disease or heart failure, SGLT2i should be preferred over GLP analogs. The approach toward these patients should be personalized. In diabetes patients with very high CV risk, instead of choosing between these 2 groups, combining these 2 therapies has be speculated.[25]

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CHAPTER

76 Challenges in Type 1 Diabetes in Adolescence

Akhil Krishna, Sujoy Ghosh

Abstract

The management of type 1 diabetes during adolescent period poses unique challenges. The period of adolescence has a great impact on type 1 diabetes and the disease per se puts huge demands on the adolescent boy or girl. Thus the disease and this critical phase of development influence each other. The glycemic control during this developmental phase is often suboptimal, mainly due to poor adherence to treatment and the hormonal changes of puberty, among other reasons. There is also higher risk for emergence of complications of type 1 diabetes during this phase, and hence it is recommended to begin screening for vascular complications at this period. Another challenge which emerge during this phase is the risk of indulging in the use of alcohol, smoking, and various illicit drugs, which can directly or indirectly impact the glycemic control and complications. Other issues to be addressed is with regard to sexual health with special emphasis on contraception and planned pregnancy. Finally, the transition from pediatric to adult care should be a planned process for optimal outcomes.

Introduction

According to WHO, adolescents are individuals in the age group 10–19 years. Individuals in 15–24 years age group are designated "youth." The term "young people" covers both adolescence and youth and includes 10–24 years.[1] Emerging adulthood usually refers to the developmental stage between 18 and 30 years.[2]

WHO emphasizes that adolescence should be considered as a phase of development rather than a fixed time frame in an individual's life. It should be viewed as an important developmental phase, which witness the appearance of secondary sexual characteristics (puberty) to sexual and reproductive maturity, the development of mental processes and adult identity and the transition from total socioeconomic and emotional dependence to relative independence.[1]

In this chapter, we shall be discussing the unique challenges in diabetes management during this phase of development.

What is the Effect of Adolescent Period on Type 1 Diabetes?

This will be discussed under following two headings:

- Effect of adolescence on Glycemic control
- Effect of adolescence on diabetes complications

Effect of Adolescence on Glycemic Control

Only about one-fifth of adolescents with type 1 diabetes meet the HbA1c goals set by American Diabetes Association (ADA) or International Society for Pediatric and Adolescent Diabetes (ISPAD).[3]

The suboptimal glycemic control during adolescence is due to varied reasons such as:

- Erratic meal and exercise patterns[4]
- Risk taking behaviors[5]
- Poor adherence[6]
- Hormonal changes during puberty

Studies have shown that females are more likely to have worsening of metabolic control during adolescence.[7]

Of the reasons listed above, poor adherence to treatment regimens and hormonal changes during puberty are discussed in more detail below.

Why Adolescents with Diabetes show Poor Adherence to Treatment Regimens?

Adolescence is a critical phase in the development when the individual's priorities changes and they try to cope up with the competing demands of social life.

Some of the intrinsic features of diabetes, like chronicity, need for frequent blood glucose measurements and dietary restrictions put more emotional stress on the adolescent. The negative emotions (like feeling frustrated, hopeless, guilty, angry, fearful), which arise from living with and managing diabetes is referred to as diabetes distress.[8] Diabetes distress is reported in about one-third of adolescents with diabetes and it negatively affects the self-management behaviors and glycemic control. Parents of type 1 diabetes are also at risk of developing diabetes distress.

Psychological comorbidities like depression, anxiety, and disordered eating behaviors are also prevalent in adolescents with diabetes. Elevated depressive disorders and depressive symptoms are reported in about 25% and anxiety disorders in about 20% of patients with type 1 diabetes. The most common disordered eating behavior seen in people with type 1 diabetes is omission of insulin in order to lose weight.

Several other factors like family dysfunction, difficult peer relationships, and poor school performance also act as hindrances to treatment adherence during adolescent period.

The consequences to poor adherence could be immediate in the form of hypoglycemia or ketoacidosis or medium to long term in the form of early appearance of microvascular complications, especially retinopathy and nephropathy. So ensuring adherence to medical and lifestyle measures should be part of the routine diabetes care in adolescents.

To improve the adherence, clinicians caring adolescents with diabetes should emphasize on:

- Maintaining a comfortable and mutually respectable relationship with the youth
- Negotiating treatment regimens with the adolescent, which are attainable and sustainable
- Building emotional strength
- Allowing adolescents to express their feelings
- Encouraging the successful activities or gains undertaken by the adolescent

Hormonal Changes during Puberty and Insulin Resistance

During puberty, insulin resistance occurs irrespective of the presence of diabetes. Insulin resistance is worse during all stages of puberty, but worst during mid puberty. Euglycemic insulin-clamp studies have shown that insulin sensitivity falls by around 30% during mid puberty (Tanner stages 2–4) in non-obese non-diabetic children when compared with prepubertal children or older adolescents (Tanner stage 5) and adults. This fall in insulin sensitivity is more marked during Tanner stage 3, in girls and in those with higher BMI.[9] Insulin resistance during this phase is due to higher growth hormone (GH) levels during puberty.[9]

Presence of diabetes cause a further dip in insulin sensitivity, mainly through alterations in GH-IGF-1 axis.

GH-IGF-1 axis in type 1 diabetes **(Fig. 1)***:*

- *Decreased upregulation of hepatic GH receptor:* In normal physiology, insulin has a permissive role in mediating GH action. Hepatic GH receptor (GHR) expression is upregulated by insulin in the portal circulation. Thus, insulin promotes the hepatic generation of insulin like growth factor-1 (IGF-1) by GH. In type 1 diabetes, where there is low insulin in portal circulation, there is decreased upregulation of hepatic GH receptor. This causes a decrease in hepatic IGF-1 generation.
- *Increase IGFBP-1:* Insulin causes a decrease in Insulin like growth factor binding protein-1 (IGFBP-1). IGFBP-1 binds to IGF-1 and causes a reduction in free bioactive form of IGF-1. Hypoinsulinemia causes upregulation of IGFBP-1 and therefore more IGFBP-1 binds to IGF-1 causing reduction in free IGF-1.
- *Chronic inflammation:* Presence of chronic inflammation in type 1 diabetes further decreases IGF-1.

In summary, decreased upregulation of hepatic GHR, elevated IGFBP-1, and chronic inflammation in type 1 diabetes causes low IGF-1, which leads to GH hypersecretion due to loss of negative feedback by IGF-1, which in turn leads to insulin resistance[10]

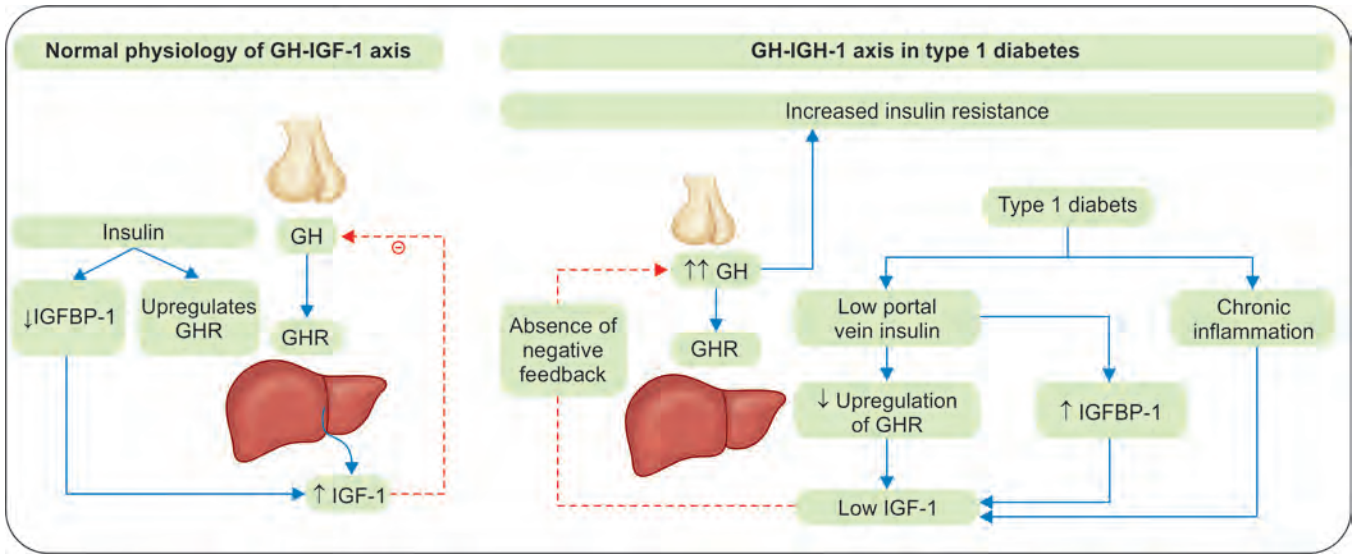

Fig. 1: GH-IGF-1 axis in normal physiology and in type 1 diabetes

- In normal physiology, Hepatic GH receptor expression is upregulated by insulin in the portal circulation. Thus insulin promotes the hepatic generation of IGF-1 by GH. IGFBP-1 normally binds to IGF-1 and causes a reduction in free bioactive form of IGF-1. By decreasing IGFBP-1, insulin causes an increase in the free form of IGF-1.
- In type 1 diabetes, where there is low portal insulin, there is decreased upregulation of hepatic GH receptor. This causes a decrease in hepatic IGF-1 generation. Hypoinsulinemia also causes upregulation of IGFBP-1 and thus a reduction in free IGF-1. Presence of chronic inflammation in type 1 diabetes further decreases IGF-1.
- Hence, decreased upregulation of hepatic GHR, elevated IGFBP-1 and chronic inflammation in type 1 diabetes causes low IGF-1, which leads to GH hypersecretion due to loss of negative feedback by IGF-1, which leads to insulin resistance.

Increased risk of Dawn phenomenon during puberty: Insulin requirements increase during early morning hours, generally between 5 a.m. and 8 a.m. causing prebreakfast hyperglycemia. This is known as "Dawn phenomenon." The reason for this is postulated to be due to increased nocturnal secretion of GH[11] and insulin clearance during early morning hours.[12] Since GH secretion is at its peak during mid to late puberty, risk for Dawn phenomenon is at its peak during this phase of development. This highlights the importance of increasing the availability of insulin during the dawn period.

Other factors contributing to insulin resistance: During adolescence, increase in BMI frequently occurs, especially in females.[13] Increase in BMI further increases insulin resistance.

Sexual dimorphism in insulin sensitivity during adolescence: Some studies have shown sexual dimorphism in insulin sensitivity during adolescence, where increase in insulin resistance is more marked in females compared to males.[9,14] This sexual dimorphism is seen during early adolescence and by the completion of puberty, both sexes have similar insulin requirement. This is thought to be due to earlier increase in adrenal androgens, estrogens, and GH in females.

Effect of Adolescence on Diabetes Complications

The period of adolescence is considered as high risk for the emergence of complications of type 1 diabetes due to various reasons like difficult to achieve optimum glycemic control and pubertal risk factors like alterations in GH-IGF-1 axis and insulin resistance.

The first signs of vascular complications of diabetes often appear during adolescence. Subclinical manifestations like early increases in urinary albumin excretion, retinal microvasculature changes, and subclinical changes in large blood vessels, like increased aortic and carotid intima media thickness and increased arterial stiffness, are common during this period.

Puberty Accelerates Diabetes Complications

The most important determinant of diabetic retinopathy and albuminuria is the duration of diabetes. But this

TABLE 1 Screening recommendations for vascular complications in type 1 diabetes (adapted from ISPAD 2018 and ADA 2020 guidelines)[22]

	When to commence screening		*Screening methods*
	ISPAD 2018	*ADA 2020*	
Nephropathy	11 years with 2–5 years diabetes duration	>10 years or at puberty (whichever is earlier), once the child has had diabetes for 5 years	Urinary albumin/creatinine ratio
Retinopathy	11 years with 2–5 years diabetes duration	≥11 years or at puberty (whichever is earlier), once the child has had diabetes for 3–5 years	Fundal photography or mydriatic ophthalmoscopy
Neuropathy	11 years with 2–5 years diabetes duration	>10 years or at puberty (whichever is earlier), once the child has had diabetes for 5 years	History Physical examination Clinical tests

ISPAD: International Society for Pediatric and Adolescent Diabetes; ADA: American Diabetes Association

becomes apparent only after puberty. Evidence suggests that risk for vascular complications is greater in those with diabetes during puberty than in those who develop diabetes after puberty.

Diabetic Retinopathy

The importance of age at diagnosis of diabetes and risk of complications is exemplified by the higher risk of developing retinopathy in those diagnosed with diabetes before 14 years compared to those diagnosed during adulthood.[15] Compared to adults with diabetes, adolescents are at greater risk of progression to more advanced stages like severe non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and/or diabetic macular edema, which are vision threatening.[15] The progression may be more rapid in the background of poor glycemic control.[16] Retinopathy can regress with improvement in glycemic control.[17]

Diabetic Nephropathy

Increased albumin excretion ratio is seen in children after 11 years of age or after puberty compared to children less than 11 years or before puberty.[18] The adolescent type 1 diabetes cardiorenal intervention trial (AdDIT) showed increased cardiovascular risk (as suggested by higher lipid levels, arterial stiffness, increased aortic intima media thickness, and signs of impaired cardiac autonomic function) in adolescents aged 10–16 years with increased urinary albumin excretion levels.[19]

One interesting observation is that the risk of developing microalbuminuria or retinopathy during adolescence is higher for girls than boys.[20,21] But in adulthood, men carries a higher risk.

Based on the understanding of adolescence as a high-risk period for diabetes complications and puberty accelerating vascular complications in diabetes, International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends screening for vascular complications starting at 11 years of age or at the onset of puberty, whichever is earlier, if duration of diabetes is 2–5 years **(Table 1)**.[22]

Alcohol, Smoking, and Illicit Drugs

Alcohol

Rates of alcohol and other illicit substance use among adolescents (15–18 years) and young adults (18–25 years) with type 1 diabetes seem similar or slightly lower than their non-diabetic counterparts.[23]

Alcohol intake typically causes delayed hypoglycemia, which occurs about 6–8 hours after intake. Alcohol also causes exacerbation of hypoglycemia unawareness. Initially hepatic glucose production is maintained by glycogenolysis, but once hepatic glycogen stores are depleted, delayed hypoglycemia occurs due to inhibition of gluconeogenesis. Alcohol is metabolized to acetaldehyde and then to acetone. This process increases NADH and decreases the availability of NAD+, which is a cofactor for

gluconeogenesis. Gluconeogenesis is further reduced by the inhibitory action of alcohol on GH release.

Adolescents with type 1 diabetes should be encouraged to refrain from binge drinking. For prevention of alcohol induced hypoglycemia, it is advisable only to drink alcohol with carbohydrates, maintain good hydration, check blood glucose levels before bedtime, and have snacks before sleep. Another issue with alcohol intake is that hypoglycemia might be confused with intoxication.

Smoking

Among adolescents and emerging adults with diabetes, smoking increases the risk of microalbuminuria and cardiovascular risk. It is also associated with very early onset of peripheral neuropathy.[24]

A smoking history should be elicited at initial and follow-up visits. Discourage cigarette smoking including e-cigarettes in those who do not smoke and smoking cessation should be encouraged in active smokers. Adolescents should be provided with specific interventions, which can help them to quit smoking like nicotine patches and cognitive behavioral therapy.

Illicit Drugs

Illicit drugs like cocaine, amphetamine, MDMA (ecstasy) can increase the risk of diabetic ketoacidosis. These drugs may also alter brain functions making diabetes management difficult.

Driving

The main factor that increases the rates of driving accidents in type 1 diabetes is hypoglycemia. To reduce this risk, ensure the following:

- To prevent hypoglycemia during driving, monitor blood glucose before driving and ensure appropriate food intake
- Encourage stable metabolic control
- Regular visual check ups

Sexual Health

Adolescent girls with diabetes should be counselled regarding following aspects of sexual health:

- Contraceptive practices
- Precautions to avoid STIs
- The importance of planned pregnancy
- The risks of congenital malformations, miscarriage, and fetal death associated with poor glycemic control

Contraception

Education about the risks associated with unplanned pregnancy should be part of the routine care of adolescents with type 1 diabetes.

Barrier Methods

- Male condoms are highly effective against unintended pregnancy and STIs when used consistently and correctly.[25]
- Female condoms and diaphragms are not recommended for adolescents.
- Coitus interruptus is associated with a high pregnancy rate and is not recommended.

Long Acting Reversible Contraceptions (LARCs)

- LARCs include intrauterine devices (IUDs) and implantable rods. They can be considered as first-line contraceptive choice for adolescents even if they are nulliparous.[26]
- The contraceptive effectiveness of implantable rods and hormonal IUDs are better than that of oral contraceptives.
- Non-hormonal IUDs may be considered if hormonal contraception is contraindicated.
- LARC methods neither protect nor increase the risk of STIs.

Combined Hormonal Oral Contraceptives

- Patients with duration of diabetes less than 20 years and without micro- or macrovascular complications may use any hormonal method.
- Combined oral contraceptives (COCs) should be avoided in patients with diabetes more than 20 years or having micro- or macrovascular complications. They may use IUDs, progestin only methods or barrier methods.
- No unfavorable effects on weight, metabolic control, or lipid profile have been seen with newer oral contraceptives containing lower dose of estrogen (≤35 mcg ethinyl estradiol) and newer progestins.
- Monitor blood pressure and side effects like headache, breast change, mood changes, and genital infections in young people taking oral contraceptives.

TABLE 2 WHO eligibility criteria of contraceptives in women with type 1 diabetes

	Combined contraceptives				*Progestin only*			*Intrauterine devices*		*Barrier methods*
	Oral	*Injectable*	*Patch*	*Vaginal ring*	*Oral*	*Deposit*	*Implant*	*Copper*	*LNG*	*Condom*
No micro- or macrovascular disease	2	2	2	2	2	2	2	1	2	1
Diabetes of >20 years duration	3/4	3/4	3/4	3/4	2	2	2	1	2	1
Nephropathy/ retinopathy/neuropathy	3/4	3/4	3/4	3/4	2	2	2	1	2	1
Macrovascular disease	3/4	3/4	3/4	3/4	2	2	2	1	2	1

1: Method may be used in any circumstances. 2: Method may be recommended. 3: Method is not usually recommended unless there are no appropriate, available, or acceptable alternatives. 4: Method should not be used.

Hormonal Injectables

- Depot medroxyprogesterone acetate injections are not recommended in adolescents with type 1 diabetes as it has been associated with reduction in bone mineral density.[27]
- For type 1 diabetes patients with erratic lifestyle and at high risk of pregnancy, monthly injections of combined hormonal contraceptives may be considered if they do not have access to LARC methods. But the safety data on type 1 diabetes patients is not available.

The WHO eligibility criteria of contraceptives in women with type 1 diabetes **(Table 2)** may be used as a guide to choose the right contraceptive for the right patient.

Transition from Pediatric to Adult Care

Society for Adolescent Health and Medicine defines transition as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems."[28]

The transition period from pediatric to adult care is associated with deterioration of metabolic control, increased occurrence of acute complications, emergence of chronic complications, and psychosocial, behavioral, and emotional challenges.[2,29]

Pediatric health-care providers should ideally begin to prepare the teen for transition to adult health care during early adolescent years and no later than 1 year prior to the transfer.[2]

Preparation should focus on diabetes self-management skills for the adolescent/emerging adult and his/her parents. The transfer of responsibilities from the parent to the adolescent should be gradual. The adolescent should acquire adequate skills in self-monitoring of blood glucose, insulin delivery, ensuring proper supply of medications, identifying and treating symptoms of hypoglycemia, and scheduling appointments.

The pediatric care provider should provide a written summary including the medications, summary of past glycemic control, results of complication screening, diabetes-related comorbidities, any mental health problems, and referrals during pediatric care.

Transition tools developed by the Endocrine Society in association with ADA are available online for clinicians, adolescents, and families.[30]

Conclusion

Management of type 1 diabetes in adolescence poses unique challenges. Glycemic control during this developmental phase is difficult due to the complex interaction of various physiological, psychosocial, and psychological factors. Adolescence is also a high-risk phase for development of diabetes complications, so screening for the same should begin during this period. Adolescents should be counseled regarding the effects of alcohol, smoking, and other illicit drugs on the disease course. Advice on safe contraceptive practices should be part of routine diabetes care. Transition from pediatric to adult care should be gradual planned process with proper coordination between pediatric and adult health-care providers.

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CHAPTER

77

Evaluation, Causes, and Management of Hypoglycemia

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Abstract

Hypoglycemia is an important entity causing the morbidity and mortality in patients with or without diabetes. This chapter deals with the risk factor, pathogenesis, and causes of hypoglycemia. The urgent treatment and long-term management are also discussed in detail. This chapter also deals with psychiatric aspect of hypoglycemia mimic. Physicians should have an open mind in finding the cause as well as aim should be decreasing the recurrence of hypoglycemia episodes.

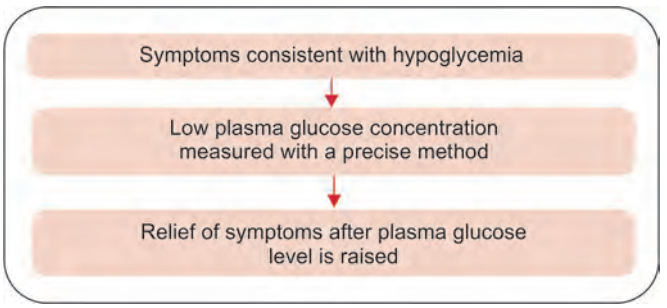
Introduction

Hypoglycemia is a state of glucose deficiency which presents with episodic symptoms. Dysregulation of glucose regulatory mechanisms leads to development of hypoglycemia. The most common cause is drugs that are used to treat diabetes. Whipple's triad is used to document hypoglycemia **(Flowchart 1)**. The lower limit of the fasting plasma glucose level is approximately 70 mg/dL. Normally, during pregnancy and during prolonged fasting (>24 hours), lower venous glucose levels occur. Hypoglycemia can be fatal if severe and should be suspected in a patient with confusion, altered sensorium or seizure.[1]

Etiology of Hypoglycemia

Hypoglycemia is caused by drugs (including anti-diabetic drugs), alcohol, sepsis, critical organ failure, inanition, non-β-cell tumors, hormone deficiencies, prior gastric surgery, and insulinoma. More elaborate causes are discussed in **Table 1**. Hypoglycemia can also be broadly classified into hypoglycemia in diabetes and in non-diabetes conditions. **Table 2** enlists causes of errors of metabolism which cause hypoglycemia.

Flowchart 1: Whipple's triad



Medications other than anti-diabetic drugs which commonly cause hypoglycemia are—Pentamidine (systemic), Trimethoprim-sulfamethoxazole, and renal failure, Propoxyphene and renal failure, Quinine, Quinidine, Salicylates, and renal failure.

Clinical Features

The symptoms are adrenergic symptoms and neurological symptoms. Adrenergic symptoms are shakiness, trembling, anxiety, nervousness, palpitations, tachycardia, calmness, sweating, dry mouth, hunger, pallor, and pupil dilation.

TABLE 1 Causes of hypoglycemia in adults[2]

Medicated or ill individual
• Drugs: Insulin/insulin secretagogue, alcohol, others • Critical illness: Hepatic, renal/cardiac failure, inanition, sepsis • Hormone deficiency: Cortisol, growth hormone, glucagon, epinephrine • Non-islet cell tumor (e.g., mesenchymal tumors)
Seemingly well individual
• Endogenous hyperinsulinism: Functional β-cell disorders (nesidioblastosis)—Non-insulinoma pancreatogenous hypoglycemia, Insulinoma, Insulin autoimmune hypoglycemia—Ab (antibody) to insulin, Post-gastric bypass, Ab to insulin receptor, Insulin secretagogue, other • Disorders of gluconeogenesis and fatty acid oxidation • Exercise • Accidental, malicious, or surreptitious hypoglycemia

TABLE 2 Hypoglycemia due to inborn errors of metabolism

Fasting hypoglycemia
• Glycogen storage disease (GSD) type 0 • GSD type I • GSD type III • GSD type IV • Fanconi-Bickel syndrome • Fatty acid oxidation defects • Gluconeogenesis defects (fructose-1, 6-bisphosphatase)
Postprandial hypoglycemia
• Glucokinase, SUR1, and Kir6.2 mutations • Congenital disorders of glycosylation • Inherited fructose intolerance
Exercise-induced hypoglycemia
• Increased β-cells monocarboxylate transporter 1 activity

Neurological presentations are irritability, paresthesia, headaches, difficulty in thinking/speaking, confusion, abnormal mentation, slurred speech, diplopia, ataxia, seizures, stupor/coma. Neuroglycopenic manifestations are direct result of CNS glucose deprivation. Cholinergic symptoms which are mediated by Ach such as hunger, sweating, and paresthesia are seen. These are from sympathetic postganglionic neurons. Heart rate and SBP are typically increased. These changes are blunted in a person who has suffered recent and repeated hypoglycemia episodes. Occasionally transient focal neurologic deficits occur. Permanent deficits are rare.

TABLE 3 Anti-diabetic drugs and hypoglycemia

Hypoglycemia causing	*Does not cause hypoglycemia*
• Insulin • Sulfonylureas • Glinides	• Metformin • Thiazolidinediones • α-glucosidase inhibitors • Glucagon-like peptide 1 (GLP-1) receptor agonists • Dipeptidyl peptidase IV (DPP-IV) inhibitors

Differential Diagnosis of Symptoms of Hypoglycemia

Many conditions are associated with episodes of symptoms similar to symptoms of hypoglycemia. These are Anxiety neurosis, Dumping syndrome, Thyrotoxicosis, Drugs (varencilline, decongestants, stimulants, and street drugs), Angina pectoris, autonomic neuropathy, renovascular hypertension, pheochromocytoma, withdrawal symptoms, hypogonadism, carcinoid syndrome, syncope and postural hypotension (including POTS), angina, cardiac arrhythmia, seizure disorders, atypical migraine, vertebral and ICA diseases, and psychiatric disorders.

Hypoglycemia in Diabetes

Recurrent morbidity is caused by hypoglycemia in most patients with type 1 diabetes and in many with advanced type 2 diabetes. It precludes the maintenance of euglycemia over a lifetime of diabetes and thus full realization of microvascular benefits of glycemic control. By producing hypoglycemia-associated autonomic failure, it also causes a vicious cycle of recurrent hypoglycemia—i.e., the clinical syndromes of defective glucose counter regulation and of hypoglycemia unawareness. Mortality rate of hypoglycemia is approximately 6–10% in T1DM. The hypoglycemia incidence is lower in T2DM than in T1DM **(Table 3)**.

The risk factors for hypoglycemia in diabetes are identified whether relative or absolute insulin excess is the sole determinant of risk **(Box 1)**.

Hypoglycemia-associated Autonomic Failure (HAAF)

In diabetes mellitus iatrogenic hypoglycemia is often a consequence of interaction between relative/absolute

BOX 1 Causes of relative/absolute insulin excess

- Insulin (insulin secretagogue) doses are ill-timed/excessive/of wrong type
- The influx of exogenous glucose is decreased (e.g., during an overnight fast, periods of temporary fasting, or after missed meals/snacks)
- Increased insulin-independent glucose utilization (e.g., during exercise)
- Increased sensitivity to insulin (e.g., with improved glycemic control, late after exercise, in the middle of the night, or with increased fitness/weight loss)
- Reduced endogenous glucose production (e.g., after alcohol ingestion)
- Reduced insulin clearance (e.g., in renal failure)

therapeutic insulin excess in addition to compromised physiologic and behavioral defenses against decreasing glucose levels. Dysfunctional counter-regulatory mechanisms compromise physiologic defense (especially decrements in insulin and increments in glucagon and epinephrine), and behavioral defense is compromised by hypoglycemia unawareness (ingestion of carbohydrate).

Hypoglycemia Unawareness

Hypoglycemia unawareness is caused by the diminished sympathoadrenal response, that is, majorly the decreased sympathetic neural response to hypoglycemia—i.e., loss of the warning autonomic symptoms that earlier allowed the patient to acknowledge developing hypoglycemia and thus to end the episode by eating carbohydrates. These patients are at sixfold higher risk of severe hypoglycemia by the intensive diabetes therapy.[3]

Evaluation of Hypoglycemia

Hypoglycemia Evaluation in DM Patients

Hypoglycemia is worrisome in a diabetic patient when the plasma glucose concentration on self monitoring is falling rapidly or ≤70 mg/dL (3.9 mmol/L). Glycemic control is advised to have long-term microvascular benefit in a diabetic patient but strict monitoring to be adhered to prevent hypoglycemia. Adjustment in treatment regimens are recommended for prevention of hypoglycemia in diabetes **(Box 2)**.[2]

The typical risk factors and compromised defenses should be evaluated in recurrent treatment-induced hypoglycemia **(Table 4)**.

BOX 2 Hypoglycemia prevention in diabetes

- Diabetes self-management (supported by education and empowerment)
- Frequent self-monitoring of blood glucose
- Flexible and appropriate insulin/insulin secretagogue regimens
- Individualized glycemic goals
- Ongoing professional guidance and support
- Consideration of each of the known risk factors for hypoglycemia

TABLE 4 Conventional risk factors and compromised defenses against hypoglycemia

Conventional risk factors	*Compromised defenses against hypoglycemia*
• Excessive/ill-timed dosing of insulin/secretagogue • Wrong type of insulin/insulin secretagogue • Conditions which reduce exogenous glucose delivery or endogenous glucose production • Increased glucose utilization • Increased sensitivity to insulin • Decreased insulin clearance	• Endogenous insulin deficiency degree • Severe hypoglycemia history • Hypoglycemia unawareness • Recent antecedent hypoglycemia • Prior exercise or sleep • Lower glycemic goals *per se*

Two/three weeks of meticulous avoidance of hypoglycemia is advised in patients with known hypoglycemia unawareness with the probability that awareness of hypoglycemia will be back in most of them.

Hypoglycemia Evaluation in Patients without DM

The history, physical examination, and all relevant laboratory data inferring to specific disorders like drugs, hormone deficiencies, critical illnesses, non-islet cell tumors must be reviewed. To ascertain the cause of hypoglycemia in an apparently well individual—plasma glucose, insulin levels, C-peptide levels, proinsulin levels, insulin antibodies, and β-hydroxybutyrate levels should be measured. Screen for intake of oral hypoglycemic agent (OHA) during spontaneous hypoglycemia episode and observe the response to glucagon 1.0 mg intravenously. These will differentiate endogenous versus exogenous causes.[4,5]

In cases where a spontaneous hypoglycemic episode is not observed, the circumstances which will lead to symptomatic hypoglycemia are recreated. One such method is a fast of up to 72 hours after a mixed meal. The findings of this test is—

- symptoms, signs, or both; with
- glucose plasma concentrations <55 mg/dL (3.0 mmol/L)
- insulin of 3.0 μU/mL (18 pmol/L) at least
- C-peptide of 0.6 ng/mL (0.2 nmol/L) at least
- proinsulin of 5.0 pmol/L document endogenous hyperinsulinism at least
- β-hydroxybutyrate levels of ≤2.7 mmol/L and rise in plasma glucose of 25 mg/dL (1.4 mmol/L) at least after IV glucagon indicate mediation of the hypoglycemia by insulin (or by an IGF)

In cases of documented fasting/PP endogenous hyperinsulinemic hypoglycemia, no circulating insulin antibodies, and negative screening for OHA suspect insulinoma. Imaging techniques used are CT or MRI, transabdominal and endoscopic ultrasonography, and selective pancreatic arterial calcium injections with insulin levels in hepatic vein measurement **(Table 5)**.

TABLE 5 Urgent hypoglycemia bundle card

Laboratory service instructions:
• This patient is having symptoms of low blood sugar • Do not give the patient anything to eat or drink, or administer any IV medication or solution until the blood sample(s) have been drawn, unless it is determined that the patient's life is at risk • Immediately see this patient and draw the urgent hypoglycemia bundle: – Medical record number – Patient's name (first, middle, last) – Ordering provider name – Ordering provider pager

Anxiety and Hypoglycemia

Anxiety associated with depression is quite commonly studied in those with diabetes mellitus. Specific phobias, in particular needle injection and fear of hypoglycemic episode, are commonly seen in those patients who are on insulin therapy.[6] Hypoglycemic phobia is a very important aspect of treatment in diabetes as these group of patients are more likely to miss glucose monitoring or insulin administration. They might also maintain chronic hyperglycemic state because of the fear of hypoglycemic episode. Clinical features shared by both hypoglycemia and anxiety are sweating, tremor, anxiety, confusion, and tachycardia. This could lead to a diagnostic challenge. Those with long standing anxiety disorder the likelihood of missing warning signs of hypoglycemia are more. Medications for management of anxiety disorders—SSRIs, benzodiazepines, and beta-adrenergic blockers could interfere with glycemic control and physiological warnings of an hypoglycemic episode.

Alcohol Use and Hypoglycemia

Prevalence of alcohol use is around 50% in diabetics.[7] Most common and a serious concern associated with alcohol use in diabetes is hypoglycemia. It includes a spectrum of alcohol-induced fasting hypoglycemia, potentiation of drug-induced hypoglycemia/reactive hypoglycemia in susceptible patients **(Box 3)**.

BOX 3 Recommendations of alcohol use among diabetics

- Assess all patients for alcohol use
- Questionnaire like CAGE should be used
- Advise nonusers to not to start and users to abstain/use in moderation
- Education on harmful effects of alcohol use
- People using insulin/insulin secretagogues should be given knowledge of delayed hypoglycemia occurring up to 24 hours after alcohol intake
- Increased awareness in T1DM patients of hypoglycemia associated with alcohol used
- Limit alcohol (for men <14 standard drinks/week and women <9 standard drinks/week)

Management of Hypoglycemia

Urgent Treatment

When patient is conscious and is able to take orally, glucose tablets/glucose-containing fluids, candy/food is appropriate in an initial dose is 15–20 g of glucose. When the patient is unable to take carbohydrates orally, because of parenteral therapy is necessary. IV administration of 25 g glucose followed by a glucose infusion guided by serial plasma glucose monitoring. If IV therapy is not practical, subcutaneous/IM glucagon (1.0 mg in adults) can be used, particularly in T1DM. Glucagon is less useful in T2DM as

it stimulates insulin secretion. Octreotide (somatostatin analogue) can be used in SU-induced hypoglycemia to suppress insulin secretion. These treatments raise plasma glucose and patients should eat soon to replete glycogen stores.

Prevention of Recurrent Hypoglycemia

This approach requires identification of cause of hypoglycemia. Discontinuation of offending drugs or reduction of their doses. Hypoglycemia caused by SUs can persist for hours or days. Treatment of underlying critical illnesses should be prompt. Replacement of deficient cortisol and growth hormone. If the tumor cannot be cured surgical, chemotherapeutic, or radiotherapeutic reduction of a non-islet cell tumor can provide relief from hypoglycemia. In such patients glucocorticoid or growth hormone administration also may decease hypoglycemic episodes. Surgical resection of an insulinoma is curative. Diazoxide/octreotide medical therapy can be used if resection is not advised. Also useful in people with a non-tumor β-cell disorder along with partial pancreatectomy. Autoimmune hypoglycemia treatment is difficult but these disorders are self limited sometimes. Treatment with glucocorticoid or immunosuppressive drugs is tried. Frequent feedings and avoidance of fasting should be followed if these treatments fail. In some patients administration of uncooked cornstarch at bedtime or an overnight intragastric infusion of glucose may be required.

Conclusion

Diagnosis of hypoglycemia by Whipple's triad is well established. Broadly approach to evaluate hypoglycemia is based on the patient's diabetes status and exogenous/endogenous factors. Prompt diagnosis and prompt treatment are the key to save permanent neurological damage in a patient with severe hypoglycemia. Avoidance of precipitating factors and patient counseling are very important aspects of reduced morbidity and mortality.

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Section 5

Section Editor: **CL Nawal**

Metabolism, Lipids, and Obesity

CHAPTER

78 Current Concepts in Etiopathogenesis of Obesity

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Abstract

Obesity is one of the most common chronic communicable diseases in the world. It is not only accumulation of adipose tissue in the body, but also a defect in homeostasis of our energy. Many factors contribute to etiology of obesity, but a complex interface between hormones, environment, and genetics play a major role. For a better understanding of pathogenesis of obesity, it can be grouped into energy consumption, energy utilization, and role of genetics. Serotonin, Dopamine, and some gut hormones influence homeostatic and hedonic pathways that control intake of energy. Reduction in resting energy expenditure, activity energy expenditure, and diet induced thermogenesis contribute to obesity via low energy utilization. Leptin gene discovery was a big breakthrough in molecular genetics research on obesity. Obesity can be a result of polygenic factors, or single gene disorders apart from various syndromes which have obesity as their predominant manifestation. Being a modern epidemic, obesity incurs significant cost to world economy and targeted therapies as per genetic profiling of individuals are the need of future.

Introduction

Obesity is a pandemic of the 20th century. It is among the one of the most common chronic non-communicable diseases throughout the world. Obesity is not only the accumulation of adipose tissue leading to weight gain; it is rather a defect in our energy homeostasis. Obesity is increasing at an alarming rate both in developed and developing countries. The etiology of obesity is multifactorial, which involves a composite interface among hormones, the environment, and genetics.[1] The aim of this article is to review the etiopathogenesis and the role of genetics in obesity.

Etiology and Pathogenesis of Obesity

Human beings consume food as energy, which is stored as well as utilized in maintaining the basal metabolism of the body. Reduction in physical activities due to sedentary lifestyles leads to excessive storage of energy of which 60–80% is as fat or adipose tissue. It leads to obesity, the fifth most common cause of non-communicable disease.[2] In the pathogenesis of obesity, multiple factors play a role, which include lifestyle affecting reduced energy expenditure, hormones affecting energy intake and the part of genetics. Gastrointestinal hormones, adipokines, and various genes including beta-3-adrenergic receptor gene peroxisome-proliferator-activated receptor gamma 2 (PPAR-γ) gene and other genetic polymorphism majorly regulates the pathophysiology of obesity.[3-5]

Pathogenesis of obesity can be divided into three ways:

- Energy consumption
- Energy utilization
- Role of genetics

Energy Consumption

Homeostatic and hedonic are the two pathways that control intake of energy. When the body is deficient in

energy, the homeostatic mechanisms stimulates the appetite, the hypothalamus as well as brainstem acts as central regulators and senses the signals including leptin, insulin, hormones, and vagal afferents. Hedonic pathway is a mediator of rewarding aspects for food intake. When both pathways and systems are uncontrolled, it leads to obesity. Two neurotransmitters serotonin and dopamine play a vital role in the energy intake.[6]

Serotonin and dopamine: Serotonin is a neurotransmitter of homeostatic pathways. Reduction in signaling by serotonin in the hypothalamus contributes to the origin of obesity as it affects the negative feedback from the food intake, which leads to over consumption. Various studies explain a strong link between hypo-serotonin environment and development of obesity.[7,8] As far as dopamine is concerned, decrease in the dopaminergic signaling also promotes overconsumption. As dopamine is a reward hormone, thus lower reward sensations lead to its effects.[9]

Gastrointestinal hormones: Gut-brain axis or feedback system plays an important role to maintain hunger and satiety. Several gut hormones: ghrelin, cholecystokinin, peptide YY, glucagon like peptide-1, oxyntomodulin are involved as messengers in this axis. Along with the function related to food digestion, these hormones equally affect specific brain areas modulating food or energy intake.

Ghrelin, the only hormone that stimulates hunger is produced by the endocrine cells of gastric fundus.[10] Ghrelin binds to the growth hormone receptor which is highly expressed in the hypothalamus. In obese subjects, the fasting levels of ghrelin are low as compared to normal weight controls. Diet induced obesity mainly occurs due to ghrelin resistance, which arises as there is reduction in the NPY/AgRP responsiveness to plasma ghrelin leading to suppression of neuroendocrine ghrelin axis.[11] Other intestinal hormones are anorexigenic which includes glucagon-like peptide 1 (GLP1), peptide YY (PYY), and cholecystokinin (CCK).[12] The over consumption of meals in obese humans is strongly associated with the reduction of activity of these anorexigenic hormones.[13]

Leptin: The revolutionary discovery of leptin occurred in 1994. It is synthesized in white adipose tissues. The level of leptin in the body correlates with the fat mass. The leptin levels in plasma and CSF will be higher in a person with excess body fat.[14] Leptin acts as an informant to the brain about the reserved adipose energy. It crosses the blood brain barrier and inhibits orexigenic NPY/AgRP neurons and stimulates POMN-expressing anorexigenic neurons in the hypothalamus. Responsiveness to leptin decreases in obesity. Leptin resistance not only affects the energy consumption but also decreases insulin sensitivity and cognition. Leptin levels are higher in obese individual due to increased production by adipocytes to compensate the low responsiveness. Inability or defect in crossing the blood brain barrier is also associated with reduced feedback by leptin.[15] Low levels of leptin or resistance of leptin impairs its ability to counterbalance the effect of ghrelin.[16]

Insulin: Sedentary lifestyle leads to increased risk of diabetes. It is associated with raised insulin levels due to insulin resistance. Hyperinsulinemia lead to weight gain and obesity because of a physiological property of insulin. Beside the effect of lifestyle factors, the pathway to obesity needs hyperinsulinemia as an important moderator in translating an unworthy lifestyle turning into gain of weight.[17] The insulin resistance, which causes hyperinsulinemia and later obesity, occurs mainly due to defect in insulin signaling in adipocytes as well as downregulation of GLUT4.[18]

As a pleiotropic effect, raised insulin levels lead to more synthesis of adipocytes from preadipocytes. It also promotes lipogenesis by stimulating ADD-1/SREBP-1c which plays the role of regulating fatty acid synthesis and lipogenesis in hepatocytes and adipocytes.[19] With the recognition of insulin resistance and hyperinsulinemia as the potential mechanism of obesity has come increases investigation and research aimed at elucidating potential insulin sensitizing agents. Thus, it's established that insulin receptor function is vital for energy homeostasis.

Circadian rhythms: Nature is always dominant. Biological rhythms play an important role in virtually all aspects of life. These rhythms are controlled in large part by circadian clocks, a molecular mechanism which is intrinsically maintained to control these biological rhythms and adapt or condition the human beings to its changing environment. Two types of clocks exist, the central and the peripheral clock. Suprachiasmatic nucleus (SCN) of the brain possesses the central clock, which responds with light. Other than SCN (including those clocks found

in other cells of the central nervous system) all other cells possess peripheral clocks which work under the influence of neurohormonal changes.

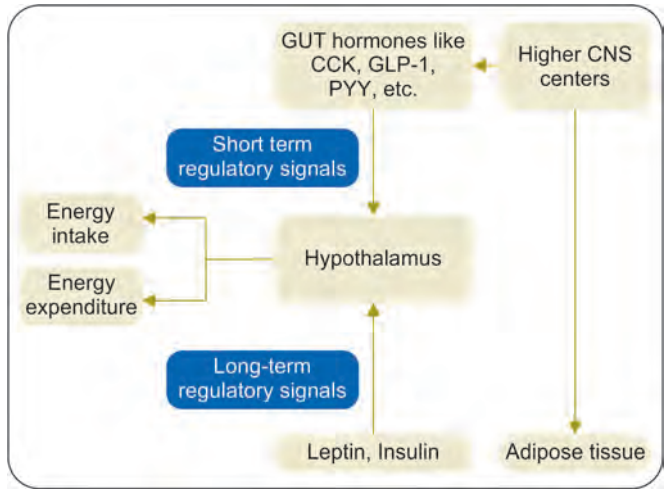
Changing lifestyles, late night working shifts alters the functioning of these clocks leading to poor anticipation of diurnal variations in the environment of the body. It could be circulating levels of glucose, fatty acids, or hormones including insulin and triglycerides. Altered molecular mechanism in the adipocytes leads to accumulation of fat and finally obesity.[20]

Gut bacteria: Our gut consists of numerous bacteria. These play an important role in digestion of food. Recent research indicates that gut microbiota also plays a part in pathogenesis of obesity. Low fecal diversity markedly leads to overall adiposity and dyslipidemia along with low-grade inflammation.[21] In obese individuals, *Firmicutes strain of bacteria are increased and Bacteroidetes* strain is markedly low in fecal samples, in comparison to lean individuals.[22] It suggests, overweight/obesity are preceded by differences in the gut microbiota. Several other studies too found change in gut bacteria composition in obese individuals but high ratio of Firmicutes:Bacteroidetes in obese individuals with excess Bacteroidetes during weight loss is not consistent.[23,24]

Energy Utilization

Low energy expenditure (LEE) contributes to development of obesity is always suggested. Reduction in resting energy expenditure (REE), activity energy expenditure (AEE), and diet induced thermogenesis (DIT) all lead to storage of energy leading to weight gain and obesity.[25] A review was done Carneiro et al. to see the comparison between energy expenditures measures and its components, namely REE, AEE, and diet-induced thermogenesis (DIT), playing role in obese and non-obese adults. Results clearly shown the obese individuals require higher absolute REE and total EE. Although no difference is seen when fat free mass and metabolically active components are involved. However, AEE and DIT can be low obese individuals, because of sedentary habits, poor physical activity, and high intake of fat.[26] Reduction in exercise associated thermogenesis and non-exercise associated thermogenesis significantly contributes weight gain in obesity. Nowadays various phenotypes of obesity like sarcopenic obesity and normal weight obesity are associated with energy expenditure in comparison to lean and thin individuals.[27]

Flowchart 1: A schematic diagram showing integration of long-term and short-term regulatory signals influencing energy intake and expenditure



Weight gain is also associated with drugs as anti-psychotics, tricyclic antidepressants, lithium, steroids, antiepileptics and insulin. Smoking cessation, due to nicotine withdrawal also causes weight gain **(Flowchart 1)**.

There is also a role of endocrine disruption chemicals (EDCs) in obesity as their exposure is associated with stimulation of adipogenesis and changes in insulin secretion, sensitivity, and metabolism of liver. EDCs like perfluorinated chemicals (PFCs) and bisphenol-A (BPA) are linked with accumulation and maintenance of excess body fat in many studies.

Role of Genetics in Obesity

For long it was proposed that obesity may also be caused due to innate biological mechanisms under influence of genetic factors. In 1977, Feinleib et al. established the fact through their study that familial aggregation for obesity results from genetic influence.[28] Stunkard and colleagues performed two studies in 1986 and 1990 amongst twins offering compelling evidence that one's weight could be determined by one's parentage. The leptin gene discovery in 1994 was a big breakthrough in molecular genetics research on obesity. Twin study suggests that heritable factors are responsible for 40–85% variation in body fat. Risk of obesity in children is 2.5–4 times high in single parent obesity, whereas it was 10 times for both parents being obese.[29,30]

The influence of genetic variables can be significantly reduced by high level of physical activity and environmental modifications.[31] Mutations in various other molecules responsible for energy balance via the hypothalamus/melanocortin pathway have been described, which contribute to obesity.[32]

Polygenic obesity: Genetic factors play a permissive role and interact with environmental factors to produce obesity. Genome wide association studies (GWAS) in European population focused on 70–80% common variations using single nucleotide polymorphism (SNP). Variation in intron-1 of Fat Mass and Obesity associated (FTO) gene has been identified as contributor to polygenic obesity.[33] MC4R gene was associated with hyperphagia and early onset diabetes. SH2B1 (Src-Homology-2 [SH2] domain containing putative adaptor protein-1) is associated with increased serum leptin. Other genes, which are highly expressed in hypothalamus and associated with obesity are KCTD15 (potassium channel tetramerization domain-containing 15), GNPDA2 (glucosamine-6-phosphate deaminase-2), MTCH2 (mitochondrial carrier homolog 2), SDCCAG8 (serologically defined colon cancer antigen 8), FAIM2 (Fas Apoptotic Inhibitory Molecule 2) and PRL (prolactin).[34,35]

One peripheral acting gene TFAP2B (transcription factor activating enhancer-binding protein 2β) is preferentially expressed in adipose tissue, which is involved in glucose transport, lipid accumulation, and adiponectin expression. New GWAS have started to appear in East Asian population promising discovery of further more loci related to genetic forms of obesity.

Syndromic obesity: A variety of syndromes with obesity as their primary manifestation have been identified. Some of the important ones with their main features have been described in **Table 1**.

Monogenic obesity: These are single gene disorders causing a highly penetrant form of disease. These genes affect the leptin/melanocortin pathway in central nervous system and have been described in **Table 2**.

Even after discovery of these numerous genetic factors, only a small fraction of obesity cases could be attributed to them. Variations in FTO and MC4R are two most important genes that are strongly linked to obesity, but still account for less than 2% of variance in adult BMI.[1] It is assumed that there must be a missing link in the heritability of obesity, and more GWAS are underway to search for them. Discovery of these factors would open up new possibilities for novel drugs, diagnosis, treatment, and prevention of obesity.

TABLE 1 Syndromes having obesity as their predominant manifestations[36,37]

Syndrome	*Gene*	*Obesity onset (type)*	*Clinical features*
Albright hereditary osteodystrophy (pseudohypoparathyroidism type 1a)	GNAS1	Early (generalized)	Short stature, round face, cognitive delay, skeletal abnormalities along with obesity
Alström	ALMS1	Age 2–5 years (central)	Obesity with acanthosis nigricans, normal cognition, blindness, deafness, chronic nephropathy, type 2 diabetes, and cirrhosis
Bardet-Biedl syndrome	BBS1, 2, 3…	Age 1–2 years (central)	Obesity with cognitive delay, polydactyly, retinitis pigmentosa, hypogonadism and renal dysfunction
Beckwith-Wiedemann	Multiple		Obesity with intolerance of fasting, hyperinsulinemic hypoglycemia
Carpenter	RAB23	(Central)	Short stature with obesity, brachycephaly, polydactyly, umbilical hernia, mental retardation high-arched palate, cryptorchidism, male hypogonadism
Cohen	COH1	Mild-childhood (central)	Hypotonia and failure to thrive in infancy, mental retardation, microcephaly, prominent central incisors; long, thin fingers, and toes
Prader-Willi	NDN, SNRPN	Age 1–3 years (generalized)	Hypotonia, upslanting eyes, cognitive delay and behavioral abnormalities along with obesity

TABLE 2 Single gene disorders causing obesity[37]

Disorder (Gene)	*Gene*	*Clinical feature*
Leptin deficiency (various mutations interfering with synthesis or secretion of leptin)	LEP	Severe early-onset obesity, hypometabolic rate, hyperphagia, pubertal delay, impaired glucose tolerance, hypothalamic hypogonadism, frequent infections. Very low or undetectable leptin levels. Obesity and hyperphagia respond to replacement with exogenous recombinant leptin
Leptin receptor deficiency	LEPR	Severe early-onset obesity, hypometabolic rate, hyperphagia, pubertal delay, hypothalamic hypogonadism. Leptin levels are high but are proportional to the degree of obesity, so they are not a useful marker for this defect. No response to treatment with exogenous leptin
Leptin dysfunction (biologically inactive leptin)	LEP (LEP p.D100Y)	Severe early-onset obesity, hyperphagia. Leptin level are high (consistent with degree of obesity) but biologically inactive. Obesity and hyperphagia respond to treatment with exogenous recombinant leptin
Pro-opiomelanocortin deficiency	POMC	Adrenal insufficiency (typically presenting in the neonatal period), severe early-onset obesity, hyperphagia, and red hair in Caucasians
Pro-protein convertase 1/3 deficiency	PCSK1, also known as prohormone convertase 1	Early-onset obesity, diarrhea, abnormal glucose homeostasis, hypogonadotropic hypogonadism, hypocortisolism, elevated plasma proinsulin and POMC
Melanocortin receptor 4 haploinsufficiency	MC4R	Early-onset moderate to severe obesity, early-onset hyperphagia, increased bone density, accelerated linear growth, severe hyperinsulinemia, mild central hypothyroidism
Melanocortin 2 receptor accessory protein 2	MRAP2	Severe nonsyndromic early-onset obesity (probably very rare)

Conclusion

A complex interaction between genetic factors, environmental factors, and human behavior influences pathogenesis of obesity. Obesity is a modern epidemic and incurs massive health-care cost to world economy. Even with all recent advances, less than 2% of interindividual variations in BMI can be attributed to discover established gene loci. Along with well-known principles of prevention and control of obesity, targeted therapies as per genetic profile of the individual are of the need in future.

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CHAPTER

79 Dilemma in the Management of Hyperuricemia

Brijesh Kumar, Mohammad Aquiqe

Abstract

Introduction: Hyperuricemia is a condition which is due to excess accumulation of uric acid in the blood either due to overproduction or under excretion or both.

Clinical Manifestations: Four stages asymptomatic, acute gout, inter-critical, and advanced gout.

Management: Asymptomatic individual usually does not require treatment but symptomatic patient may require pharmacological and non-pharmacological treatment.

Conclusion: Symptomatic patient with or without complications may require treatment.

Introduction

Hyperuricemia is a disorder of purine metabolism in which last product of metabolism, that is, uric acid is increased either due to overproduction or under excretion or both of the process. Hyperuricemia is defined as serum urate concentration 405 μmol/L (6.8 mg/dL) [serum urate level of 7.0 mg/ dL (415 μmol/L) and in men 5.7 mg/dL (340 μmol/L) for women].[1]

Causes

- Urate under excretion Primary hyperuricemiais—or idiopathic; Secondary hyperuricemia, due to—inhibition of urate secretion, abnormally decrease in renal function.

  Drugs which causing under excreation—ethumbutol salicylate and laed etc.
- Urate overproduction—
  - Primary hyperuricemia due to enzyme defect.
  - Secondary hyperuricemia due to
    - purine rich diet,
    - increase nucleotide turnover,
    - ATP degradation
      - Glucose-6-phosphatase deficiency,
      - Tissue hypoperfusion
  - Over alcohol intake.[2]

Hyperuricemia is related with cardiovascular conditions, obesity, and metabolic syndrome etc.[3]

Clinical Manifestation

Stage 1: Asymptomatic hyperuricemia: this condition is most common but does not constitute disease, if urate deposited then damage the organ directly but not found in all and evidence suggests that no need of treatment in this stage.[4]

Stage 2: Acute gout-in this stage patient develop local deposition of urate particles and any minor trauma can produce release of urate crystals in joint space and condition of acute gout.[5]

Stage 3: Intercritical period.

Stage 4: Advanced gout. Chronically deposition of urate crystals and patient develop stiff joint. This progression is variable from person to person.[6-9]

Complications

Most common is gouty arthritis and other complications are nephrolithiasis, urate nephropathy, and uric acid nephropathy.[10-12]

Investigations

- Twenty-four hours uric acid excretion: Normal uric acid excretion is 600 mg/day in a purine-free diet individual if this value exceeds then it suggests that hyperuricemia is due to overproduction and if this value decreases then it means hyperuricemia is due to under excretion of uric acid, but if patient on regular diet then normal uric acid excretion value up to 800 mg/dL.
- Complete blood count (CBC), lipid profile, calcium, and phosphate levels. These laboratory studies assess for underlying disease leading to elevated uric acid.
- Joint radiographs for joint swelling or deformity etc.[13]
- Renal ultrasound is done for uric acid stones.
- Consider joint aspiration to evaluate for uric acid crystals, look for negatively birefringent less polarized microscopy.[13]

Treatment

Hyperuricemia does not constitute a disease condition. Treatment depends on cause and potential consequences and complications in every patient.[18]

- Asymptomatic hyperuricemia is mainly treated by non-pharmacological interventions like lifestyle modifications, purine free diet, weight reduction, decrease in the quantity of alcohol soft drink consumption.[18] As mentioned earlier metabolic syndrome is a risk factor for hyperuricemia so treat the accompanying diabetes mellitus, hyperlipidemia, high blood pressure and morbid obesity.
  - *Body Weight and Exercise:* In a cross-section analysis it is found that with increase in body weight serum level of uric acid increases and also positive correlation with metabolic syndrome. So weight reduction done via dietary modification and exercise can decrease the serum uric acid level also reducing the risk of gout. Gradual decrease in body weight is more valuable than drastic reduction. Because abrupt fall in weight can lead to ketosis and in turn this will lead to increase absorption of uric acid and ultimately increase in level of uric acid in serum.[14-17]
  - *Dehydration and Rehydration:* Uric acid excretion is directly proportional to urine flow so one of the risk factor for gout is dehydration and thus gout patients are advised to take lots of fluid. If taking adequate amount of fluid 24 hours before gouty flare then there is definite decrease in gout attacks.[18,19]
  - *Dietary Factors:* An open labeled study suggest that there is some role of dietary factors in prevention of hyperuricemia and gout. But some also have ability to increase the level of uric acid. It is also found that those patient who are having hyperuricemia have a poor diet.[20]
  - *Purine-Rich Foods:* Those foods which are rich in purine, on ingestion can increase the serum uric acid level. But not all purine rich foods lead to increase serum uric acid level.

    Duration of food ingestion is also important. For example, if taking diet which is rich in purine for 7–10 days then only slight change level of serum uric acid and for some duration only, and also if we are taking diet which is low in purine content for 1–2 weeks then only 1–2 mg/dL decrease in serum uric acid. So this menas strict restriction of purine derivative foods in diet has not much role in uric acid control.[21]
  - *Fructose:* Fructose is the only sugar in fruits, which can increase the level of serum uric acid. Thus, fructose consumption is one of the factors in recent, which increases the prevalence of gout nowadays.[22]
  - *Dairy Products:* Dairy product reduces the risk of development of gout because the can decrease the serum uric acid level, which is suggested by some studies also.[23,24]
  - *Cherries:* Cherry from many decades used as alternative therapy for gout. Gout ingestion lead to decrease pain of gout. First study done in 1950.[25]
  - *Mediterranean Diet:* This diet is very helpful in patients of diabetes and coronary disease etc. It contains legume, cherry, olive oil, moderate fish consumption, etc.[26]
  - *Alcohol:* Alcohol promotes hyperuricemia it increases urate level by increased production by

the accelerating the hepatic breakdown of ATP and also led to decrease excretion of uric acid via kidney. Alcohol consumption also induces hyperlactacidemia, which inhibit uric acid secretion, consumption of bear confers a greater risk of gout than liquor and moderate wine intake does not increase gout risk.[27]

Pharmacological treatment: Earlier there is a relation found in between hyperuricemia and cardiovascular disease and renal disease so this lead to the evidence that treatment of asymptomatic hyperuricemia started with urate lowering drugs.[28]

Nowadays asymptomatic hyperuricemia is not treated by pharmacological therapy, that is, with antihyperuricemic agents.

Pharmacological treatment is given when—

- Two or more acute gout attacks per year,
- Presence of tophi,
- Stone formation, and
- Those individuals who were taking cytolytic drugs for malignancy in the past.[29]

Most common drug used for lowering of serum uric acid is allopurinol by blocking uric acid production.

Side effects: Diarrhea, headache, skin rash with itching.

Other toxicities are pyrexia, increase in leukocyte and eosinophils, hypersensitivity syndrome, etc.[30,31]

Oxypurinol is a metabolite of allopurinol, which is used as an alternative for allopurinol. It is used when severe adverse effects of allopurinol occurs.[32]

Uricosuric drugs: These drugs are named as probenecid and sulfinpyrazone. They have less side effects stilt use is very limited.[33] These drugs decrease the serum uric acid level by uricosuric effect so also increase uric acid in urine and increase the chance of development of uric acid stones.[34]

Thus, for better effect of these uricosuric drugs, kidney function should be normal, that is, creatinine clearance should be more than 55–60 mL/min and also patient should take at least 2 liters of fluid everyday with no history of nephrolithiasis.

- Symptomatic Hyperuricemia is treated with antihyperuricemic drugs. Basic aim of giving urate lowering agent is to decrease the total uric acid pool and serum uric acid should be below 6.5 mg/dL. Symptomatic hyperuricemia can present as—
  - Acute gouty arthritis
  - Nephrolithiasis
  - Uric acid nephropathy

A. Acute gouty arthritis: Risk of gouty arthritisis in those who are hyperuricemic individuals with high level of urate. Usually hyperuricemic person does not develop gout, and there is no need of prophylactic treatment. Also there is no structural kidney damage and no tophi are identifiable before first attack of gout.

Urate lowering agents should be started in those who are not managed by low purine diet, high fluid intake, moderation of alcohol intake, decrease in body weight and not on diuretics, etc.

Hypouricemic therapy started or not decision depends on—

- The number of acute attacks of gout
- More than 9.0 mg/dL of serum uric acid
- Nephrolithiasis

- Uricosuric agents like—
  - Probenecid are used when kidney function is normal, that is, when 24-hour urine sample contains uric acid less than 600 mg (underexcrete) and also need large amount of fluid intake, that is, about 1.5 liter of water intake per day. Starting dose of probenecid is 250 mg bid daily and maximum can be given up to 3 gm/day.
  - Other uricosuric agent like benzbromarone is more effective in CKD patients.
  - Some other agents which are not a hypouricemic drug but have little uricosuric effect are losartan, fenofibrate, and amlodipine are also use.
- Dose of xanthine oxidase inhibitor, allopurinol, is usually start with 100 mg once daily in morning and if required then can be reach maximum up to 800 mg daily morning.

  Dose reduction is required for allopurinol in chronic kidney disease patients on the basis of serum creatinine level.

Allopurinol toxicity is more when—
- Patient on thiazide diuretic
- Patient allergic to penicillin and ampicillin
- In Asian who expressing HLA-B 5801

- Febuxostat is approved in the United States and dose is 40 or 80 mg once a day and this drug also needs adjustment in mild to moderate renal disease.
- If patients cannot tolerate or fail to take full dose of above mentioned treatment then another drug is available named as pegloticase, which is a pegylated uricase. This drug is very potent given as 8 mg in every 2 weeks via intravenous route and reduces serum uric acid level very fast.
- Along with hypouricemic drugs an anti-inflamatory drug, that is, colchicine is also given.

  The prophylactic dose of colchicine is 0.6 mg once daily or bid and stops when—
  - Patients serum uric acid level is normal
  - No gout attack up to 6 months
  - As long as tophi present[35]

B. Nephrolithiasis: Antihyperuricemic therapy is recommended for the individual who has both gouty arthritis and either uric acid or calcium-containing stones, both of which may occur in association with hyperuric aciduria. Regardless of the nature of the calculi, fluid ingestion should be sufficient to produce a daily urine volume 2 L.

Active metabolite of allopurinol, that is, oxypurinol has a long half-life (18 hours) so given as single daily dose. Allopurinol is also useful in patients of gout and those with hyperuricemia or hyperuric aciduria without gout having recurrent calcium oxalate stones.

Potassium citrate (30–80 mmol/day orally in divided doses) is an alternative therapy for patients with uric acid stones alone or mixed calcium/uric acid stones.

Allopurinol is also used when 2,8-dihydroxyadenine kidney stones are present.[35]

C. Uric acid nephropathy: This condition is a rapidly worsening of kidney function seen when hyperuric aciduria occurs. In this condition deposition of uric acid crystals occurs in the renal interstitium and tubules leading to partial or complete obstruction of collecting ducts, etc.

For prevention of this condition, allopurinol or rasburicase is given prior to treatment with cytotoxic drugs.

For prevention of deposition of uric acid crystals, iv hydration and diuretics like furosemide given and maintain flow of urine above 100 mL/hour.

Acetazolamide and sodium bicarbonate for urine alkalanization and solubilization of uric acid in urine. During this ensure that pH remains 7.0 and no volume overload.

In addition to this hemodialysis may be required.

Urate oxidase (rasburicase) can also be administered IV to prevent or to treat tumorlysis syndrome.[35]

Conclusion

Hyperuricemia is a purine metabolism disorder, asymptomatic condition usually does not require treatment while symptomatic individuals with or without complications may require urate lowering agent therapy.

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CHAPTER

80 Risk Factors for Gout Flare

Udas Chandra Ghosh, Asish Mondal

Abstract

Gout, the most common form of crystal induced inflammatory arthritis, has developed flares due to some modifiable and non-modifiable risk factors. Male sex, increasing age, specific race, and ethnicity with some genetic preponderance are the non-modifiable risk factors. Alcohol, mutton, seafish with other purine rich foods in diet, diuretics, antitubercular medicines, etc. in drugs, chronic kidney disease, diabetes mellitus, hypertension, obesity, dyslipidemia, cardiovascular disease etc in comorbidities are modifiable risk factors. Lifestyle modification, dietary habits, and urate lowering therapy with patient education are important to prevent gout flare.

Introduction

Gout is the most common form of crystal induced inflammatory arthritis, mostly affecting the men. The clinical stages of gout are asymptomatic hyperuricemia, recurrent flares of inflammatory arthritis (gout flare), intercritical gout, chronic gouty arthritis, and tophus formation.

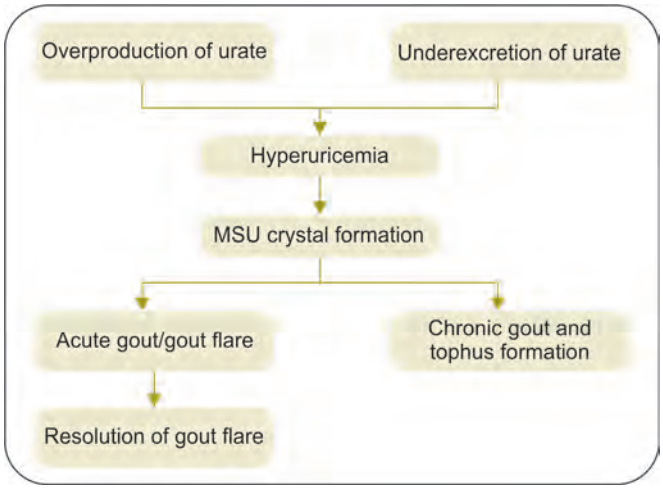
When there is super-saturation of serum uric acid concentration (i.e., ≥6.8 mg/dL in physiological pH and temperature), the monosodium urate (MSU) crystals are deposited in joints and subcutaneous tissues, which lead to acute inflammation and pain. Upon deposition of MSU in human fibroblast-like synoviocytes (FLS), it releases reactive oxygen species (ROS) and reactive nitrogen species (RNS), which lead to FLS necroapoptosis. MSU also can directly cause cytotoxicity and inflammation resulting necroapoptosis of synovium and is mediated by the receptor-interacting protein RIPK-1, RIPK-3, and the pseudokinase mixed-lineage kinase domain-like (MLKL)-driven necroapoptosis pathways. It is said that this necrosis is the primary event of crystal-induced necroinflammation. On the other side, MSU also involve caspase-1-activating NALP3 inflammasome, and produce active interleukin (IL)-1β and IL-18, the proinflammatory cytokines, which lead to influx and activation of neutrophils.[1] Activated neutrophils recruit and activate macrophages to release proinflammatory cytokines like IL-1, IL-6, IL-8, TNF-α, (COX)-2, and LTB-4 at the same time degranulation or lysis of cell membrane of the activated nutrophils results release of inflammatory mediators. The resolution of gout flare occurs due to increase concentration of negative regulatory factors of the inflammation which is initiated by aggregation of neutrophil extracellular trap structures (NETs) and also there is dissolution of MSU or protein coating of MSU crystals, which leads to turning off the ongoing inflammatory process.[2]

In the pathogenesis of gout there have a number of key regulatory points **(Flowchart 1)**. *At some of these points therapeutic interventions or risk factors elimination may retard the development of gout or prevent flare* **(Fig. 1)**.

Risk Factors

Risk factors for gout flares can be subdivided by non-modifiable and modifiable risk factors **(Table 1)**.

Flowchart 1: Key points of pathogenesis of gout



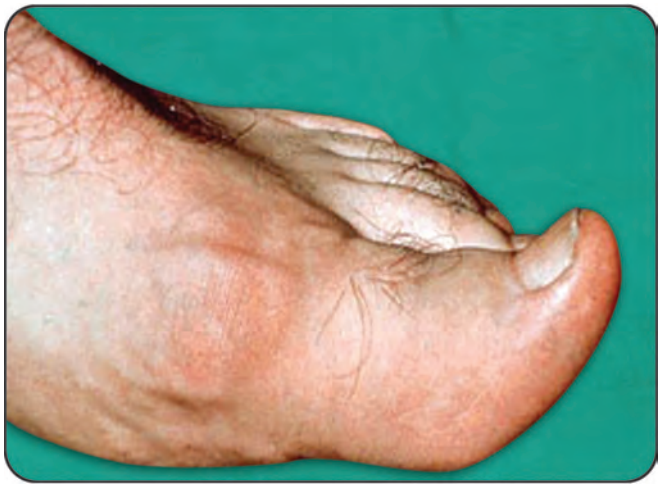


Fig. 1: Gout flare in first MCP joint

TABLE 1 Risk factors for gout flares

Non modifiable risk factors	*Modifiable risk factors*
• **Sex** • **Age** • **Race/ethnicity** • **Genetics**	• **Dietary factors** – Alcohol – Purine-rich foods: like meats, seafoods – Soft drinks, fructose consumption – Dairy product (protective effect) – Vitamin C (protective effect) – Cherry (protective effect) • **Drugs** – Diuretics – Anti tubercular drugs : Pyrazinamide, Ethambutol – Aspirin – Immunosuppressive agents Cyclosporine, Tacrolimus • **Comorbidities** – CKD – Hypertension – DM – Obesity – Cardiovascular disease – Hypertriglyceridemia & hypercholesterolemia • **Others** – Immunization – Post surgical periods – Urate lowering therapy (ULT) – Coffee

Non-modifiable Risk Factors

Sex

In below 65 age group people, male to female prevalence ratio is 4:1, but above 65 age group people this ratio reduced to 3:1. Mean age of onset in males is about 10 years younger than the females. This may be attributed to enhancement of renal tubular urate clearance in premenopausal women partly due to decrease post-translational expression of urate transporter 1 (URAT1), glucose transporter 9 (GLUT9), sodium-coupled monocarboxylate transporter 1(Smct1), and urate efflux transporter ATP-binding cassette sub- family G member 2(ABCG2) by the estrogen and progesterone resulting decreased reabsorption of urate from renal tubules. Male gender has higher numbers of gout flare than females.[3] The risk of incident gout was seen to be higher among the postmenopausal women but the women with surgical menopause or premature menopause (age <45 years) have higher incidence than to those with natural and average age of menopause. In postmenopausal women there is increased incidence of insulin resistance, which can reduce the urate excretion, and therefore hyperuricemia is more common in them than the premenopausal.

Age

The risk of hyperuricemia is strongly associated with increasing age. The chronic illness like diabetes, hypertension, cardiac diseases, renal diseases, etc. are more common in older age and also increases use of

diuretics are the another reasons for increased prevalence of hyperuricemia. The incidence of first flare is constant across the all age group and in female the incidence of first flare is more in older age group. Over all lower number of flare has been seen in older age group in a large population-based study in the UK.[4]

Race/Ethnicity

Study revealed African Americans had increased risk of gout than the Caucasian and the incidence rate were 3.11 and 1.82 respectively per 1,000 person-years, may be attributed to genetic predisposition with increased incidence of hypertension and use of diuretics in African Americans. In another study over the 20 years of follow-up, African American and Caucasian males had equal risk of incident hyperuricemia (HR 1.12, 95% CI, 0.88-1.40), whereas African American females had 2.3 times higher risk of hyperuricemia (95% CI, 1.34-3.99) than the Caucasian females.[5] Prevalence of hyperuricemia is more in the Māori population than the Europeans (27.1% vs. 9.4% in males and 26.6% vs. 10.5% in females, respectively) in New Zealand. This high prevalence is due to genetic predisposition with high prevalence of comorbidities like obesity, diabetes, hypertension in the background of genetic predisposition. In Southern China, higher prevalence of gout seen in the Minnesota Hmong males (6.1%) than the non Hmong males (2.5%). Age of onset of gout in Hmong males also have significantly younger than the Caucasians (37.4 vs. 55 years).[6]

Genetics

A study involving twins has found that gout is strongly heritable where 90% of the variation in gout concordance attributable to genetic factors. A similar approach revealed that 60% heritability of renal urate clearance and 87% heritability of the fractional excretion of urate. Recently the genome-wide association scanning (GWAS), a human genome project has enabled us to find out the genetic basis of hyperuricemia and gout to some extent. It is evident that the primary cause of gout in 90% of patients is renal under-excretion while renal excretion of uric acid is heritable. So the genetic variation in urate transporter plays a significant role to control serum urate level. The first reported association of the *SLC2A9* gene with serum urate concentrations in Italian cohorts was utilized in the Framingham and Rotterdam Heart Studies. Up to 5% variation of serum urate concentration in Caucasians has been explained by genetic variation of the *SLC2A9* gene. This variation also influences the risk of gout in Caucasians with odds ratio between 1.3 and 2.2. The said variants also become an extremely significant risk for gout in Māori of New Zealand and Pacific Island with a 500% increased risk (OR=5), and >98% of Māori and Pacific Island patients homozygous for the risk allele compared with 79% of NZ Caucasian patients.

SLC2A9 gene encodes glucose transporter type 9 (GLUT9), which is responsible for reabsorption of a large portion of urate. So mutation of *SLC2A9* can be suspected in patient of hypouricemia without mutation of other genes like *SLC22A12*. There are number of studies which have correlated polymorphisms in *SLC2A9* with uric acid levels and gout.

SLC22A12 encodes urate anion transporter 1 (URAT1), which is seen in the brush border of proximal tubules and also have significant role for reabsorption of urate. It was first identified in a Japanese patient having hypouricemia and the said gene was found to be mutated. Polymorphism has also been seen in *SLC22A12*.

ABCG2 encodes the adenosine triphosphate (ATP)-binding cassette transporter 2 (ABCG2), which mediates utrate secretion across the apical membrane of proximal tubules. The variants were indentified through GWAS and mutation of it can cause hyperuricemia.[6,7]

Modifiable Risk Factors

Dietary Factors

Alcohol: We all know that consumption of ethanol beverages, especially beer, is significantly associated with higher risk of incident gout. In few study, wine appears to protective against gout flare but Tuhina Neogi et al. (2014), concluded that the episodic alcohol consumption, regardless of type of alcoholic beverage, was associated with higher risk of gout flares.[8] Beer contains significant amount of guanosine, which is most readily absorbed purine, responsible for high urate production. A study to compare increase of serum uric acid level between alcoholic beer to nonalcoholic beer revealed that plasma uric acid levels had increased 6.5% and 4.4% ($p<0.05$), respectively points out that purine load alone had a significant effect on uric acid level. Ethanol increases uric acid production by increasing ATP degradation to uric acid precursors. It also causes lactic academia, which results in decrease urate excretion.

Purine-rich foods: Uric acid is the end product of purine degradation. Intake of purine rich foods such as meat or sea food is associated with hyperuricemia and incident gout.[9] Choi et al. found in their study that the differences in uric acid levels between the extreme quintiles of intake were 0.48 mg/dL for total meat (95% confidence interval [95% CI] 0.34, 0.61; P < 0.001 for trend), 0.16 mg/dL for seafood (95% CI 0.06, 0.27; P = 0.005 for trend), after adjusting for age.[10] Yuqing Zhang and his colleagues proved that 2 days intake of highest quintile of purine, mainly from animal source increases the risk of flare almost five times than the lowest quintile of purine and the association was independent of other risk factors like sex, alcohol consumption, diuretics or allopurinol use. Long-term moderate amount of purine rich vegetables (like—lentils, spinach, mushrooms, peas, and cauliflower) intake are not associated with gout flare.[10] Although soy has moderate purine content, it also not been shown to be associated with gout rather it may be inversely associated with hyperuricemia.

Soft drinks, fructose consumption: In first step of fructose metabolism there is phosphorylation by ATP, which accelerates purine catabolism and de-novo purine synthesis. Fructose may increase the risk of insulin resistance which can cause reduction of renal excretion of urate and leads to hyperuricemia. Sugar sweetened soft drinks and fruit juices contain high concentration of fructose, the intake of which is associated with high level of serum urate and may be an important risk factor for frequent gout flare. NHANES, a cross-sectional study showed increased in urate of 0.33 mg/dL (95% CI, 0.11-0.73) in participants drinking 1-3.9 sugar-sweetened servings per day than those drinking none after adjustment for diet including total energy intake, age, sex, medications, hypertension, and glomerular filtration rate. Men who ingested the highest 5th of fructose incurred double the risk of gout than those in the lowest (RR 2.02, 95% CI, 1.49-2.75) after adjustment for intake of total carbohydrate.[11]

Dairy products: Increased amount of dairy products intake is associated with decreased level of urate and incident gout. It has been shown in a study that the glycomacropeptide (GMP), a milk fragment and G600 milk fat extract have anti-inflammatory effects and they acts by decreasing interleukin-1β (IL-1β) expression, which may be the second protective role of dairy product.

Vitamin C: Vitamin C has a protective role against gout. It increases renal clearance of urate by increasing fractional excretion of uric acid. Vitamin C competitively inhibits the urate reabsorption in proximal tubules. In an RCT where significant reduction of serum uric acid levels was seen with supplementation of 500 mg/day of vitamin C and the mean uric acid reduction was 0.5 mg/dL (95% CI, -0.6 to -0.3).[12]

Cherry: In a case-cross over study, consumption of cherry was found to lower recurrent gout attacks by 35%. This beneficial effect of cherry may be due to its effects on glomerular filtration and probable inhibition of xanthine oxidase along with having its antioxidant properties.

Drugs

Diuretics: Diuretics can cause hyperuricemia by increasing uric acid reabsorption in the proximal tubules, increasing secretion of uric acid and contraction of plasma volume. Increased level of urate usually seen few days after initiation of diuretics and the association is dose dependent, and the concentration persists for prolonged period of administration. Hunter et al. (2006) pointed out that recent use of diuretics is associated with a significantly higher risk for gout flare.

Anti-tubercular drugs: Pyrazinamide can cause more than 80% reduction in renal excretion of uric acid at 300 mg therapeutic daily dose and precipitate gouty attack. The active metabolite of pyrazinamide has a trans-stimulatory effect on URAT1, a member of the organic anion transporter (OAT) family, resulting reabsorption of urate from renal tubules. So patient having first attack of gout should monitor the uric acid level and needs prompt discontinuation of the drug on recurrent gout flare. Another drug, *Ethambutol*, can also increase SUA and precipitate the attack.

Immunosuppressive agents: Cyclosporine use in an organ transplant recipient is most important predictors of incident gout and gout flare. Recently *Tacrolimus* also to be seen associated with hyperuricemia and gout flare but relatively less in frequency may be due to impairment of renal functions which is seen more frequently in cyclosporine use.

Aspirin: Studies shows that low dose *aspirin* can cause hyperuricemia but in contrast high dose aspirin is shown to have uricosuric effect. This paradoxical effect is due to fact that low dose of aspirin acts as facilitator of urate reabsorption and high dose acts as inhibitor of urate reabsorption through Renal Urate Transporter (URAT1).[13]

So intake of low dose aspirin can causes acute or recurrent gout flare and acts as an important risk factor.

Comorbidities

Hyperuricemia is commonly seen in chronic kidney disease (CKD) and is frequently associated with incident gout and recurrent gout flare, which requires adequate ULT. Hyperuricemia in CKD is due to decrease urinary clearance of uric acid. Approximately two-thirds of uric acid is excreted through kidney and is severely impaired in depressed renal function. Obesity shows to a strong risk factor for incident gout and flare in those having previous attack. Hypertension is consistently seems to be another risk factor for flare up especially with diuretic use. It is concluded in various studies that in hypertension and cardiovascular disease there is increased xanthine oxidase activity and high serum urate level. Diabetes is an independent risk factor. Suppiah et al. (2008) demonstrated that gout is highly prevalent in patients with type 2 diabetes and highest (41%) in men over the age of 65 years and requires early recognition and management. Hypertriglyceridemia and hypercholesterolemia both are associated with gout flare.

Other Risk Factors

Immunization is a pro-inflammatory trigger, which can also acts as a trigger for gout flare. An internet-based case-crossover study showed that immunization doubled the risk of a gout flare within the ensuing 48 hours of vaccination compared with periods in not vaccinated people (odds ratio [OR] 1.99, 95% CI 1.01-3.89).[9]

There is an increased incidence of gout flare in *post-surgical periods*. Study shows patient having a previous history of gout who undergoes laparoscopic gastric bypass surgery can frequently develop gout flare. Increase release of fat, starvation, volume contraction may all responsible for high serum urate levels in post-surgical periods.

Initiation of *urate lowering therapy (ULT)* may precipitate a gout flare, especially in early months but in long-term use it can prevent or reduce the frequency of flare. So adequate anti-inflammatory prophylaxis overlap for some duration may sometimes be needed while initiating ULT.

Intake of *coffee* is protective for gout flare. It increases renal blood flow, and hence increases urate excretion. Again it may increases the insulin sensitivity, which has a positive role for urate clearance.

Conclusion

Gout flare is very much common and a large number of patients of incident gout develop at least one flare in their lifetime. The predisposing factors for gout flares act on various points of its pathogenesis. Few factors have protective effect also. For prevention of gout flares daily consumption of alcohol must be reduced or stopped, composition of diet is to be changed, dietary supplementation like Vit. C, cherries is to be given, ideal body weight must be maintained, comorbidities should adequately be managed and anti-inflammatory prophylaxis may be needed in early months of initiation of ULT in an incident gout patient. Moreover, patient's education is important for proper lifestyle modification and pharmacological therapy other than ULT in gout patients with comorbidities.

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CHAPTER

81 Vitamin D—A Hope or Hype?

Sanjay Dash

Abstract

Healthy bone is dependent on interplay between vitamin D, calcium, and phosphates. In addition to its important role in maintaining bone health, a new area of vitamin D's role in pleiotropic activities unrelated to skeletal metabolism is now recognized and it is now increasingly being clear that optimum levels of vitamin D is also important in preventing several other dreaded chronic diseases including DM, CVD, and malignant diseases. Osteoporosis and fractures are common in elderly population and one of the most important causative agents is hypovitaminosis D. Hypovitaminosis D prevalence in India is widespread. Correction of vitamin D deficiency improves skeletal health and prevents rickets in younger population, osteoporosis, and fractures in elderly population. There are plethora of research suggesting the extra-skeletal benefits of vitamin D.

Introduction

Healthy bone is dependent on interplay between vitamin D, calcium, and phosphates. Vitamin D facilitates absorption of calcium from gut and plays a major role in calcium and phosphate balance in the body.

The major source (90%) of its availability is through dermal synthesis in the presence of Sunlight. Vitamin D is also ingested in the diet as vitamin D_2 (ergocalciferol), mainly from some plants and UV irradiated yeast & mushroom and vitamin D_3 (cholecalciferol) from animals (oily fish and fish liver oils).

Its deficiency accelerates bone turnover and bone loss leading to rickets in children, where the cartilage is not formed, osteomalacia, where the newly formed bone matrix (osteoid) is not mineralized and osteoporosis, the latter causing falls and fractures in elderly people. In addition to its important role in bone health, it also has some role in preventing several other dreaded chronic diseases including diabetes mellitus (DM), cardiovascular disease (CVD), and malignant diseases.

Metabolism

The precursor of vitamin D, 7-dehydrocholesterol, present in the epidermis and dermis, is converted nonenzymatically to pre-vitamin D_3 during exposure to solar rays (UV-B radiation of wavelength 290–320 nm). At body temperature this undergoes rearrangement of its structure and gets converted to vitamin D_3. Vitamin D_3 from the skin or vitamin D_2 from plant sources is biologically inactive. They enter the circulation bound to vitamin D binding protein (DBP) and reach liver and get converted enzymatically to 25(OH) vitamin D. It reaches kidneys bound again to DBP. The crucial active vitamin D1, 25-dihydroxyvitamin D or calcitriol is synthesized here. Both serum calcium and phosphorous as well as serum parathormone (PTH) have important role in regulating its synthesis in kidneys.[1] As serum calcium and phosphate levels rise the production of $1,25(OH)_2D$ falls. Vitamin D level in turn regulates its own synthesis. As its level becomes optimal the synthesis of PTH decreases. From the kidneys $1,25(OH)_2D$ reaches intestine and bone

where its major action in increasing calcium absorption from the gut happens. Also, through osteoclastic activity in bone, calcium and phosphorous are drawn out. All these help in maintaining serum calcium and phosphorous levels. Vitamin D receptor (VDR) presents in these tissues helps in this action. VDR acts in the nuclei of vitamin D target cells to regulate the expression of genes whose products control diverse, cell type–specific biological functions. $1,25(OH)_2D$ stimulates the absorption of calcium in the duodenum and increases calcium influx in distal tubules of kidney through nuclear VDR; latter action is specifically regulated by PTH level. It also stimulates intestinal phosphate absorption, directly suppresses PTH release from the parathyroid gland, regulate osteoblast function. It allows PTH-induced osteoclast activation and bone resorption.

Normal Value of Vitamin D and Defining Hypovitaminosis

Though brief casual solar exposure is equivalent to ingestion of 200 IU/day, this depends on variables like the skin type, latitude, season, time of day, atmospheric pollution, solar zenith angle, and melanin pigmentation. The solar zenith angle is more oblique in winter season and during early morning and late afternoon. Before 10 am and after 3 pm the UV-B rays penetrating the earth is at minimum levels and Vitamin D synthesis through skin layers is negligible during this time period. Prolonged UV-B radiation converts pre-D3 to lumisterol and tachysterol, its inactive metabolites, protecting the body from vitamin D toxicity.

As 25(OH)D levels rise serum PTH falls. Once vitamin D level reaches 40 ng/mL PTH level stops rising further.[2] Intestinal absorption of calcium increases from 45% to 65% when vitamin D level increases from 20 ng/mL to 32 ng/mL in women.[3]

Currently serum total (25[OH]D) concentration (sum of 25-hydroxyvitamin D_3 and D_2) is considered the best biomarker to define vitamin D status.[4] It has a long half-life of 2–3 weeks. Its deficiency leads to rickets and osteomalacia and with adequate intake of vitamin D both these diseases disappear with increase in vitamin D levels. A level below 12 ng/mL usually causes rickets and osteomalacia. For a healthy bone, levels between 20 ng/mL and 50 ng/mL is required.[5]

A minimum level of 20 ng/mL of serum 25(OH) D is enough for roughly an entire population (97.5%) requirement. A level above 50 ng/mL may cause undesirable effects.[6]

Biochemically, a deficient state is defined when 25(OH)D levels are less than 20 ng/mL and an insufficient state when levels hover between 20 ng/mL and 29 ng/mL.[7]

ICMR/FSSAI's recommendation on RDA of vitamin D is 400 IU—all age groups. Other scientific organizations have developed RDA basing upon age to 400–800 IU.[7,8]

Magnitude of Hypovitaminosis D in India

Hypovitaminosis D prevalence in India is widespread. Community-based studies[9-12] report a prevalence varying from 56% to 93% indicating widespread prevalence in both sexes and all age groups. Most of these studies have taken a cut off value of 25(OH)D as less than 20 ng/mL.

Vitamin D Deficiency and Its Effects on Skeletal Health

A vitamin D deficient patient is able to absorb only 10–15% of dietary calcium and about 60% of dietary phosphorus. Hypophosphatemia and hypocalcemia are a consequence. Persistent vitamin D deficiency leads to secondary hyperparathyroidism. This in turn causes increased synthesis and secretion of PTH. By increasing calcium absorption from kidneys PTH keeps calcium levels at near normal levels. It also stimulates osteoclastic activity. The net result is, though the serum calcium level increases but the casualty is bone matrix which becomes weak and osteopenia and osteoporosis sets in. Hip fracture is an unfortunate consequence of secondary hyperparathyroidism. Chronic severe vitamin D deficiency results in bone demineralization causing osteomalacia in adults and rickets in children. This also leads to increased bone pain. So, Vitamin D is a bridge between a healthy bone and calcium-phosphorus balance in the body.

Non-calcemic Functions of Vitamin D

For the last several decades scientists are trying to ascertain if there is a role of vitamin D in preventing various chronic metabolic, cardiovascular, autoimmune, and neoplastic diseases. They have detected the presence of VDR in almost all cells and tissues in the body including

neurons in the brain, gut, breast tissue, immune cells and several other cells. It has been shown that the conversion of 25(OH)D to $1,25(OH)_2D$ is possible in many tissues and cells besides kidneys. This realization has opened a new area of vitamin D's role in pleiotropic activities unrelated to skeletal metabolism. This active form of vitamin D gets metabolized into calcitroic acid and become inert locally and does not reach the circulation to act on skeletal metabolism. Only $1,25(OH)_2$ D, which is produced in kidneys can be exported to the blood stream. This locally produced active form of vitamin D influences several genes which prevent proliferation of cells and can cause apoptosis too.

Cancer

Studies have shown at least 14 cancers, including colorectal, breast, and prostate are related to vitamin D deficiency.[13-15]

Serum vitamin D level ≥33 ng/mL, compared to ≤12 ng/mL was associated with 50% lower risk of colorectal cancer.[16]

WHO working group has found link between increased risk of colorectal cancer with low serum vitamin D levels.[17]

A meta-analysis of prospective studies has shown that the risk of cancer breast decreased with vitamin D levels between 27 and <35 ng/mL with flattening of effects above 35 ng/mL in postmenopausal women.[18]

Several studies have underlined the fact that countries which are at a distance far away from equator have more risks of suffering from certain cancers. This may be because of less sun exposure and decreased UV radiation causing less vitamin D synthesis in higher altitudes.[19-22]

Several observational studies and a few RCTs[23-25] have shown that high normal vitamin D levels are linked to decreased incidence of several malignancies including colorectal, breast, prostate, etc. Some have also shown decreased mortality rates due to cancer.[25]

Immune System

VDR and vitamin D metabolic enzymes are present in almost all cells of innate and adaptive arms of immune system including dendritic cells, B and T cells, and macrophages. Researchers have found that all these cells produce active vitamin D without calcium homeostatic regulation.[26]

Researchers have found that vitamin D reduces activation of acquired immune system whereas it activates the innate immune system particularly monocytes and macrophages.

Multiple sclerosis in north and south hemisphere, T1DM and RA in north hemisphere are found in increasing numbers at higher altitudes where UVR is less. Studies have shown that UVR downregulates cellular immunity by attenuating T helper T cell mediated immune responses. UVR thus might be beneficial in MS, T1DM, and RA. One of the possible mechanisms for downregulation involves UVR induced vitamin D synthesis. Thus, vitamin D may have a protective role in preventing T1DM.[27]

Observational studies have found a strong link between prevalence of MS and less than normal vitamin D levels.[28,29]

Risk for developing active TB and its link to low levels of vitamin D has been found in one meta-analysis,[30] whereas vitamin D supplementation can enhance rapid clearance of sputum in active TB;[31] it can also protect against respiratory infections.[32]

In conclusion, a link between vitamin D endocrine system and immune system is highly plausible, but whether its deficiency has real implications for infections or autoimmune diseases is yet to be confirmed by large scale RCTs.[33]

Cardiovascular Diseases

Several genes playing important roles in CV system are targets of vitamin D signaling, including those encoding renin, PAI, and thrombomodulin.

Conclusion from a meta-analysis of 19 prospective studies is that risk of CVD is inversely associated with vitamin D levels of 8–24 ng/mL.[34] Similar conclusion is derived from another meta-analysis of 34 publications related to vitamin D levels and CVD events and mortality.[35] In contrast, VIDA trial did not support such an association.[36]

In northern hemisphere as one goes from south to north the incidence of hypertension increases. One reason could be reduction of solar induced vitamin D synthesis. Animal studies have shown VDR null mice develop high renin hypertension.[37] Some studies support inverse relationship of BP and vitamin D levels[38] whereas others do not.[39]

Vitamin D and Skin

Keratinocytes express all enzymes of vitamin D metabolic pathway and skin can synthesize its active form in presence of solar UV-B rays. Active vitamin D produced locally controls keratinocyte proliferation and differentiation as well as epidermal barrier integrity. Topical application of vitamin D analogues reduces the symptoms of psoriasis, probably due to its anti-inflammatory properties and effects on epidermal cell proliferation.

The same wave lengths of UV-B solar rays, which are required for dermal synthesis of vitamin D, are also oncogenic. It is therefore a difficult choice to make how much of solar rays one must be exposed to while avoiding long-term risk of developing skin cancer.[33]

Vitamin D and Muscle Weakness

Muscle strength correlates positively with vitamin D levels in elderly male patients.[40]

Proximal muscle strength may modestly improve with vitamin D supplementation given to elderly subjects with vitamin D levels <12 ng/mL.[41]

Some studies[42] have found no effect on reducing risk of falls with vitamin D supplementation.

Overall, the data suggests vitamin D supplementation in elderly vitamin D deficient subjects may modestly improve muscle function, improve balance, and decrease the risk of falling.[33]

Type 2 DM

The risk of developing T2DM is reduced with higher vitamin D levels.[43]

Mortality

A recent meta-analysis of observational studies and RCTs which reported associations between vitamin D and cause specific mortality outcomes has concluded that there is inverse relationship between vitamin D levels and risk of death due to CV disease, cancer, and other causes and also vitamin D supplementation significantly reduces overall mortality among older adults.[44]

Treatment of Vitamin D Deficiency

The usual adult dose for treatment of vitamin D deficiency is 60 K IU of vitamin D_3/week given for 8–12 weeks followed by maintenance dose of 60 K IU once every month.

Conclusion

Vitamin D deficiency is quite prevalent in India. It is now recognized as an important health problem, which needs to be addressed by stakeholders. Vitamin D deficiency and skeletal consequences are well known. There is significant improvement in rickets when treated with vitamin D supplements. Though several researchers have pointed out the relationship between vitamin D status and non-skeletal diseases, more research is required to conclusively prove the link.

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CHAPTER

82 Hyponatremia—An Update on Diagnosis and Treatment

Samir Sahu

Abstract

Hyponatremia, defined as serum sodium concentration of less than 135 mEq/L, is a common electrolyte disorder that often poses a diagnostic and a therapeutic challenge. The primary aim of the diagnosis is to differentiate between acute (<48 hours) versus chronic (>48 hours), symptomatic versus asymptomatic and hypotonic versus non-hypotonic hyponatremia. Further, hypotonic hyponatremia is differentiated on the basis of volume status, urine sodium, and urine osmolality. The treatment for hyponatremia is decided on the basis of duration and symptoms. For acute symptomatic hyponatremia and severe chronic hyponatremia, bolus of 3% hypertonic saline is the initial treatment of choice. Though the first-line therapy for most forms of chronic hyponatremia is fluid restriction, therapy to increase renal-free water excretion like vasopressin receptor antagonists, loop diuretics, and urea are often necessary.

Introduction

Hyponatremia is a common electrolyte disorder, defined as sodium concentration below 135 mEq/L.[1] It is a state of relative water excess to sodium. With the expanding use of various medications and the growing elderly population, the incidence is on a rising trend. Among the inpatients, especially in ICUs, the incidence is up-geared to 15–30%.[2] Consequences will be catastrophic, if not treated with prompt measures. Hence, a well-directed investigation from the gamut of tests available helps in quick and accurate diagnosis. Incorporating the recent concepts in the management reduces the morbidity and mortality.

Definition and Background

Plasma Osmolality (P_{osm}): It's the ratio between plasma solutes and water. The major contribution of plasma solutes is provided by sodium salts while rest by other ions (e.g., potassium), glucose, and urea.

$$\text{Plasma osmolality} = 2 \times [\text{Na}] + [\text{glucose}]/18 + \text{blood urea nitrogen}/2.8$$

Urine Sodium (U_{Na}): Urine sodium is a measurement of the concentration of sodium in the urine. On spot estimation, the values are normally more than 20 mEq/L.

Urine Osmolality (U_{osm}): Urine osmolality is the measure of number of dissolved particles per unit of water in the urine. Urine osmolality in an individual with a normal diet and normal fluid intake ranges 500–850 mosm/kg water.

Osmotic Demyelination Syndrome (ODS): A dreaded disorder characterized by the wide spread development of demyelination in the pontine as well as the extrapontine regions usually because of rapid correction of hyponatremia.

Classification and Symptoms of Hyponatremia

See **Table 1**.

TABLE 1 Classification of hyponatremia based on duration, serum sodium, and symptoms

Severity	*Serum sodium*	*Duration*	*Neurological symptoms*
Severe	<120 mEq/L	Acute (<48 hours)	Vomiting, seizures, coma, cardiorespiratory distress
Moderate	120–129 mEq/L		Nausea without vomiting, confusion, headache
Mild	130–134 mEq/L	Chronic (>48 hours) or duration unknown	Altered mood, concentration and cognitive deficits, gait disturbances, falls

Evaluation

History

A history of electrolyte-rich fluid loss (vomiting, diarrhea, or diuretic therapy) may indicate hypovolemia. Past history of CNS disease, malignancy, HIV infection, and plasma cell dyscrasia may add important clue to the diagnosis.[3] History of common drugs causing hyponatremia (thiazide diuretics, mannitol, antidepressants, antiepileptics, antipsychotics, and ecstasy (methylenedioxymethamphetamine) should not be missed.

Physical Examination

Peripheral edema and/or ascites may be a manifestation of renal failure, cirrhosis, or heart failure. Look for signs of extracellular volume depletion such as decreased skin turgor, tachycardia, orthostatic or persistent hypotension.[3] Sometimes patient may present with only signs of adrenal insufficiency or hypothyroidism.

Investigations

Laboratory testing is almost always essential to establish the diagnosis. Investigations helpful in the initial evaluation of hyponatremia include: complete blood count, serum glucose, urea, creatinine, sodium, potassium, chloride bicarbonate, calcium, lipid profile, and liver function test. U_{osm} and U_{Na} play an inevitable role in the evaluation of hyponatremia **(Flowchart 1)**.

Differential Diagnosis

Hyponatremia may be divided into:

- Pseudohyponatremia
- Isotonic or hypertonic hyponatremia
- Hypotonic hyponatremia

In the first two situations, hyponatremia and hypoosmolality are discordant; these are important to recognize, as they represent situations where hyponatremia need not be treated.

Pseudohyponatremia

Hyperlipidemia, hyperproteinemia, plasma cell dyscrasia.[4]

Isotonic or Hypertonic Hyponatremia

Sodium concentration falls by approximately 2 mEq/L for each 100 mg/100 mL rise in glucose concentration. Other causes include mannitol, IVIG, and absorption of glycine or sorbitol, the irrigation solutions during transurethral resection of prostate.[1]

Hypotonic Hyponatremia

Most have hypotonic hyponatremia, as serum sodium concentration remains one of the major determinant of tonicity. Evaluation of hypotonic hyponatremia has to be done meticulously **(Flowchart 1)**. Severely reduced glomerular filtration rate (GFR) and intake of thiazide diuretics are important causes of hypotonic hyponatremia.

Severely Reduced GFR: Free water excretion is significantly reduced in advanced renal impairment (e.g., GFR <15 mL/min) leading to hyponatremia.

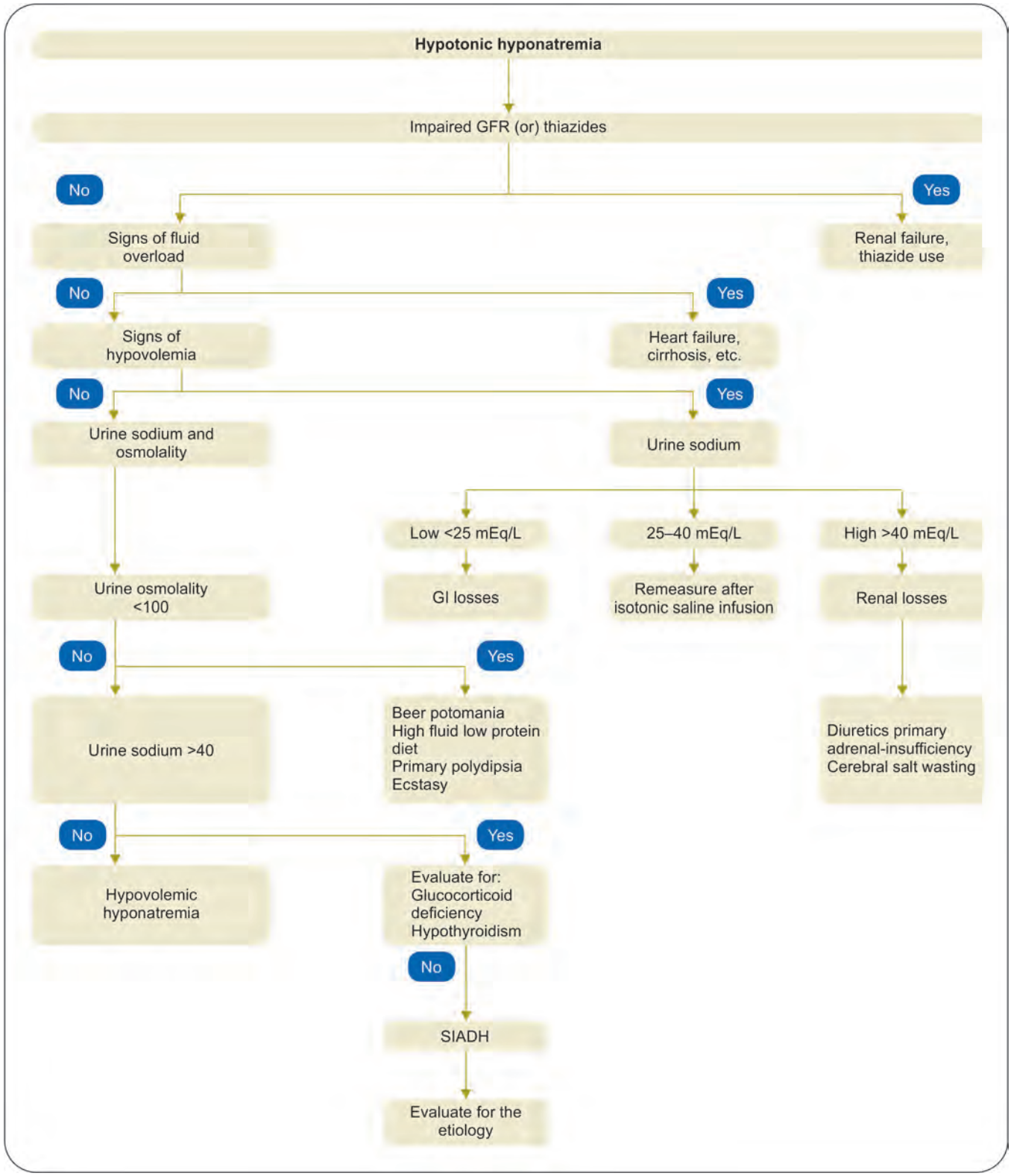
Thiazides: An occasional but a severe complication of thiazide typically begins soon after onset of therapy; but at times occur on long-term therapy. Improvement on discontinuation helps to distinguish from syndrome of inappropriate antidiuretic hormone (SIADH), which also shares similar features.[3]

Those patients, who do not have either of the above, should be evaluated for the evidences of fluid overload. They can be classified as hypervolemia, euvolemia and hypovolemia.

Hypervolemia

The major causes of hyponatremia in fluid overload conditions include heart failure (HF) and cirrhosis, typically in advanced stages. In spite of excess plasma and extracellular volumes in the above, the carotid sinus baroreceptors sense a reduced pressure, because

Flowchart 1: Approach to determine the cause of hypotonic hyponatremia



of a fall in cardiac output in heart failure and arterial vasodilatation in cirrhosis.

Hypovolemia

Clinical features of hypovolemia are not always diagnostic. It may be either due to a renal fluid loss or an extrarenal fluid loss. Measurements of U_{Na} and Urine chloride (U_{Cl}) concentrations distinguishes both.[5]

- *Low U_{Na} (<25 mEq/L):* Seen in patients of gastrointestinal fluid losses (e.g., diarrhea) and in renal fluid loss due to diuretics, if measured after the diuretic effect has abated.
- *High U_{Na} (>40 mEq/L) with low U_{Cl} (<25 mEq/L):* Seen among hypovolemic hyponatremic patients with metabolic alkalosis caused secondary to vomiting.
- *High U_{Na} and U_{Cl} concentration (>40 mEq/L):* Commonly seen during diuretic therapy with its effect still on. Other causes of renal fluid loss with hyponatremia are primary adrenal insufficiency and cerebral salt wasting syndrome (CSW). Clinical features of hypovolemia differentiates CSW from SIADH.[6]

Euvolemia

- *Low U_{Na} (<25 mEq/L) with Low U_{osm} (<100 mosmol/kg):*
  - *Primary polydipsia:* It is usually seen in psychiatric patients. It may cause hyponatremia when water intake is so high that it exceeds the normal excretory capacity in spite of it being normal. Once water intake stops, the serum sodium concentration will increase spontaneously.
  - *Malnutrition:* It occurs in beer drinkers (beer potomania) or in those on a low-protein, high-water diet, in which dietary solute intake (sodium, potassium, protein), and therefore solute excretion is so low that the rate of water excretion is markedly diminished even though urinary dilution is intact.
- *High U_{Na} (>40 mEq/L) and U_{osm} (>300 mosmol/kg):*
  - *SIADH:* The most common cause of hyponatremia in euvolemic patients is a diagnosis of exclusion. The patient may also have other corroborative features like hypouricemia (<4 mg/dL), and low blood urea nitrogen (<5 mg/dL). The underlying mechanism is presumed to be due to increased clearance of uric acid and urea respectively, as a result of water retention and volume expansion in the SIADH and stimulation of V1a receptor via an uncertain mechanism.[7] Administration of normal saline worsens the hyponatremia.
  - *Reset osmostat:* They present similar to SIADH, with a moderately reduced plasma sodium concentration (usually between 125 and 135 mEq/L), that is stable on multiple measurements.
  - *Severe hypothyroidism:* Causes hyponatremia via uncertain mechanisms.
  - *Cortisol deficiency:* Secondary adrenal insufficiency (hypopituitarism), in contrast to primary adrenal insufficiency, presents with euvolemic hyponatremia and biochemical features similar to SIADH. The mechanism is found to be due to the interruption of negative feedback loop of cortisol on antidiuretic hormone (ADH) secretion and hypersecretion of ADH as a result of reductions in systemic blood pressure and cardiac output.[1]

Treatment

Aims of Therapy

- *Prevention of further fall in serum sodium:* The patients prone to develop are self-induced water intoxication and parenteral fluid administration.
- *Prevent brain herniation:* The vulnerable are, patients with acute hyponatremia and associated intracranial pathology.
- *Relieve symptoms of hyponatremia:* Even the most severe symptoms can be relieved by a correction of sodium levels by 4–6 mEq/L during the first 24 hours.
- *Avoid over correction:* Rapid correction of chronic hyponatremia may lead to ODS.[1] To avoid this, the **maximum rate of correction** should be 8 mEq/L in any 24-hour period. The risk factor of ODS are mentioned in **Table 2**.

Indications for Hospitalization

- Acute hyponatremia
- Symptomatic hyponatremia
- Severe hyponatremia

Acute Symptomatic Hyponatremia (or Chronic with Severe Symptoms)

Severe symptoms are reflective of brain edema, small increase in serum sodium concentration may be sufficient

TABLE 2 Risk factors for ODS

Risk factors
• Serum sodium ≤105
• Hypokalemia
• Alcoholism
• Malnutrition
• Liver disease

enough to improve edema and prevent herniation;[7] failing, death may follow rapidly. Since there is no brain adaption with acute hyponatremia, chances of ODS is little.

Intravenous (IV) infusion of 150 mL, 3% saline over 20 minutes to achieve a target of 4–6 mEq/L increase in serum sodium. The same dose shall be repeated with serum sodium monitoring after every infusion. In non-responders, continue infusion with 3% saline aiming at 1 mEq/L/hr increase in serum sodium concentration.[8] Adrogué–Madias equation [Change in Serum Na = (infusate Na – serum Na)/(tbw+1)] may be used for estimating the correction rate, while serum sodium being monitored 4 hourly. Etiology specific treatment is preferred once the desired levels are attained.

Acute Asymptomatic Hyponatremia

Even though the symptoms are not much pronounced, an acute drop in serum sodium to a level more than 10 mEq/L, may worsen the clinical condition. Hence, patients at risk are to be treated with a single IV infusion of 150 mL 3% saline, so as to prevent further drop.[8] Serum sodium to be monitored every 4 hourly, till the cause specific treatment is initiated.

Chronic Asymptomatic Hyponatremia

These patients are particularly predisposed to develop ODS from rapid correction. If the hyponatremia is severe (<120 mEq/L), initiate IV infusion of 3% saline at 15–30 mL/hr targeting a maximum correction of 8 mEq/L. After sodium correction in these patients and also in cases of mild to moderate hyponatremia, provide a cause specific treatment.[8]

Treatment of Specific Hyponatremia

- *Hypovolemic hyponatremia:* Gastrointestinal losses, vomiting, and diarrhea and renal loss secondary to diuretics are accompanied by hypokalemia, where measures should be taken to correct hypokalemia first rather than hyponatremia.[8] Sodium and potassium being the exchangeable ions, with correction of potassium, sodium levels are restored; however, correcting sodium levels first, risks ODS, due to the rapid correction. Extracellular volume must be restored with IV infusion of 0.9% saline or a balanced crystalloid solution at 0.5–1.0 mL/kg/hr[9] to achieve the desired sodium levels. In primary adrenal insufficiency after the initial measures, fludrocortisone may be added along with hydrocortisone.
- *Euvolemic hyponatremia:* This area remains a challenge in clinical practice. The clinical presentation varies and often has some underlying disease.
  - *SIADH:* Fluid restriction is conventionally considered as the first line of treatment. However, the response to therapy depends on the levels of AVP. Oral salt may be added among patients with serum sodium above 120 mEq/L and very mild or absent symptoms. Loop diuretics shall be used as a concurrent therapy in patients with urine osmolality above 500 mosmol/kg. Urea is considered as an alternative to the combination of loop diuretics and oral salt.[10] It has the advantage over any, as it corrects hyponatremia gradually without risk of over correction.[9] However, poor palatability and azotemia had made its use limited in clinical practice. Vasopressin (V2) receptor antagonists (Vaptans) can be added if adequate response is not noticed. Tolvaptan, an oral V2 receptor antagonist initiated at 15 mg/day, can be gradually titrated by 15 mg/day to a maximum dose of 60 mg/day. The commonly noticed side effects are dry mouth, thirst, increased urinary frequency, dizziness, nausea, and orthostatic hypotension.[11] Although hepatotoxicity was not noticed in the recent studies, early trials had shown elevation of alanine aminotransferase (ALT). Hence, its use should be restricted to 30 days and not to be used in patients with underlying liver diseases. Of utmost importance is liberal fluid intake, especially during first 24–48 hours, since Vaptans clear free water and there are high chances for rapid correction with fluid restriction.[1] Monitor serum sodium concentration 6–8 hourly till 48 hours.

- *Hypothyroidism:* Thyroxine replacement along with fluid restriction suffice.
- *Glucocorticoid deficiency:* Nearly always responds to glucocorticoid replacement. Prompt water diuresis following initiation of glucocorticoid treatment supports the diagnosis.
- *Primary polydipsia:* Counseling for fluid restriction and alternative methods such as wetting the mouth with ice chips, ameliorates sensation of thirst and helps to reduce fluid intake. Studies had shown favorable role of antipsychotic drugs in reduction of polydipsia and prevention of recurrent hyponatremia.[1]

- *Hypervolemic hyponatremia:* Hyponatremia in hypervolemic conditions such as liver cirrhosis, HF, and end stage renal failure heralds a poor prognosis. Notwithstanding the cause, the primary treatment rests on sodium and water restriction. Fluid restriction to 50–60% of daily fluid requirement or a gross restriction to daily input of less than 800 mL/day is generally followed. Loop diuretics interferes the counter current mechanism in the thick ascending loop of Henle, giving rise to a state of ADH resistance, resulting in less concentrated urine. Vaptans can be added in HF and liver cirrhosis.

Treatment of Sodium Overcorrection

In situation where there is over correction of hyponatremia, electrolyte-free water is infused at 10 mL/kg over 1 hour while urine output and fluid balance are strictly monitored. In addition, IV desmopressin 2 µg, not more than 8 hourly, may be considered after expert opinion.[8]

Conclusion

The laboratory investigations plays a key role in diagnosis of specific causes of hyponatremia, besides the goal directed history and physical examination. Amongst them, the widely and cheaply available U_{Na} and U_{osm} are the crucial decision-makers. The recent evidence supports bolus infusion of hypertonic saline, for certain serious conditions of hyponatremia. Correction rate should not exceed 8 mEq/L in any 24 hours, irrespective of the duration and severity.

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CHAPTER

83 Osteoporosis "The Battle Still to Overcome"

Niraj Lodha, Divyansh Mathur, Naman Lodha

Abstract

Osteoporosis is common silent disease. Its prevalence increasing due to increase in geriatric population. It is associated with increase in morbidity and mortality in elderly population. Prevention of first fracture and targeting young population for primary prevention is key in successful management of this chronic problem.

Introduction

With the increase in the life expectancy, the geriatric population is rising worldwide; therein increasing the cascade of "Non-infectious chronic diseases". Amongst them, osteoporosis being a silent killer is one of the important causes of mortality and disability.

Osteoporosis is defined as low bone mineral density (BMD) caused by altered bone strength ultimately predisposing patients to low impact fragility fractures. Strength of bone is assessed by its mass and quality. Osteoporosis is a process that develops gradually over many years as we age.[1]

Incidence

Decrease bone strength and fragility fractures are common worldwide. It is estimated that around 13–18% of women above 50 years of age are osteoporotic. Fracture risk in these women is around 40% in the remaining life. In a longitudinal study in USA on 200,000 asymptomatic women above 50 years without known osteoporosis, BMD test was performed.[2] In this study 40% had osteopenia or low bone mass and 7% had osteoporosis. About 93% of women above 80 years are either osteoporotic or having low bone mass.[2]

Morbidity and Mortality

Both spine and hip fractures are associated with increased disability and mortality. Impact of fragility fracture is equivalent to stroke and myocardial infarction in geriatric population. Hip fractures have 34% excess mortality in first year in men. In female excess mortality is 20–24%.[3] Death rate for hip fracture in elderly woman has now exceeded from stroke in certain European countries. Likelihood of death after 50 years of age in women is equal with breast cancer and hip fracture.[4]

Most patients after hip fracture are not able to live independently. About 40% patients are not able to return to previous functional status.

Institutionalization/death rate is 39.2% within 2 years in female (>60 years) after hip fracture while it is 19.7% in control population. In male it is 52.1% while in normal population it is 12.4%.[5]

Hospital bed occupancy days are much higher with hip fracture (568,000) in comparison to other chronic disease. In stroke it is 352,000 days while in chronic obstructive pulmonary disease it is 35,300 days.[5]

Osteoporosis is not limited to female gender as 20% cases occur in male. In the United States, 2 million males are osteoporotic while many more are osteopenic.[6]

Fragility fracture is the most drastic complication of low BMD that occur following minimal trauma.[7]

Risk factors for fragility fracture:

- Low BMD (twofold increased risk for one SD decrease of BMD)
- Age (after 60 years with each decade risks increases by twofold)
- Previous fragility fracture (fivefold increased risk)

Economic Effect

In the USA, annual cost of fracture-related expenses secondary to osteoporosis was 13.8 billion in 1995 in comparison to asthma, which was 7.5 billion and congestive heart failure 20.3 billion.[8] As baby boomers hit retirement age the cost by year 2050 will reach around 130 billion. In 2010, the cost of fragility fracture in the European Union was 37 billion and based on demographic changes it is predicted to double by 2050.

Investigations

BMD is measured by Dual-Energy X-Ray Absorptiometry (DXA). It is most commonly used test because of its accuracy and ease of using.[9]

Bone densitometry report includes:

- *T Score:* Patient value is compared with young normal subject (peak bone mass) and expressed as number of SD above or below.
- *Z Score:* Patient value is compared with mean value of age matched normal subject and expressed as number of SD above or below.

Absolute BMD—It is the measured BMD (unit GM/CM^2)[8]

Limitation of DXA

It measure bone density, that is, hydroxyl apatite per bone area. But it is altered by atherosclerosis (Aorta) and other degenerative changes due to calcification.[10]

As two dimensional images in DXA, it does not identify minor details of the bone and its poor fracture prediction ability led to the development of new technique like TBS, HR PQCT.[10]

BMD of spine and hip can predict fracture risk but there is a paradox, as most patients with fracture are osteopenic because of high population of this group.[11]

Indications of BMD Measurement

- Age ≥65 (women) and ≥70 (men)
- Female with menopause and one risk factor
- Deformity, fracture, and osteopeniea of vertebrae
- For analysis of response to therapy for osteoporosis
- Glucocorticoid therapy for more than 3 months
- Primary hyperparathyroidism
- Fracture in adults after age of 50[12]

Risk Factors for Osteoporosis

Non-modifiable

- Age
- Race (Asian, Caucasian)
- Gender (female)
- Menopause (early)
- Built (slender)
- Family history[5]

Modifiable

- Diet low in calcium and vitamin D
- Lack of estrogen
- Lifestyle (sedentary)
- Smoking
- Alcohol (more than two drinks/day)
- Caffeine (more than two serving/day)[5]

About 70% of men with Osteoporosis have secondary cause. Among it alcohol abuse, glucocorticoid use, hypogonadism, and treatment with gonadotropin-releasing hormone (GnRH) analog are common causes.[13]

Diagnosis of Osteoporosis

- T Score ≥1 (Normal)
- T Score between –1 and –2.5 (Osteopenia)
- T Score ≤–2.5 (Osteoporosis)[8]

Common Associated Conditions with Osteoporosis/Osteopeniea

Diseases

- *Endocrine disorder:* Thyroid disorder (hypo- and hyperthyroidism), hyperparathyroidism, hyperprolactinemiea
- *Deficiency disorder:* Osteomalacia[14]

- *GI disorder:* Inflammatory bowel disease
- *Connective tissue disorder:* Rheumatoid arthritis[5]
- *Renal failure*

Drugs

- Steroids
- Excess thyroid hormone
- Anti-epileptics
- Proton pump inhibitors[15]

Treatment and Prevention

Non-pharmacological measures:

- Regular resistance and aerobic exercises
- Adequate calcium—1,000–1,200 mg/day for premenopausal women, men. For postmenopausal women and men 65 years or older it is 1,200–1,500 mg/day
- Adequate vitamin D (800–1,200 U/day)
- Limitation of alcohol and caffeine consumption, smoking cessations
- Fall prevention in elderly (risk for frequent falls are sedative, cognitive and visual impairment, disability, and obstacle to ambulation)[16]

Pharmacological Therapy for Osteoporosis

Indications:

- Anyone with vertebral or hip fracture (fragility fracture) BMD not required
- T Score <2.5
- For osteopenia follow FRAX tool. Treatment is recommended for those having 10-year risk of 3% or more for hip fracture or 20% or more for other osteoporotic fracture[1]

Types of medications:

- Antiresorptive agents:
  - Bisphosphonates
  - Raloxifene
  - Calcitonin
  - Estrogen
  - Denosumab (monoclonal antibody against RANKL)[17]
- Anabolic agents:[12,18]
  - Teriparatide (34 amino acid fragment of intact PTH)
  - Abaloparatide
  - Romosozumab

There is 30–70% reduction of vertebral fracture by these drugs. Osteoanabolic drugs reduces incidence of nonvertebral fracture 40–50% while antiresorbtive drugs reduce it by 20–25%.

To determine efficacy of treatment BMD is repeated after 2 years. To determine serial changes, least significant change for particular instrument must be known.[10,14]

There is a definitive treatment gap. As 40–95% of high-risk fracture patients do not receive treatment. In spite of benefit of treatment there is 50% reduction in the use of bisphosphonate in the USA. It is documented from 2008 to 2012 (crisis in osteoporosis).[16]

Prevention of Fragility Fracture

- Prevention of first fracture is the most important step. There is five times high incidence of another fragility fracture after first fracture. Fracture liaison services (FLS) have been started in many countries to close the care gap. It is further evolved to identify the high risk groups to prevent the first fracture. In it dedicated coordinators work with endocrinologist and rheumatologist. They take care of all the aspects (identification, investigation, and intervention) of the disease.[16]
- Frequent fall can be prevented by discontinuation of sedatives, correcting visual impairment, prescribing ambulatory aids, and hip protectors.[4]

Conclusion

- Targeting young population for primary prevention will ultimately lead to decrease in health-care cost, disability, and death in geriatric population. So ultimate aim will be adequate bone mass in youth and policy for this is urgently needed.
- Most of the patients are not well informed about osteoporosis and its long-term impact and most patients believe that there is low to no increase in fragility fracture after first, despite contrary evidences.
- Like other chronic medical problems, osteoporosis also needs successful strategies for identification and treatment. As the population ages, number of patients will increase and there will be acute need for screening and prevention.
- Weak bone in elderly is a significant concern because it is associated with low quality of life and disability. Like in stroke, cancer, and myocardial infarction, fragility fracture is also linked with increased deaths, hospital admission, and impairment of health in elderly.

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CHAPTER

84 Intermittent Fasting in Obesity—Hope or Hype?

Soumitra Ghosh

Abstract

Intermittent fasting is a form of calorie restriction that allows calorie intake on few days of the week (e.g., 2:5) or specific hours of the day (e.g., 8:16 or 10:14) and restricting the calorie intake at other times. It may be divided into alternate day fasting (ADF), modified ADF (MADF), and time restricted eating (TRE). In TRE food intake is limited to 8–10 hours in a day or lesser in sync with the external light-dark cycle and internal circadian clock. It has been seen that night shift workers are at increased risk of obesity, other metabolic diseases, and cancers. Short-term studies in humans have shown that TRE results in modest weight loss, fat loss, with improvements in insulin sensitivity, inflammatory markers, and triglyceride level. Intermittent fasting may offer greater improvements in body composition, metabolic, and inflammatory markers. Intermittent fasting may be advised to motivated individuals as one of the options of Calorie Restriction, keeping in mind that we have insufficient evidence on its beneficial effects on long-term obesity and chronic metabolic outcomes. Though it has been hyped by the press and the lay public, the scientific community has the hope and the wisdom to accept its promises as well as its limitations.

Introduction

Obesity is the result of an interplay of genetic, epigenetic, and environmental factors that impair the neurohormonal signaling that controls the satiety and hunger, and the calorie storage and expenditure. Despite the burgeoning problem, the treatment options of obesity are limited. Pharmacotherapeutic agents are limited by their insufficient targeting of obesity pathogenesis and significant adverse effects. Metabolic surgery, though currently the most effective means to treat obesity and its complications, has its share of short-term and long-term complications. Lifestyle modification in the form of appropriate diet, physical activity, and behavioral change forms the cornerstone of therapy.

Daily Energy Restriction: Challenges

An important component of lifestyle modification is restriction of energy intake to promote weight loss. Daily energy restriction (DER) where daily calorie intake is restricted is often not sustainable in the long run due to increased hunger, reduced energy expenditure, defense of body weight and other unknown factors. Research and advancements in intermittent energy restriction (IER) also known as intermittent fasting (IF) has raised from the quest for an alternative, more effective, and sustainable forms of energy restriction.

Intermittent Fasting/Intermittent Energy Restriction

Intermittent fasting is a form of calorie restriction (CR) that allows calorie intake on few days of the week or specific hours of the day and restricting the calorie intake at other times. There is no consensus on the exact definition of IF and different studies used different definitions. Broadly it may be divided into alternate day fasting (ADF), modified ADF (MADF), and time restricted eating (TRE). In ADF,

patient fasts on alternate days. In MADF, patients fast on few days in a week, for example, 5:2. In TRE food intake is restricted to few hours of the day, 8–10 hours or less, for example, 8:16 or 10:14. There is no consensus on the amount of energy intake on fasting days, with energy intake ranging from 0% to 50% of non-fasting days in different studies.

Potential Mechanisms of Benefit of Intermittent Fasting

One basic idea of IF is that individuals do not fully compensate on non-fasting days for the reduced/absent calorie intake on fasting days thereby decreasing total calorie consumption. Proponents of intermittent fasting claim that it improves body composition and other obesity comorbidities.

"Fasting physiology" are adaptations developed by organisms during evolution to promote good health and to prolong survival by allowing repair and regeneration. In one very basic life-form yeast, addition of nutrients like glucose and amino acids blocks survival response and removal of these improves survival,[1] while addition of water protects against DNA oxidative damage and use of alternative fuels by yeast as sources of energy.[2]

In studies in both animals and humans, fasting has been found to reduce oxidative stress and promote autophagy. Autophagy is an evolutionary programmed cell repair process that recycles damaged organelles and misfolded proteins so as to prolong the lifespan of the cell. Autophagy is impaired in obesity, diabetes mellitus, and ageing. Fasting was also found to reprogram age-related pathways and hormones like Sirtuin 1, mTOR pathway, and IGF-1.[3,4]

Another form of intermittent fasting (IF or IER) is TRE. In TRE food intake is limited to 8–10 hours in a day or lesser. Every organism has an internal circadian clock that is programmed to work in sync with the external light-dark cycle. The circadian system consists of a master clock in the suprachiasmatic nucleus of the hypothalamus and peripheral clock situated in other brain areas and the periphery. The entrainment factor (zeitgeber) for the master clock is light. The cellular oscillator is composed of a positive limb (CLOCK and BMAL-1) and a negative limb (CRYs and PERs). CLOCK and BMAL-1 dimerize in the cytoplasm and translocate to the nucleus. Transcriptional activators CLOCK and BMAL-1 promote the transcription of target genes period (PER) and cryptochrome (CRY) among others. The product of the target genes then forms a repressor complex which inhibits transcription of CLOCK and BMAL-1. Through this transcriptional-translational feed-back loop the master clock modulates rhythmic physiology of metabolism and other body rhythms. In normal circumstances cross-talk between the master and peripheral clocks synchronizes circadian rhythm with feeding behavior so that food intake occurs during the light period. From the metabolic perspective the circadian clock and circadian physiologic and biochemical rhythms partition metabolic processes according to the time of the day. Peripheral clocks are entrained by food too. Thus, when food intake occurs in the dark period, there is a desynchrony between the master and peripheral clocks, resulting in misalignment of metabolic processes resulting in obesity and its downstream complications.

The character of the gut microbiota is altered in obesity. A healthy gut microbiota is vast, complex, diverse, and have cyclical fluctuations in response to diet. The diurnal fluctuations in the gut microbiota in response to feeding and fasting modulate the activity of the gut microbiota, which in turn modulates metabolism. Therefore, fasting and eating in sync with the circadian rhythm would promote good metabolic health.

Evidences in Animal Models

TRF in rats in line with the circadian timing system (i.e., feeding during the active phase) improved glucose tolerance during the active phase,[5] while TRF desynchronized with the circadian timing system (i.e., feeding during the inactive phase) worsened glucose tolerance. TRF increased bile acid synthesis, enhanced cholesterol excretion, and protected from inflammation.[6,7]

A study in rats found that IF compared to daily CR protected the myocardium against ischemia-induced cellular damage and inflammation.[8] IF was found to improve cognitive performance.[9] CR and IF was found to improve longevity and resistance to age-related diseases in animal models.[10]

In a study three groups of mice were subjected to either daily CR, ADF (with ad libitum food on every alternate day), or ad libitum food intake daily for a period of 20 weeks. It was seen that ADF mice compensated for periods of fasting by almost doubling the food intake on fed days. Therefore, the weight gain in ADF group was similar to

daily ad libitum feeding group. But the daily CR mice had significantly lesser weight. However, despite weight gain in the ADF, fasting glucose and insulin concentrations were similarly improved in ADF and daily CR groups, but such benefit was not seen in the daily ad libitum fed group.[11] The findings suggest that the "fasting physiology" could have played a favorable effect on the improved metabolic profile and CR on fed days is equally essential for weight loss in ADF.

Evidences in Humans

Night shift workers are at higher risk for obesity, other metabolic diseases, and cancers.[12] The increased risk of obesity is independent of calorie intake.[13] Circadian misalignment for 10 days was associated with increased postprandial glucose, serum insulin, and increased mean arterial pressure.[14]

Short-term studies in humans lasting from 4 days to 16 weeks have shown that TRE results in modest weight loss and fat loss.[15,16] Improvements in insulin sensitivity, inflammatory markers, and triglycerides were seen.[17]

In humans, restriction of food intake to lesser hours in TRE was associated with a reduction in total calorie intake by 20%. This resulted in weight loss of ~4% at 16 weeks and was sustained for up to a year.[18] However, the timing of TRE is very important. It may be early TRE (eTRE), that is, eating in the morning or delayed TRE (dTRE), that is, eating in the evening. In two weight loss intervention studies greater weight loss was seen in eTRE compared to dTRE, highlighting the importance of not only restricting the eating duration and prolonging the fasting duration; but also eating in sync with the circadian clock.[19,20] In another 4-day randomized cross-over study, 11 overweight adults ate between 8 am and 2 pm (eTRE) and between 8 am and 8 pm (control schedule). Compared to control schedule, eTRE significantly decreased mean 24-hour glucose levels as well as glycemic variability. In eTRE group, a rise in ketones, cholesterol, expression of the stress response, anti-aging gene SIRT1 and the autophagy gene LC3A were seen before breakfast. It was thus concluded that eTRE improved 24-hour glucose levels, favorable lipid metabolism, circadian clock gene expression and autophagy, and may have anti-aging effects in humans.[17]

Overweight subjects who consumed a low calorie (500 Kcal) but relatively high protein diet for 2 days in a week for 6 months (MADF) had lower abdominal fat, blood pressure, and improved insulin sensitivity.[21] However, a review by Barnosky et al. found that daily CR was better than IF for weight loss, though both regimens improved insulin sensitivity and decreased visceral fat.[22] A recent meta-analysis found that both IER and CER produced equivalent weight loss.[23]

Another RCT comparing ADF, daily CR, and no-intervention found weight loss was similar between ADF and CR at 6 or 12 months. However, there was greater dropout in the ADF group.[24] DEXA and MRI at week 24 found no difference between fat mass, lean mass, visceral, and adipose tissue mass between ADF and CR groups.[25] In another small study of 11 patients, ADF participants had higher muscle expression of the SIRT1 gene.[26] SIRT1 is known to be associated with longevity in humans. Unlike rodent studies most evidences suggest that calorie intake in ADF is not markedly increased on eating days in humans.

Limitations of Current Evidences

Most of the studies in animal and humans were small in size and of short duration. Therefore, effect of IER on long-term weight maintenance is unknown. There was no unanimity on the definition of IF across studies. Most studies did not study the effect of IF (IER) on other important parameters like appetite, mood, behavior, sleep, and physical activity. However, one reassuring fact of ADF in humans is that humans tended to not compensate (overeat on fed days) for the reduced calorie on fast days unlike rodents exposed to ADF with ad libitum food intake on fed days. Most evidences in humans suggest equivalent weight loss in DER and IER; proposing that CR is responsible for the weight loss. However, few studies reported improvements in metabolic and inflammatory parameters in IER highlighting the importance of "fasting physiology" and "circadian synchrony" that improves health and survival outcomes in humans. However, the optimal eating window in TRE is not clearly defined.

There are concerns about the applicability and the durability of IF in real world settings, where family and social factors, appetite, mood, and behavior pose challenges. Larger and longer studies in real world settings are needed to answer these questions. This will help answer the questions raised and also identify the individuals who would benefit from such a fasting regimen. There is an urgent need to have standardized definitions for the different forms of IER (IF); uniform methods

for monitoring food intake; and optimal timing of food intake in TRE. The fasting regimens are not applicable in patients of diabetes mellitus on hypoglycemic agents. The long-term effect of IF on chronic diseases like diabetes, cardiovascular disease, cancers, and other degenerative disease is currently unclear.

Conclusion

Currently available evidence is insufficient for health-care professionals to recommend IF as standard practice. It is apparent that IF may benefit those who are motivated to lose weight. Any other energy restriction regimen would benefit only the motivated individuals and thus IF is no exception. Evidences in humans suggest that IF may offer greater improvements in body composition, metabolic and inflammatory markers despite similar weight benefits compared to DER. Therefore, currently IF may be advised to motivated individuals as one of the options for CR, bearing in mind that the benefits on weight loss may be similar to DER with possibly better improvement in other metabolic parameters with IF, and also accepting that we have insufficient evidence on its long-term applicability in real world settings or its beneficial effects on long-term chronic obesity outcomes. We may thus conclude that IF is another form of CR. Though it has been hyped by the press and the lay public, the scientific community has the hope and the wisdom to accept its promises and limitations.

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Section 6

Section Editor: **Man Mohan Mehndiratta**

Neurology

CHAPTER

85 Advances in Epilepsy Management and Current Perspectives

Man Mohan Mehndiratta, Natasha Singh Gulati, Vasundhara Aggarwal

Abstract

Epilepsy is common neurological disorder attended in Neurology clinics accounting for ~1% of the global disease burden across all ages. Neurologists worldwide now aim at seizure remission in patients with epilepsy because recurrent seizures lead to significant morbidity and mortality and also affect the quality of life (increased health-care use, unemployment, or even sudden death) of the patient and the caregiver. The first step toward accurate diagnosis, therapy, and prognostication of epilepsy is adequate knowledge of its definition and classification. After the appropriate diagnosis is made the two key questions are what and when to start pharmacological treatment and when is non-pharmacological treatment required. Activity modification and restrictions also play an important role in customized treatment. This chapter provides a useful insight into the current perspectives and recent advances in management of epilepsy.

Introduction

Major advances in epilepsy management have surfaced in recent years. In recent years there have been many improving definitions, guidelines, diagnostic, and treatment protocols that have come to the fore. The causes and consequences of epilepsy have been more deeply explored. It is very important to fine tune our knowledge and keep updated. It's rightly said "Staying Updated Is Our Commitment to Our Patients."

Definition and Classification—Recent Changes

The first step toward accurate diagnosis, therapy, and prognostication of epilepsy is adequate knowledge of its definition and classification. One of the most eminent international organizations dedicated to epilepsy care, education, and research is the International League Against Epilepsy (ILAE). **Table 1** describes the 2014 ILAE Epilepsy Operational (practical) definition.

Seizure is defined as "occurrence of transient signs and/or symptoms due to abnormal excessive or synchronous neuronal activity within the brain."

ILAE published "position papers" on the latest classification of epilepsies and seizures,[2] as well as an "instruction manual" for use of seizures operational classification[3] in 2017. Position paper of the "ILAE Commission for classification and terminology 2017" states a new multilevel Classification **(Fig. 1)**, which requires a diagnosis at all three levels. First of all it is assumed that the patient is having epileptic seizures as defined by the latest 2017 ILAE Seizure Classification. It starts with Level 1: Seizure type diagnosis. The next step is Level 2: Epilepsy type diagnosis, including focal epilepsy, generalized epilepsy, combined generalized, and focal epilepsy, and also an unknown epilepsy group. The next is Level 3: Epilepsy syndrome diagnosis.

It also incorporates and emphasizing the requirement to considering etiology at each step of diagnosis. The *etiology* is broken into six subgroups **(Fig. 2)**, keeping in

TABLE 1 2014 ILAE operational (practical) definition of epilepsy[1]

Epilepsy: A disease of the brain defined by any of the three following conditions			
At least two unprovoked (or reflex) seizures which occur >24 h apart	One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (i.e., at least 60%) after two unprovoked seizures, which can occur over the next 10 years	An epilepsy syndrome diagnos	Epilepsy is considered to be resolved for individuals who have past the applicable age and had age-dependent epilepsy syndrome or individuals who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years

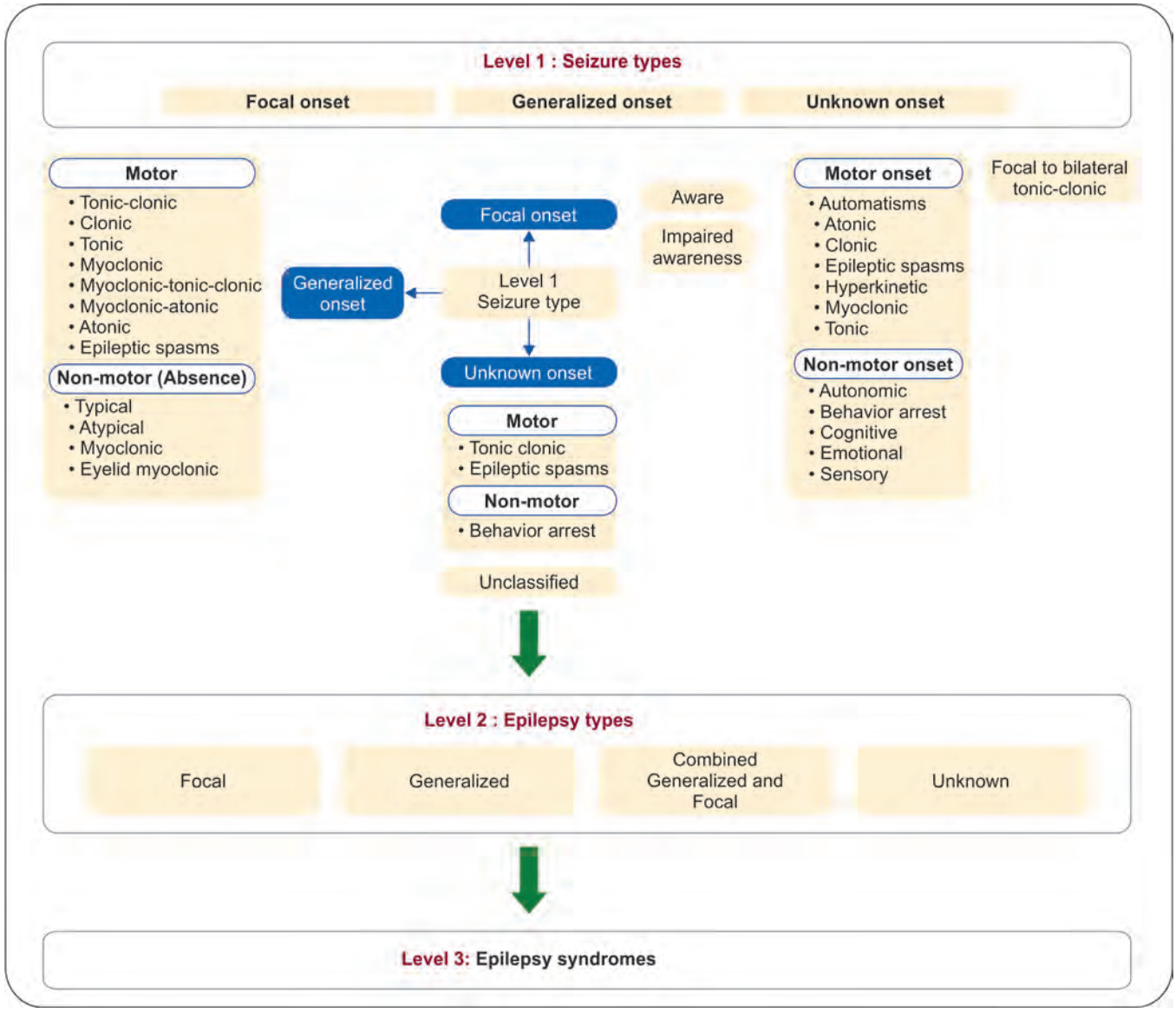

Fig. 1: New multilevel classification of approach to diagnosis of epilepsy

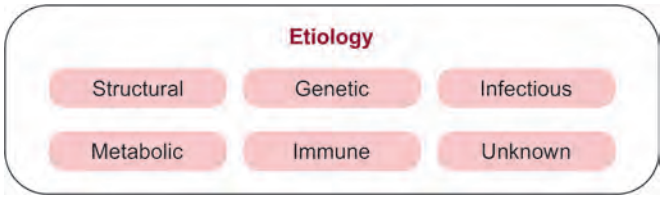

Fig. 2: Six broad subgroups of etiology of epilepsy

mind the possible therapeutic consequences. It lays special emphasis on diagnosing a genetic cause of epilepsy. It also emphasizes to consider *comorbidities* including depression, anxiety, migraine, cognitive impairment, etc., which can affect the progression and management. There are certain drugs to be preferred and avoided in epilepsy with comorbidity. The understanding of etiology and comorbidities will help targeted therapies to the specific type of disease and etiology.[2,4]

New Regarding the Classification of Epilepsy[4]

- Combined generalized and focal epilepsy type added (it cannot be just focal or generalized)
- "Benign" are now termed "self-limiting" or "pharmaco-responsive" (where therapy can spontaneously resolve it)
- New term added epileptic encephalopathy and developmental and epileptic encephalopathy
- Psychosocial and other comorbidities included

New Regarding the Classification of Seizures[3-5]

- Newly added types and terms in ILAE 2017 classification:
  - New focal seizure types include automatisms, autonomic, cognitive, behavior arrest, emotional, sensory, hyperkinetic, and focal to bilateral tonic–clonic seizures. Atonic, clonic, myoclonic, epileptic spasms, and tonic seizures, which can be either generalized or focal.
  - New generalized seizure types include epileptic spasms, absence with eyelid myoclonia, myoclonic–tonic–clonic, myoclonic–atonic, and myoclonic absence.
- The discontinued terms are:
  - Simple/complex partial
  - Convulsions
  - Dyscognitive
  - Psychic
  - Secondarily generalized
- Changed terms:
  - Simple to aware
  - Complex to impaired awareness
  - Partial seizure to focal (onset) seizure
  - Secondarily generalized clonic to focal to bilateral tonic–clonic
  - Hypermotor to hyperkinetic
  - Psychic/experiential to cognitive
- Seizures of unknown onset can still be provisionally classified
- Bilateral versus generalized: The term "bilateral" for tonic–clonic seizures is used when it propagates to both hemispheres and "generalized" for seizures that seemingly originate in both hemispheres simultaneously
- Classifiers used in the classification:
  - Onset:
    - Decides focal/generalized if there is 80% confidence level
    - The first prominent sign/symptom is used to classify seizure type
  - Awareness:
    - Used as classifier of focal seizures
  - Motor/nonmotor
  - Additional descriptors: After classifying seizure type based on initial signs and symptoms, additional descriptions of other signs and symptoms, called as descriptors can be added. However, these do not alter the seizure type.[2-4]

Approach to Management of Epilepsy

Pharmacological Management[6-8]

The mainstays of treatment are anti-epileptic drugs (AEDs). Two key questions "When and What to Start"??

When to Start Antiepileptic Drugs: Treatment Indicated??

Definitions[7]

- Unprovoked seizure can have an unknown etiology or can occur in relation to a preexisting brain lesion or progressive nervous system disorder. In the later cases, it is often referred to as a remote symptomatic seizure.
- Provoked seizures has an acute condition, which provokes seizure such as a head trauma, toxic, or metabolic disturbance or acute stroke (also called acute symptomatic seizures).

First Unprovoked Seizure

- Decision must be individualized and guided by following factors:
  - High seizure recurrence risk of to meet criteria for epilepsy according to ILAE
  - High risk clinical variables
  - Remote symptomatic cause revealed by clinical history or neuroimaging, e.g., brain tumor, head injury with loss of consciousness brain malformation, prior infection of central nervous system, or prior brain injury or brain surgery scar
  - Prior brain insult
  - Epileptiform abnormalities on electroencephalogram (EEG)
  - Significant abnormality on brain imaging
  - Nocturnal seizure
  - Abnormal focal findings and intellectual disability on neurologic examination
  - Significant side effect profiles in individual patient comorbidities and age
  - Social consequences

What to Start: Which and How Many Antiepileptic Drugs

Start with a single AED introduced at a small dose (except status epilepticus or frequent seizures). Monotherapy advantages being:

- avoids drug interactions
- decreases the likelihood of adverse effects
- less cost than polytherapy

The dose is then gradually increased to the lowest effective maintenance dose.

The drug is to be tailored to *factors such as disease related factors, drug related factors and individual person characteristics*—No single AED that is ideal for all patients.

First generation AEDs remain valuable first-line therapies, which are discussed in **Table 2**.

Second generation AEDs **(Table 3)** offer advantages in terms of drug resistance, fewer drug interactions, and improved tolerability and tailoring treatment **(Table 3)**.

AEDs can also be divided based on their mechanisms as given in **Table 4**.

Example: If first generation AED carbamazepine fails to control the seizures then second generation AED like lamotrigine, topiramate, tiagabine, gabapentin, levetiracetam, oxcarbazepine, pregabalin, and zonisamide can be considered (new anticonvulsants are generally considered second-line therapy, however, can be used as first-line therapy in some patients).

TABLE 2 First generation AEDs[6]

First generation AEDs	• Valproic acid
	• Benzodiazepines
	• Phenobarbital
	• Primidone
	• Carbamazepine
	• Phenytoin
	• Ethosuximide

TABLE 3 Second generation AEDs[6]

Second generation AEDs	• Lamotrigine
	• Levetiracetam
	• Topiramate
	• Zonisamide
	• Oxcarbazepine
	• Perampanel
	• Vigabatrin
	• Rufinamide
	• Felbamate
	• Eslicarbazepine acetate
	• Lacosamide
	• Pregabalin
	• Gabapentin
	• Tiagabine
	• Brivaracetam
	• Everolimus
	• Stiripentol

If seizures persist on the first AED despite optimal up-titration to the maximally tolerated dose, exclude non-compliance and reappraise the diagnosis and treatment.

If an AED change is required switch to an alternative monotherapy.

Polytherapy is usually offered after failure of two or three sequential monotherapies (except in a difficult to treat form of epilepsy unlikely to respond fully to monotherapy).

Drug Resistant Epilepsy: ILAE defines drug-resistant epilepsy as "failure of adequate trials of two tolerated,

TABLE 4 AEDs based on mechanism of action[8]

Mechanism	*Name*
Drugs Blocking repetitive activation of the sodium channel	Phenytoin, oxcarbazepine, carbamazepine, eslicarbazepine, topiramate, lamotrigine, cenobamate
Drugs Enhancing slow inactivation of the sodium channel	Lacosamide, rufinamide
Drugs blocking N-methyl-D-aspartic acid (NMDA) receptor	Felbamate
Drugs enhancing Gamma-aminobutyric acid (GABA)–A receptor	Phenobarbital, clobazam, and benzodiazepines
Drugs blocking T-calcium channel	Ethosuximide, valproate
Drugs blocking Alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor	Perampanel and topiramate
Drugs modulating H-current	Gabapentin and lamotrigine
Drugs blocking N- and L-calcium channel	Lamotrigine, zonisamide, topiramate, and valproate
Drugs Blocking unique binding sites	Gabapentin, perampanel and levetiracetam
Neuronal potassium channel (KCNQ [Kv7]) opener drugs	Ezogabine
Carbonic anhydrase inhibitors drugs	Topiramate, zonisamide
Other anticonvulsants	Cannabidiol, stiripentol

appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained freedom from seizures."

Factors Influencing Choice of AEDs

Disease-related Factors: Anticonvulsants for Specific Seizure Types[8]

- Ethosuximide—For absence seizures alone
- Valproic acid or lamotrigine, or topiramate—If other seizure types along with absence seizures (e.g., generalized tonic–clonic seizures, myoclonic seizures)
  (Caution: Drugs may exacerbate absence seizures—carbamazepine, gabapentin, or tiagabine)
- Broad-spectrum AEDs—Lennox-Gastaut syndrome with seizures
- Adjunctive therapy with rufinamide, clobazam, extended-release topiramate, cannabidiol and stiripentol—Seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex
- Valproic acid, lamotrigine, and topiramate—Juvenile myoclonic epilepsy JME and myoclonic seizures—(JME has a high recurrence rate)
- Levetiracetam—As adjunctive therapy of JME
- Valproic acid, topiramate, or lamotrigine and adjunctive therapy with Levetiracetam, perampanel—Primary generalized tonic–clonic seizures
- Valproate should remain the drug of first choice for generalized and unclassified epilepsies except in women of childbearing age
- Monotherapy with carbamazepine, cenobamate, lacosamide, lamotrigine, oxcarbazepine, and topiramate adjunctive therapy with levetiracetam, tiagabine, gabapentin, pregabalin, lacosamide, cenobamate, or ezogabine—Focal-onset seizures
- Lamotrigine—First line in elderly subjects (patients aged ≥60 years)

Standard and New Antiepileptic Drugs (SANAD) Trial

The largest individual randomized trial examining different antiseizure drugs as monotherapy for the initial management of epilepsy **(Fig. 3)**.

Drug-related Factors[7]

See **Box 1**.

Individual-related Factors[8]

Specific patient populations and conditions-related considerations

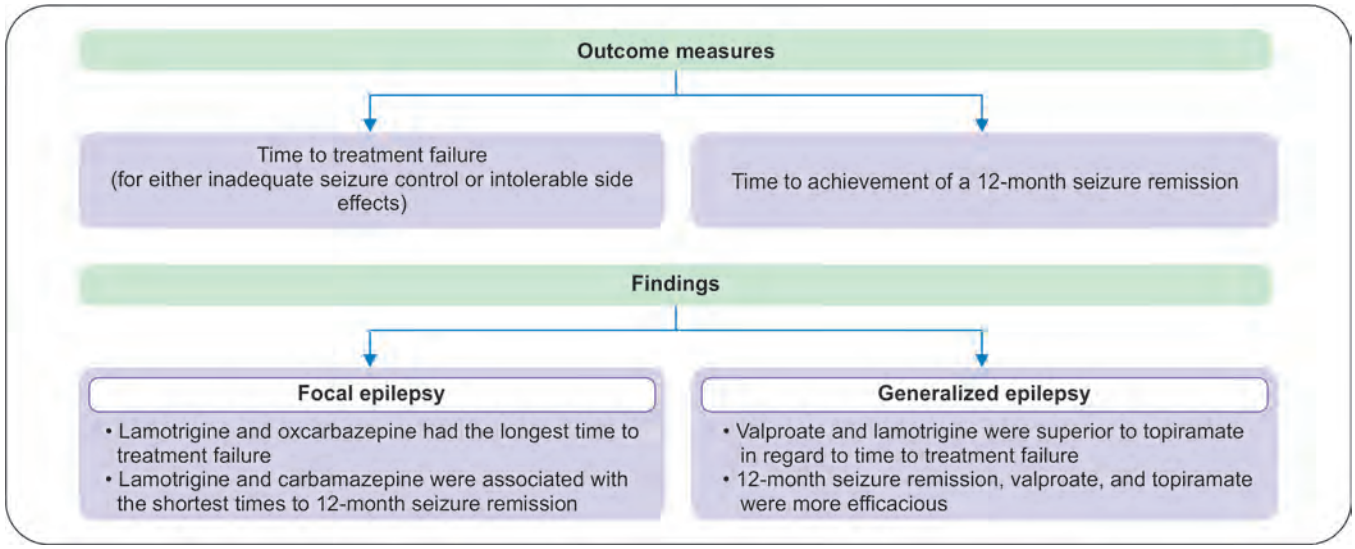

Fig. 3: SANAD trail

BOX 1 Drug-related factors influencing choice of AEDs

- Comparative efficacy
- Dosing frequency
- Drug interactions
- Aging
- Neuro-cognitive side effects
- Hypersensitivity reactions; Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
- Suicidality
- Weight loss or gain
- FDA indications
- Cost of medications

- Neonates and children:
- Adjust doses per kg body weight
- Tend to metabolize the drugs quicker
- Rapid rise in the total volume of distribution

Elderly patients: Need less initial dose and maintenance doses because of slow hepatic metabolism, decreased renal clearance and decreased volumes of distribution.

Women on oral contraceptive pills:

- AEDs that induce hepatic enzyme decrease the efficacy of oral contraceptive pills—carbamazepine, phenytoin, primidone, felbamate, phenobarbital, lamotrigine, topiramate, and oxcarbazepine.
- High-dose estrogen-progesterone contraceptive can be administered to counteract this effect.
- Can use alternative method of contraception.

Women of childbearing age and pregnant women:

- Obstetric complications, changes in seizure frequency, teratogenesis, vitamin K, folic acid, blood levels of AEDs, and breastfeeding are nicely covered in 2009 new guidelines for the management of antiepileptic drugs (AEDs) during pregnancy by the American Academy of Neurology and the American Epilepsy Society.
- Not recommended: Switching medications during pregnancy and polypharmacy.
- Drug serum levels should be obtained frequently.

Renal insufficiency:

- Gabapentin, zonisamide, oxcarbazepine, levetiracetam, lacosamide, and pregabalin doses should be altered as they are excreted mostly by means of renal clearance.
- Nephrolithiasis could be associated with topiramate and zonisamide.

Hepatic disease:

- In patients with chronic liver disease, levetiracetam, pregabalin, gabapentin, and vigabatrin as they do not undergo hepatic metabolism.

- Phenytoin, valproic acid, carbamazepine, and felbamate should be used with caution as they have been associated with acute hepatic injury.[7,8]

Post-stroke epilepsy: Consider impact of the antiseizure drug on post-stroke functional recovery and the potential for drug interactions with warfarin and salicylates.

Brain tumors: Consider possible drug interactions with chemotherapeutic agents and increased possibility for allergic cutaneous reactions during radiotherapy.

Psychiatric disorders:
- Depression correlates more strongly with a poor quality of life than the frequency of the seizures.
- Some AEDs also appear to have mood stabilizing properties while some AEDs cause or exacerbate a depressed mood.

Migraine: Valproate, gabapentin, and topiramate are antiseizure drugs that have demonstrated efficacy for migraine prevention in placebo-controlled trials.

Osteoporosis risk: AEDs in chronic use have been associated with bone loss. Moreover seizures are also associated with falls and associated bone fractures. Monitor bone density, routinely supplement vitamin D, and calcium. A consistent exercise regimen is also required.[7]

Discontinuing AEDs

After an individual has been seizure free for typically 2–5 years, many consider discontinuing AEDs. Patients with juvenile myoclonic epilepsy (JME) have high recurrence rate (of about 80–90%) during adulthood.

Risks of Seizure Recurrence

After drug discontinuation, risk of relapse increase if there are:
- Abnormalities on imaging such as on brain MRI scan and epileptiform or focal abnormalities on an EEG
- Higher number and frequency of seizures
- Longer duration of epilepsy before the seizures-free period
- Specific seizure type, e.g., tonic or atonic seizures
- Shorter duration of freedom from seizure

During tapering AEDs and for at least for first 3 months after discontinuation of AEDs, advise patients to observe strict activity and lifestyle precautions (e.g., not to drive, etc.)

Non-pharmacological Therapy

There have been rapid advances in surgical technology and neuroimaging and parallel understanding of developments in epilepsy neurobiology.

Surgical Procedures

The types of surgery performed in patients for refractory epilepsy include:

Anterior temporal lobectomy (ATL): Most common surgical procedures performed in temporal lobe epilepsy in adolescents and adults.

Extratemporal resection: In early childhood, this is the most common type of surgery performed with etiologies being cortical development malformations, vascular malformations, and tumors.

Lesionectomy: Lesionectomy involves the resection of circumscribed epileptogenic lesions, including tumors, vascular malformations, and well-delineated malformations of cortical development.

Hemispherectomy: When little or no functional cortex remains and the entire hemisphere is considered epileptogenic. For example, in Rasmussen's encephalitis, Sturge-Weber syndrome or large hemispheric infarction.

Corpus callosotomy (CC): The procedure is performed in patients with symptomatic generalized epilepsy who are poor candidates for resective surgery. Occasionally done in frequent secondary generalized tonic–clonic, tonic and atonic seizure leading to falls and injuries.

Multiple subpial transection (MST): Occasionally used in focal epilepsy arising in or around eloquent areas.

Thermal ablation: Minimally invasive type of laser surgery. Laser destroys the small well-defined focal point of seizure in brain tissue without damaging the surrounding tissue.

Devices for Brain Stimulation

Intracranial systems (implant device): Deep brain stimulation (DBS) and Responsive neurostimulation (RNS)

Extracranial systems:
- Focal cooling and uncaging
- RTM—Repetitive Transcranial Magnetic Stimulation

- TDC—Transcranial Direct Current Stimulation
- TNS—Trigeminal Nerve Stimulation
- VNS—Vagus Nerve Stimulation

Devices Detecting Seizures

Helps in alerting the individual and their care givers and thus helps in monitoring and managing the seizure behavior. However, these devices also have their own limitations:

- Wearable device—Accelerometer, Medpage ST-2, SeizAlert, Protective Headwears
- Sensor implant device—BrainGate™ Neural Interface System
- Mobile-phone-based device—Epdetect and Epilert
- Watch-based device—SmartWatch Alert
- Software-based multichannel sensor device—NeuroPort System
- Cortical stimulators and mapping—Rehabilicare
- Working mats—Safety Place Mat®

Devices for Surgery

Include Cyber knife®, Functional MRI, Gamma knife®, High-resolution brain Single-photon emission computed tomography (SPECT), Magnetoencephalography, Near-Infrared Spectroscopy (NIRS), Signal Modeling For Real-Time Identification And Event Detection (SIGFRIED), and Tractography and diffusion tensor imaging.

Responsive neurostimulation (RNS) **(Fig. 4)** is the first generation "closed loop" device using Brain Computer interface (BCI). The device is set to particular EEG (depending on the patients individual EEG) and whenever there is a seizure the implant helps to detect and record the EEG pattern. It then sends an electrical signal to disrupt that pattern of seizure activity. The FDA in November 2013, approved the NeuroPace RNS System for the controlling seizures in patients with drug-resistant epilepsy particularly partial-onset epilepsy.

Transcranial magnetic stimulation (TMS) is another method for brain stimulation magnetic field induced brain currents were introduced with the help of magnetic stimulator coil from a safe distance to stimulate focally and deeply in the brain tissues.

Vagal Nerve Stimulation (VNS) is FDA approved in patients above 12 years of age to treat medically refractory focal-onset epilepsy. Candidates for VNS should meet the following criteria:

- Medically refractory seizures.

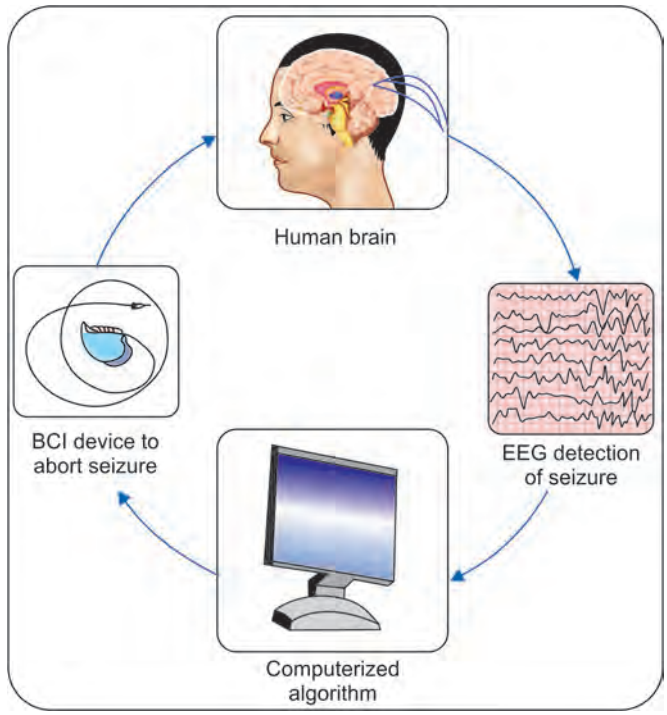

Fig. 4: Responsive neurostimulation (RNS)

- Adequate trials of at least 2 or 3 AEDs (preferably with different mechanism of action).
- Exclusion of nonepileptic events.
- Not a good candidate for epilepsy surgery.

If the patient is a good candidate for focal resective surgery, then it should be preferred over VNS, as this procedure has a superior seizure free rate.

The noninvasive brain stimulation technique of VNS is transcutaneous vagus nerve stimulation (tVNS). It uses a bipolar electrode (external device) to stimulate the left auricular branch of the vagus nerve at the ear conch. It is a newly developed CE (Cerbomed GmbH, Erlangen, Germany) certified tVNS (NEMOS®) device.

Radiosurgery

Radiosurgery is also an alternative to drug resistant epilepsy and other epilepsy surgeries. For example, CyberKnife® and Gamma Knife®. However, due to the radiosensitivity, the safety of the normal tissues around the lesion is at risk.

Diet Therapy

Ketogenic diet (KD): In patients with drug-resistant epilepsy and where surgery is not feasible, Ketogenic diet

consisting of high fat and low carbohydrates and proteins, i.e., 3:1 or 4:1 (fat:carbohydrate and protein) ratio by weight can be given.

Modified atkins diet (MAD): It is a modified traditional KD. Here diet consists of approximately 1:1 (fat:carbohydrate and protein) weight ratio. It is preferred as it is more palatable and less complex compared to KD. Efficacy in children with drug resistant epilepsy is similar to KD.

Software

Analysis of user defined seizure events logged in a database over a given time period and converting it into reports and graphs leading to high-tech seizure pattern analysis. Many software tools are presently available. For example, include EpiTrax, eemagine EEG, Epivista, Epilexia, iPlan® Net, IdentEvent™, Leonardo Brainmap, Neuroport Software System, NeuroScore NeuroGuide Deluxe QEEG 2.5.5, Net Station 4.3 and many more.[9]

Activity Modification and Restrictions

Seizure Lifestyle Precautions

Driving Motorized Vehicles

Driving laws vary from country to country. Generally it is not advisable for persons with epilepsy to drive during the first 2 years of treatment. The USA permits a person to drive if she/he is seizure free between 3 and 18 months. In the UK, a driving license can be granted if a person is seizure free for 1 year. In Australia, driving licenses are issued to those who've been seizure-free for a period of 6 months to 2 years. As of today, the Government of India has no provision to issue special driving licenses to People with Epilepsy (PWE), no matter how long they have been seizure free.[10]

Water Precautions

PWE should not swim alone, have adult lifeguard while swimming, and wear a lifejacket on a boat. Even a simple task of taking bath may be risky.

Heights, Fire, and Power Tools

Use of safety devices for example. Having automatic shut-off switch in operating these tools is recommended.[8]

Epilepsy and Law

A book was published jointly by the Indian Epilepsy Association and the Indian Epilepsy Society in 2017.[10]

Conclusion

Epilepsy is a complex neurological disorder with complex pathogenesis. Understanding the updated definitions and classifications and the advanced pharmacological and non-pharmacological approach for its treatment will definitely improve the patient care. Introducing activity modification and restrictions in the treatment protocol will help in customized care of clinical condition of the patient. What we know till date is just the tip of the iceberg. Despite all the ongoing researches, any definitive curative treatment is still a remote possibility. We have miles to go before we relax.

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CHAPTER

86 Emerging Concepts in Anti-MOG Syndrome

MK Roy, Hema Krishna P

Abstract

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein present on the surface of myelin sheath. It accounts to only 0.5% of the central nervous system (CNS) myelin sheath and is present only in the CNS. It is considered to have a role in regulating microtubule stability of oligodendrocytes, mediate complement cascade and also help in adhesion of myelin fibers. In spite of its very low concentration, its highly immunogenic nature and presence on surface of myelin sheath make it an easy target to antibodies in CNS autoimmune responses.

MOG antibodies were a topic of interest for past three decades and their role in CNS inflammatory diseases has been supported by their detection in sera and cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients using ELISA and Western blot. Thus, these were thought to be involved mainly in MS pathophysiology. These techniques used denatured MOG peptides as antigens. However, recent techniques using cell based assays showed strong association of antibodies to intact, full length human MOG protein with recurrent optic neuritis, myelitis and brainstem encephalitis like presentations than with classic MS. This has led to the recognition of a new entity, MOG antibody disease (MOG-AD) in patients who have clinical phenotype not fitting into either classic MS or Neuromyelitis optica (NMO), but testing positive for MOG-IgG antibodies. While NMOSD is an astrocytopathy, MOG-AD is a disorder of oligodendrocytes wherein astrocytes are typically spared. Though there is significant clinical and radiological overlap between (MOG-AD) and other related CNS demyelinating disorders like MS and Aquaporin 4 positive NMO, it is important to distinguish these in view of different therapeutic and prognostic implications.

Introduction

We, as treating physicians, are well acquainted with acquired inflammatory demyelinating disease called multiple sclerosis (MS). However, there has been a sea change in our present understanding of demyelinating disorders due to emergence of newer entities, especially Myelin oligodendrocyte glycoprotein associated disease (MOG-AD).[1] It is important to identify this as a distinct clinical entity in view of its different therapeutic and prognostic implications.[2]

Clinical Significance

MS and MOG-AD have considerable features in common like relapsing course,[3] certain radiological features, and in fact in adults with MOG-AD, about 33% meet McDonald's criteria for MS at least once during disease course,[4] leading to misdiagnosis and thus have serious therapeutic consequences as many drugs used for MS are ineffective and at times leads to clinical worsening in a case of MOG-AD. Thus, patients with suspected MS with worsening on treatment need to be screened for MOG-IgG. Early identification of MOG-AD is important because:

- Few drugs approved in MS (interferon beta, natalizumab, fingolimod) can actually be harmful in MOG-AD.[3,5]
- Immunopathogenesis for MOG-AD is different from MS.
- MOG-AD requires high dose steroids and careful and slow steroid taper (high risk of flare up).[6]

- In MOG-AD, for:
  - *Acute attacks:* antibody depleting treatments are very effective (plasma exchange;[3] IVIG in children).
  - *Long term:* B-cell targeted therapy (Rituximab).

Evolving Spectrum of Demyelinating Disorders of CNS (Fig. 1)

Based on site of involvement, clinical, radiological and serological findings, central nervous system (CNS) demyelinating disorders are classified as:[2]

Types of acquired demyelinating diseases are depicted in **Flowchart 1**.

MOG-AD: Pathophysiology

MOG is a glycoprotein of immunoglobulin superfamily presents exclusively in CNS and many of its epitopes are highly immunogenic. Several studies revealed that T cell/B cell cooperation is an important factor in pathogenesis of CNS autoimmunity. During ongoing inflammation, immune cells enter CNS and recognize CNS MOG and export antigen recognition and expose these antigens to peripheral immune system while draining to cervical lymph nodes. This results in MOG antibody production by peripheral B cells, which further trigger new waves of CNS infiltration.[8] Pathologically, there is inflammation and myelin destruction with astrocytes being spared (unlike in NMOSD), as evidenced by CSF analysis (elevated MBP, absence of GFAP). Brain biopsy showed demyelinating lesions with marked infiltration of T cells and macrophages (with myelin degradation products) with preserved astrocytes and axons along with B-cell infiltration and IgG and complement deposition consistent with pattern II MS lesions.[9]

Prevalence

The exact incidence and prevalence of MOG-AD is yet to be elucidated. However, studies showed that it constituted 7.4% of all NMOSD, 6.3% of inflammatory demyelinating diseases of CNS.[10] Among AQP4-IgG negative patients with bilateral and recurrent ON, 40% were MOG-IgG positive

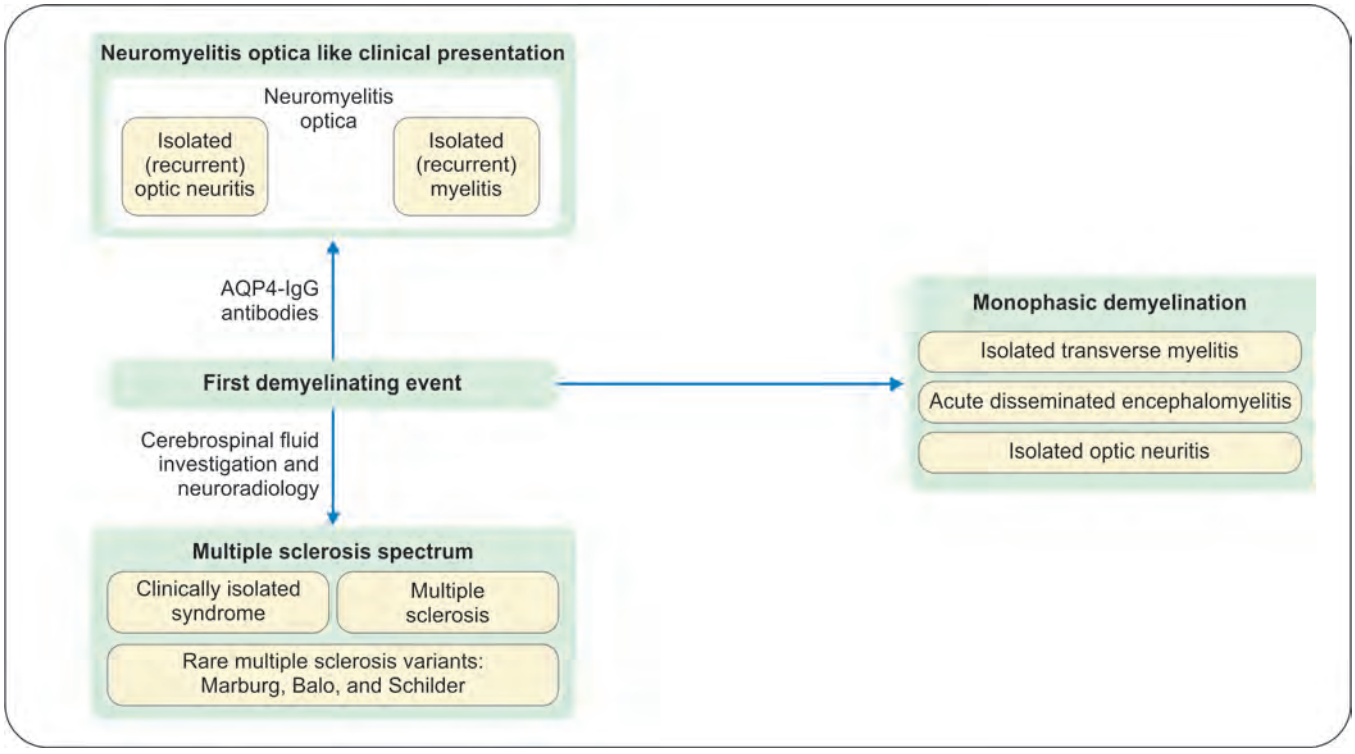
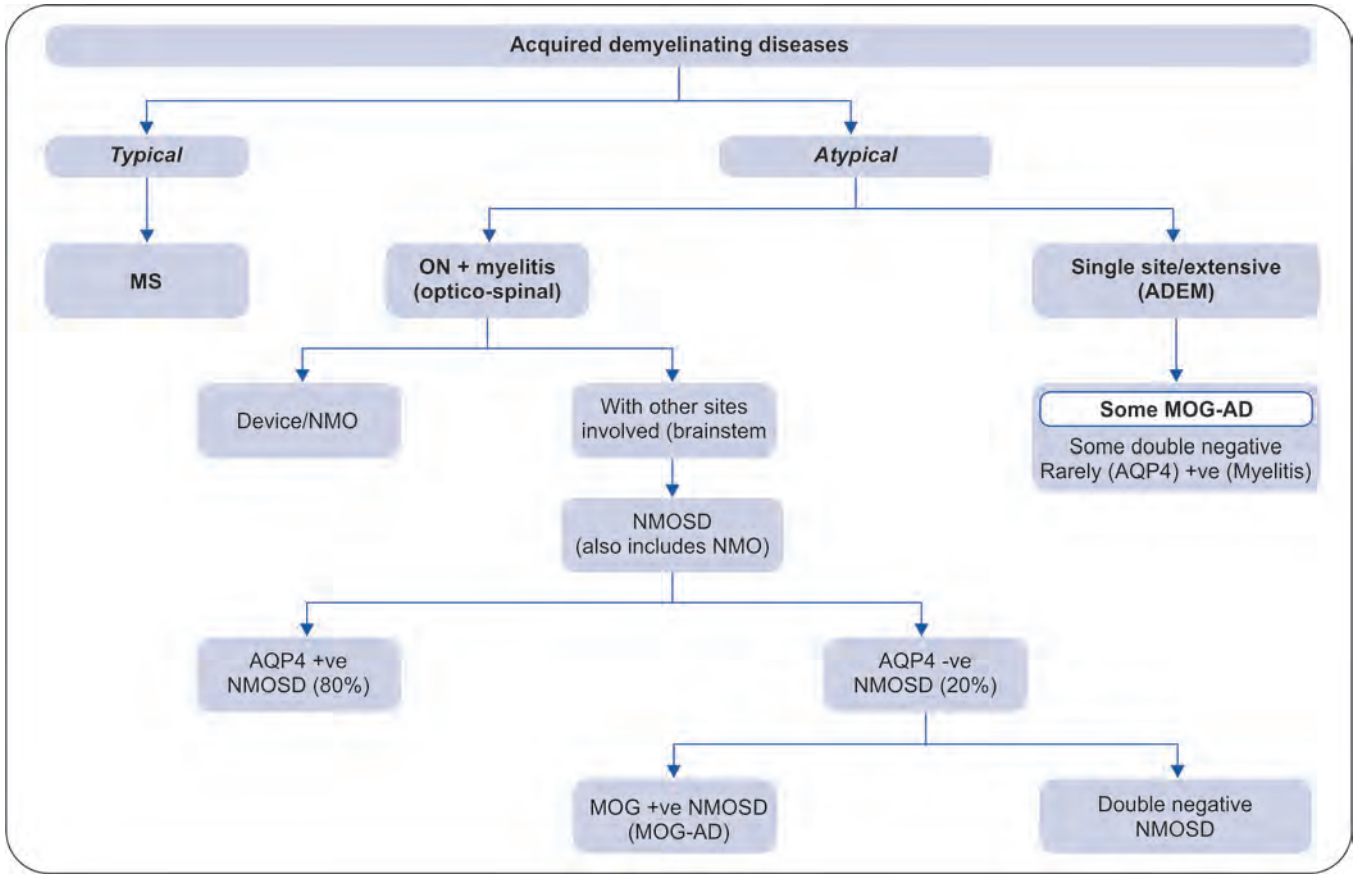


Fig. 1: Spectrum of acquired CNS inflammatory demyelinating diseases[3,7]

Flowchart 1: Types of acquired demyelinating diseases



and with respect to LETM, 7.4–23.2% had MOG antibody.[2] The prevalence among children was higher constituting 50% of definite NMO cases and 80% of recurrent optic neuritis.[11]

Demographics

MOG-AD is relatively more common in males compared to NMOSD with a female to male ratio of 2.8:1 vs. 9:1 in NMOSD.[1] It has no predilection to specific ethnic groups; however, few studies showed higher occurrence among Caucasians. It is more common among children and young adults (third decade), although any age can be affected.

Clinical Phenotype

Most of MOG antibody positive patients have optic neuritis, encephalitis with brain demyelinating lesions and/or myelitis, which lead to a new term MOG-IgG-associated ON, encephalitis, and myelitis (MONEM).[12] ON is the most common phenotype (41–63%),[3] followed by LETM (29–31%), NMO (6–24%), and encephalomyelitis (2–6%).[2] Also, concomitant occurrence of both ON and transverse myelitis is more common in MOG-AD than AQP4-IgG patients. Overall, MOG-AD patients have a favorable prognosis compared to MS and AQP4-NMOSD patients **(Fig. 2)**.

ADEM, Acute disseminated encephalomyelitis; AQP4-NMOSD, Aquaporin 4 positive neuromyelitis optica spectrum disorder; LETM, Longitudinally extensive transverse myelitis; MY, Myelitis; ON, Optic neuritis

Clinical Features

A preceeding infectious prodrome occurs in many cases in the form of fever, malaise, cough, and rhinorrhea. Though most of cases occur without any predisposing events, post-infectious demyelination after HSV, Borrelia,

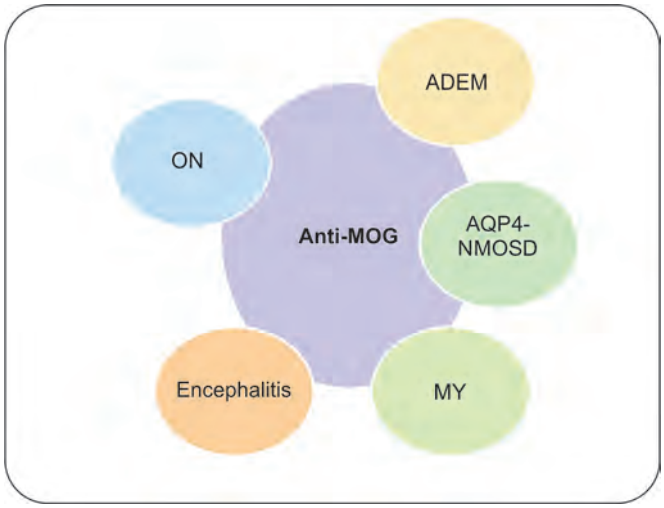


Fig. 2: Clinical phenotypes of MONEM[12]

and EBV have been seen. Studies have described cases of LETM after influenza infection, vaccination, and ADEM after infectious mononucleosis. However, whether these are causative or silent bystanders are yet to be established.

Some patients have a monophasic illness while others may have a relapsing course. Relapse occurs in 44–83% of patients and is mostly optic neuritis. Studies have shown that MOG-AD has higher percentage of single attacks and few relapses compared to AQP4-NMOSD.[2] Also, median time for second attack was longer in MOG-AD (11.3 years vs. 3.2 years in AQP4-NMOSD).[13] Common clinical manifestations of MOG-AD include:

- Optic neuritis:
  - Though unilateral ON is a more common presentation, 30–50% of MOG-AD patients have bilateral ON (bilateral ON is less common in AQP4-NMOSD, rare in MS).
  - Characterstic feature is significant optic disc edema in almost 86% of cases with more than 50% optic nerve affection (anterior part) and relative sparing of optic chiasma.[14]
  - It has better visual outcomes compared to AQP4-NMOSD, though recurrence of ON is more frequent in MOD-AD.
  - Some patients may develop steroid dependent optic nerve involvement called chronic relapsing inflammatory optic neuropathy.
- Myelitis:
  - Typically causes LETM (involving >3 vertebral segments) in almost two-thirds of cases. Short segment involvement is seen in one third of cases especially in elderly. Usually, motor symptoms predominate. Severity of myelitis is more than MS but less than AQP4-NMOSD.
  - Preferential involvement of thoracolumbar and Conus[2] (explains disproportionate sphincter and erectile dysfunction) region occurs.
  - Central/lateral cord lesion.
  - Clinically may resemble enterovirus associated acute flaccid myelitis.
  - Recurrent LETM is rare (<2%).[2]
  - TM at onset is the most important predictor of long term disability.
- ADEM/ADEM like:
  - More common in children. Can occur at onset in up to 18% of patients.
  - MOG antibodies are present in almost 50% of all multiphasic ADEM patients.[1]
- Brainstem syndrome:
  - Area postrema syndrome presenting as intractable nausea and vomiting is less common than in AQP4-NMOSD.
  - Can be seen in 6–15% of cases.[2]
- Cortical encephalitis:
  - It is a less common presentation and is usually due to unilateral mild edematous cortical lesion best seen on FLAIR sequences.
  - Patient may present with seizures, abnormal behavior or focal symptoms and it has a very good prognosis **(Fig. 3)**.[1]

Diagnosis

Imaging: MRI

Optic nerve:

- During ON, orbital MRI with coronal T2 fat suppressed images shows extensive anterior optic nerve segment T2 hyperintensity (sparing optic chiasma and retrochiasmatic parts) with evidence of optic disc edema.[15]
- Inflammation and enhancement of perioptic nerve sheath is seen in one third of cases **(Figs. 4A and B)**.

Spinal cord:

- During myelitis, may show evidence of LETM (T2 hyperintensity involving ≥3 vertebral segments lengthwise and >50% of the axial section of the medullary cord). Cloud like heterogeneous enhancement may be noted.

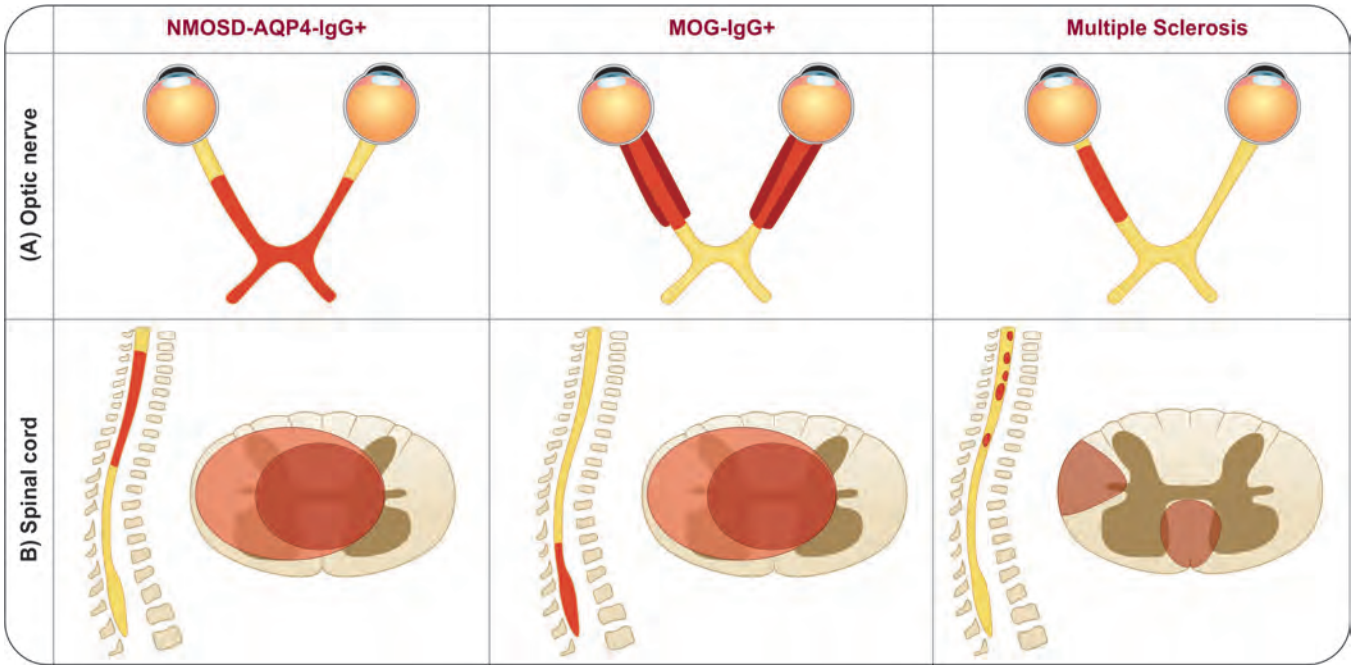
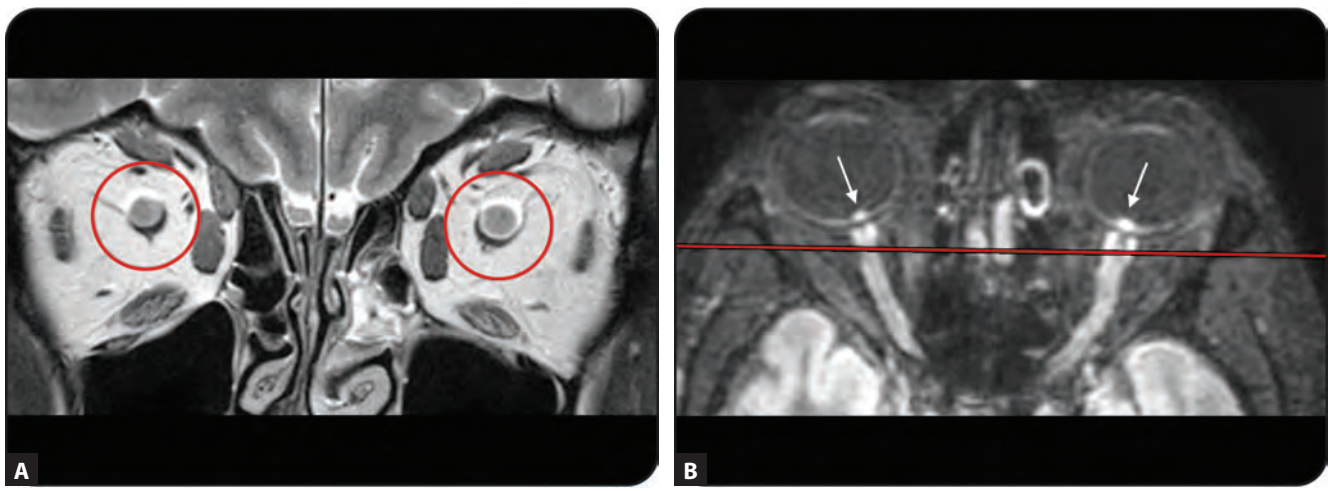


Fig. 3: Comparitive patterns and sites of involvement. AQP4-NMOSD: Bilateral, long segment, posterior optic nerve involvement involving optic chiasma; central/gray mater, complete, LETM, thoracolumbar cord involvement. MOG-AD: Bilateral, long segment, anterior optic nerve involvement including optic nerve head, sparing optic chiasma; central/lateral, complete, LETM, consu involvement is characteristic. MS: Unilateral, short segment optic nerve involvement, frequent chiasmal involvement; peripheral, short, partial, multiple cordlesions

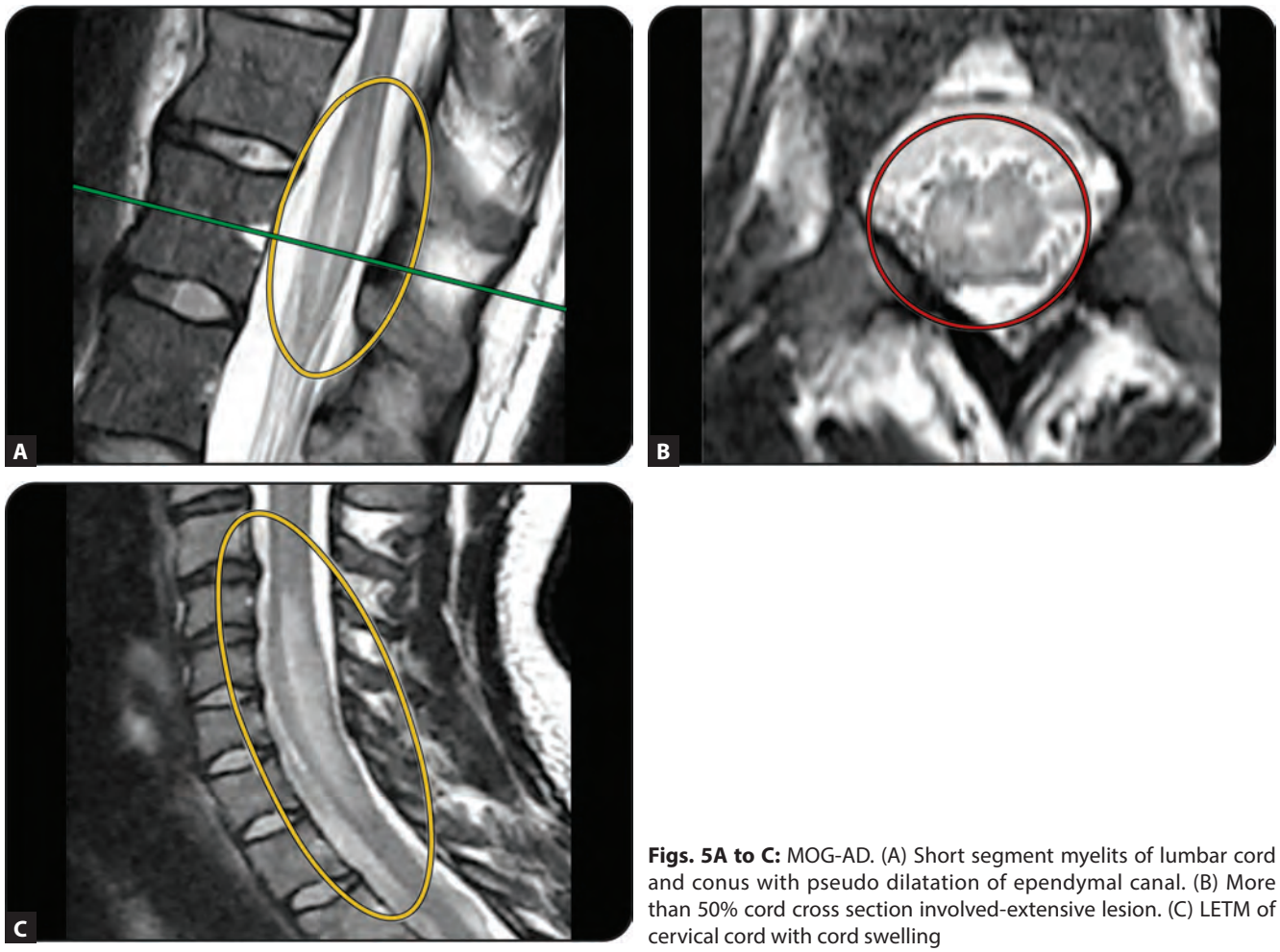


Figs. 4A and B: MOG-AD patient with bilateral optic neuritis. (A) Bilateral optic nerve swelling, (B) Longitudinaly extensive ON withoptic nerve head swelling (arrows)

- Short lesions involving less than 2 vertebral segments can be seen especially in elderly. Conus involvement is highly specific for MOG-AD.[16]
- Lesions are usually central and associated with cord swelling.

Brain:

- It is abnormal in 45% of cases at onset of disease.[16] Lesions are usually bilateral and fluffy.
- Thalamic and pontine lesions are common, subtentorial (brainstem) in one third of cases.



Figs. 5A to C: MOG-AD. (A) Short segment myelits of lumbar cord and conus with pseudo dilatation of ependymal canal. (B) More than 50% cord cross section involved-extensive lesion. (C) LETM of cervical cord with cord swelling

- Dawson's fingers, U shaped ovoid lesions close to body of lateral ventricle are less common **(Figs. 5A to C)**.

CSF

CSF findings during an acute attack are variable:

- 50% of the patients have elevated white cell counts (in 5–10%, lymphocyte count can be 100–300 cells/μL) and an elevated CSF protein (>1 g/L in 10%).
- 10% of patients have an elevated protein with normal white cell count.
- Oligoclonal bands are less common (6–17% of patients).[1]

Serum

- IgG MOG antibody tests should be done only in selected patients with clinical and paraclinical features of MOG-AD, in view of chance of false positivity.
- A cell based assay using full length human MOG as target antigen is preferred.

Biposy

Biopsy findings suggestive of pattern II MS lesions can be noted, but not commonly performed.

Diagnostic Criteria (International Panel of Experts—Jarius et al.)[17,18]

MOG-related disorders should be diagnosed in patients who meet all of the following criteria:

- Monophasic or relapsing acute ON, myelitis, brainstem encephalitis, or any combination of these symptoms.
- MRI or electrophysiological (visual evoked potentials in patients with isolated ON) findings compatible with CNS demyelination.

TABLE 1 When to test for MOG antibody[19]

Test if	• Clinical/paraclinical feartures are suggestive of MOG-AD (2018 International Recommendations) • Diagnosis of MS is made, interferon beta or natalizumab has been started, but efficacy is unexpectedly poor and clinical/paraclinical features are compatible with MOG-AD
Retest if	• MOG antibody positive, but clinical/paraclinical features not suggestive of MOG-AD (red flags) • Clinical/paraclinical features continue to be suggestive of MOG-AD, but MOG antibody is negative • Likelihood of further events is sought, after diagnosis of MOG-AD

TABLE 2 'Red flags'—conditions that suggest probable false positive result and thus should be retested with a different cell-based assay[3]

Disease course
• Chronic progessive disease (rare in MOG-AD), including SPMS (especially SPMS without relapses) and PPMS • Sudden symptom onset e.g., <4 h from onset to maximum (ischemic cause), or continuous worsening over weeks (tumor, sarcoidosis, etc.)
MRI
• Lesion adjacent to lateral ventricle that is ovoid/round or associated with an inferior temporal lobe lesion, or Dawson's fingers • Active brain MRI over time with silent increase in lesion burden between relapses
CSF
• Bi or trispecif MRZ reactions (MS)
Serology
• MOG-IgG levels at or just barely above the assay-specific cut-off, especially if clinical picture is atypical • Positive MOG-IgM and/or MOG-IgA result with negative MOG-IgG (? significance) • MOG-IgG positivity in the CSF but not in the serum (MOG-IgG is produced extrathecally) • AQP-4 IgG/MOG-Ifg "double-positive" test results (extremly rare; should retest for both antibodies)
Others
• Clinical or paraclinical findings suggesting diagnoses other than MOG-EM, NMOSD, or MS (e.g., neurotuberculosis, neuroborreliosis, neurosyphilis, neurosarcoidosis, Behcet syndrome, SACD, Leber's hereditary optic neuropathy, vasculitis, CNS lymphomoa, gliomatosis cerebri, paraneoplasmic neurological disorders, PRES, PML, and evidence for CNS infection) • Combined central and peripheral demyellination (MOG is not expressed in the PNS)

MRZ, Measles, Rubella, Zoster virus

- Seropositivity for MOG-IgG as detected by means of a cell-based assay employing full length human MOG as target antigen.

Treatment-related indications for testing: Particularly good response to antibody depleting therapies (PEX), immunoadsorption (IA), and B-cell depleting therapies (rituximab, ocrelizumab, and ofatumumab), but relapse immediately after reoccurrence of B cells.

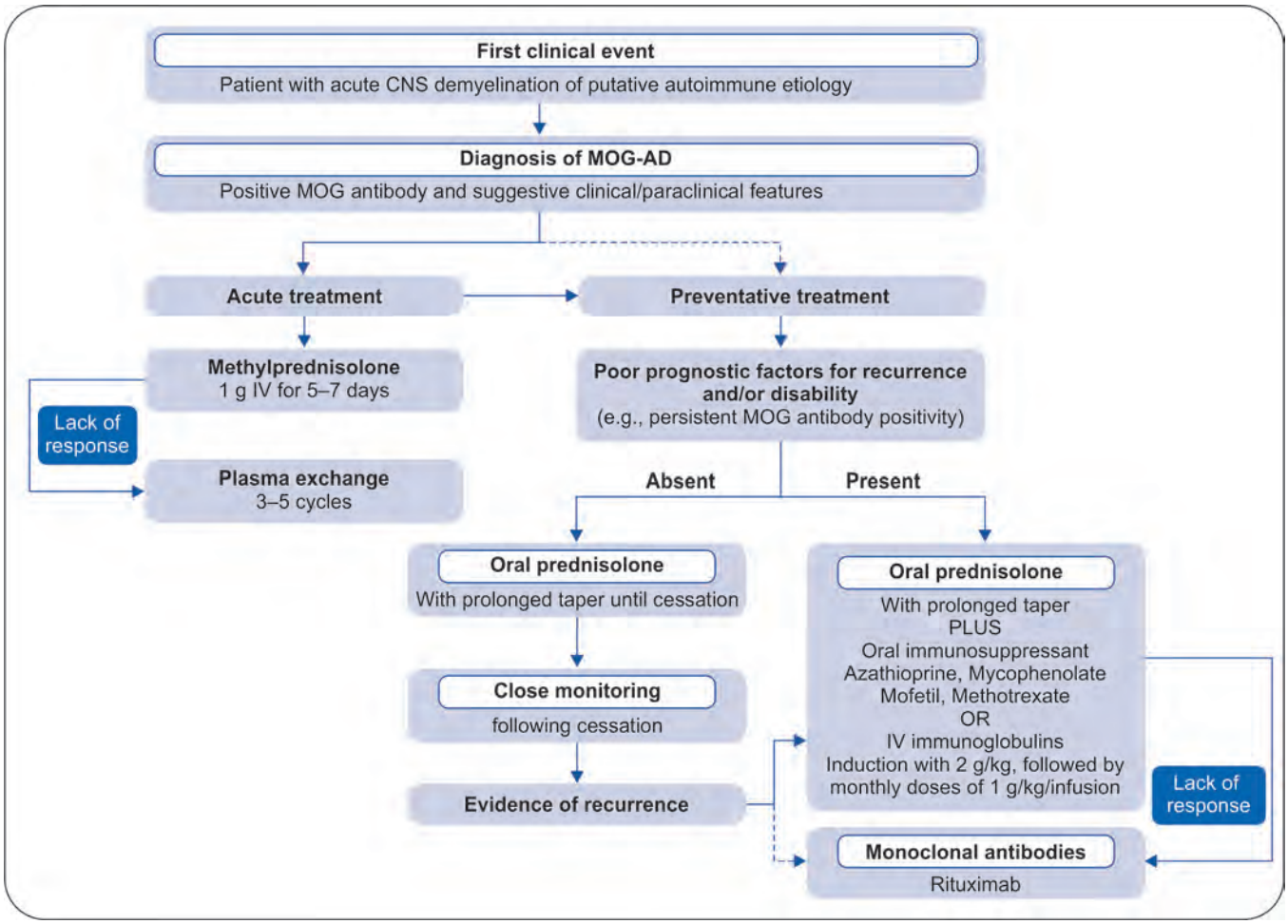
Tables 1 and 2 depict the conditions when MOG antibody should be tested and the Red flags should be considered respectively for avoiding the wrong diagnosis in appropriate clinical scenario.

Special Features

MOG-AD has some differences compared to AQP4-NMOSD:

- Optic nerve involvement more than spinal cord. Optic nerve involvement is bilateral commonly and caudal spinal cord (conus) affection is characteristic.[16]
- Mostly monophasic or may have few relapses. Has a relatively less female preponderance.
- More brainstem and cerebellar involvement with few supratentorial lesions.
- Has a wider spectrum and is less commonly associated with other autoimmune disorders.

Flowchart 2: Algorithm for management of MOG-AD[3,16]



- Responds to B-cell depleting agents and has a better prognosis with good recovery after attacks and minimal disability.[16]

Treatment

Currently, there are no controlled treatment trials in MOG-AD and consensus regarding preferred drug, candidates for immunosuppression and duration of therapy is still uncertain.

Acute Treatment

During acute phase, high dose IV methylprednisolone (1–2 gm/day for 3–5 days), is usually effective with partial or no response in 50%. In steroid resistant cases, plasma exchange (3–5 cycles) results in improvement in around 40% of cases.[3]

Disease Modifying Treatment

Several studies have shown that long-term immunosuppression reduces annual relapse rate in MOG-AD patients. The optimal duration of initial immunosuppression after first attack is not clear. However, since relapse risk is maximum early after disease onset, it is reasonable to continue low dose prednisolone (10 mg) for 6 months after 1st attack (change to steroid sparing agent if side effects occur). MOG antibody should be retested after 6 months and if negative, prednisolone should be gradually withdrawn since disappearance of MOG antibody indicates remission. If antibodies are persistently present, since relapses usually occur only in these patients, immunosuppression may be continued up to 12 months.[16]

However, not all patients with persistent antibodies relapse. Possible risk factors for relapse include: initial

severe attack and persistent MOG antibody. If relapse occurs, steroid sparing agents like azathioprine, methotrexate, mycophenolate mofetil, maintenance IVIG, and rituximab may be started with gradual tapering of steroids.[16] Rituximab however may cause a temporary rise in B-cell activating factor and autoantibody levels resulting in new attacks within 1st few weeks of infusion **(Flowchart 2)**.[3]

Conclusion

MOG-AD constitute a group of acquired inflammatory demyelinating disorders of CNS, which share clinical and radiological features with MS and AQP4-NMOSD, but their distinct pathophysiology and certain specific features delineate them from their counterparts, and hence considered a separate disease entity by themselves with distinct therapeutic and prognostic implications. The diagnosis of MOG-AD relies on presence of suggestive clinical and paraclinical features with positive MOG-IgG antibody. It is important to identify them early because few conventional therapies used in MS can be harmful in MOG-AD and their early diagnosis and treatment aids in improving recovery and minimizing disability.

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CHAPTER

87

Rapidly Progressive Dementia

K Mugundhan

Abstract

Rapidly progressive dementia (RPD) is a rapid decline in one or more cognitive functions which interfere with independent daily living within a period of 1–2 years from symptoms onset. Most of the causes of RPD are treatable and early diagnosis is essential to prevent irreversible neurological injury. Serum vitamin B12, thyroid function test, and MRI brain are the investigations recommended by American Academy of Neurology in any patients with typical dementia apart from routine blood investigations. But the diagnostic workup in RPD needs additional investigations based on clinical profile and stepwise diagnostic approach should be followed including invasive biopsy.

Introduction

Rapidly progressive dementia (RPD) is a group of neurological disorders, which behave quite differently from the slowly progressive neurodegenerative dementias requiring an appropriate diagnostic workup and management. There is no classical definition for the time frame for the onset of dementia; however, these constitute a group of conditions in which first onset symptom to dementia progress in less than 1–2 years, but commonly over weeks to months.[1,2] RPDs often cause distress to the patients and caretakers but presents a real challenge to the clinicians as an array of investigations and nimble decisions on management has to be made to protect as much as viable neural tissue. As many of these conditions can be treated and cured, a prompt and accurate diagnosis of the disease causing the dementia is mandatory. Various etiologies have been contributing to this entity are listed in **Table 1**.[3]

The differential diagnoses of RPD are numerous; nevertheless, a meticulous approach is required to arrive at the accurate diagnosis. A precise history entailing the time course of progression of events is very important.

TABLE 1 Etiologies of rapidly progressive dementia

Etiologies of RPD
• CJD and other spongiform encephalopathies
• Vascular disorders
• Autoimmune and paraneoplastic encephalopathies
• Malignancies
• Metabolic, endocrine, and toxic disorders
• Subacute central nervous system infections

The use of the mnemonic VITAMINS (Vascular, Infectious, Toxic-Metabolic, Autoimmune, Malignancy, Iatrogenic, Neurodegenerative, and Systemic) will help us consider the manifold etiologies, evaluating a case of RPD.[2] The prototype is the prion disease, Creutzfeldt-Jakob disease (CJD).

Diagnostic Approach

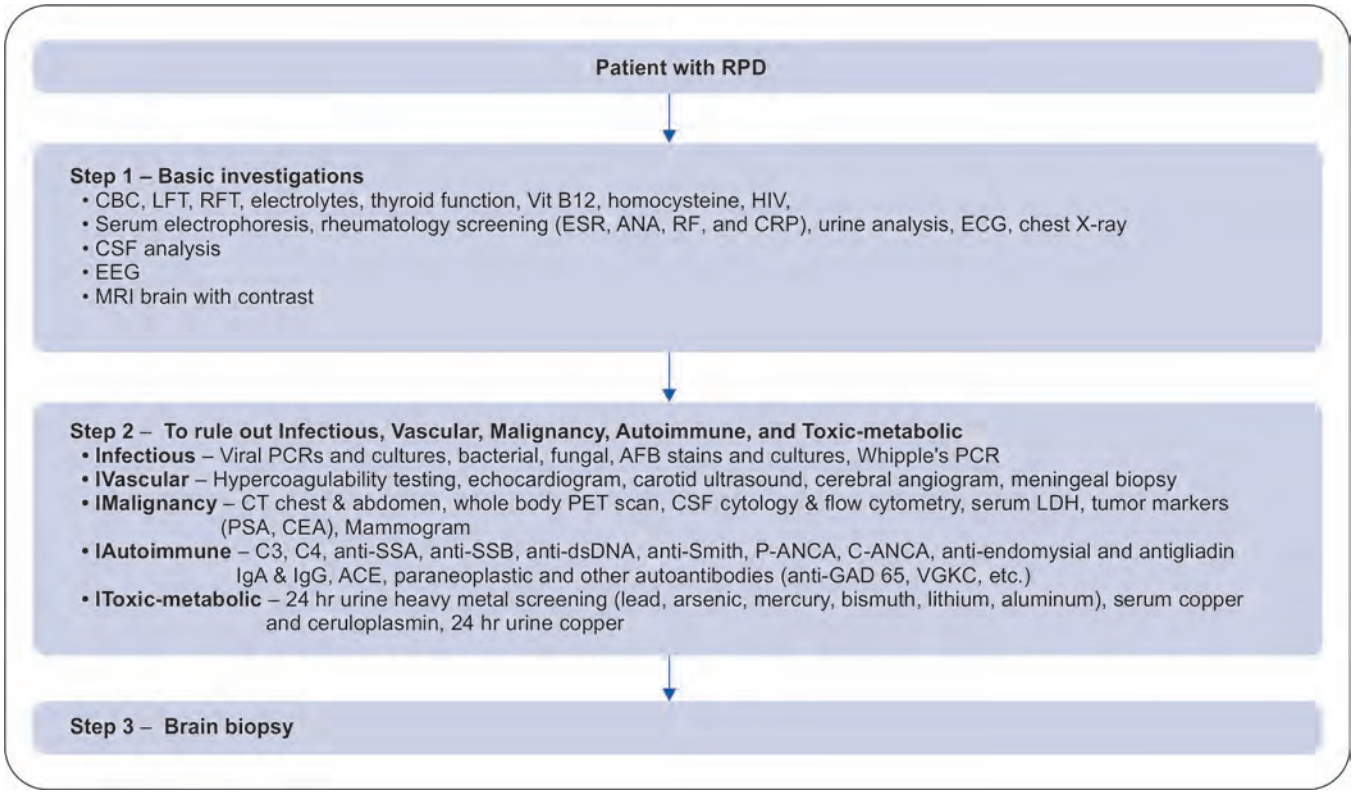
Diagnostic workup of a case of RPD should primarily involve ruling out delirium and its causes. A complete blood count with differential, basic metabolic screening

(calcium, sodium, magnesium, phosphorus), liver function tests, rapid plasma reagin, rheumatologic screening (ANA, ESR, CRP), thyroid function tests, vitamin B12 level, HIV, medication levels according to treatment history (e.g., lithium, phenytoin levels), urine analysis should be done as a part of initial evaluation. Cerebrospinal fluid (CSF) analysis for cell count, protein, glucose, IgG index, oligoclonal bands, VDRL, neuron specific enolase ELISA, 14-3-3 protein western blot, total tau enzyme linked immunosorbent assay, real-time quaking induced conversion test, cryptococcal antigen, viral antibodies, cultures and PCR, bacterial, fungal, acid fast bacilli cultures, and stains are the recommended screening for diagnostic evaluation of a case of RPD. MRI with or without contrast is the initial imaging modality of choice. It should include T1, T2, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging, apparent diffusion coefficient map, and hemosiderin sequences. EEG should also be done, as epilepsy, nonconvulsive status, transient epileptic amnesia should be contemplated when working up a case of dementia. Screening for mood disorders, assessment of hearing loss, sleep dysfunction, and medication overuse should be always kept in mind and ruled out, as these conditions are potentially reversible. The stepwise investigations in approaching RPD are described in **Flowchart 1**.

Neurodegenerative Disease with Rapid Course

Most of the neurodegenerative diseases presenting as dementia is marked by their tardy course of progression, however, can present as RPDs occasionally. Alzheimer's disease (AD) has a median survival rate of 12 years can present occasionally as RPDs, especially in association with amyloid angiopathy. Although the CJD is the commonest cause of RPD, AD represented one among frequent non CJD causes of RPD.[3] Frontotemporal lobar degeneration (FTLD) was yet another common cause for RPD, which presents earlier in life than AD and an overlapping FTLD–motor neuron disease and FTLD–parkinsonism syndromes often predispose a faster

Flowchart 1: Stepwise investigations in rapidly progressive dementia



progression of the disorder. The tau-related pathologies like corticobasal degeneration and progressive supranuclear palsy (PSP), was reported as cause of RPD by multiple studies.[1,3,4] Dementia with Lewy bodies mimics CJD, and progress as RPD, although it lacks its classical MRI imaging properties and single photon emission computed tomography with 123 I-ioflupane can aid the diagnosis.[3]

Creutzfeldt-Jakob Disease

CJD can present with rapid cognitive decline (in weeks or months) associated with gait disturbances, visual hallucinations and behavioral disturbances, myoclonus and extrapyramidal symptoms.[5] It is caused by the transformation of the normal neuronal prion protein, resulting in its abnormal accumulation within the neurons. The disease presents as a sporadic form (sCJD), a familial/genetic form and a variant form (vCJD) of which the sCJD is the commonest, accounting for approximately 85% of cases. sCJD usually has late presentation at 50–70 years of age and affecting both sexes identically. Prognosis is often worse with survival rate of 15% at end of 1st year. Mutations of the prion protein gene are accountable for the genetic forms of CJD and include familial CJD, Gerstmann–Sträussler–Scheinker and fatal familial insomnia. Even though they have a similar clinical presentation, the progression is often slower. The EEG is often characterized by focal or diffuse slowing in the initial period but as with the disease progression, pseudo-periodic and, eventually, periodic 1–2 Hz triphasic sharp waves characterize the picture which is highly pathognomonic, even though late in appearance. Normocytic CSF with elevated protein is often seen with 14-3-3, tau proteins and neuron specific enolase having specific diagnostic values.[6] Hyperintensities involving the striatum (caudate and Putamen) and thalamus in the FLAIR and DWI sequences are seen earlier in the disease with "cortical ribboning" (hypersignal delineating the cortex) in the parietal, temporal, and frontal cortices is of statistical importance (sensitivity and specificity of 92% and 94%, respectively) in diagnosing the disease and can be seen even before the EEG findings. However, a definitive diagnosis requires demonstration of prions in the brain. The clinical criteria for probable sCJD require progressive dementia with at least two of the following: pyramidal and/or extrapyramidal symptoms, visual or cerebellar symptoms, myoclonus, akinetic mutism, and positivity in at least one out of three tests (EEG, 14-3-3protein, and MRI). No effective treatment is found for delaying this fatal condition and only palliative treatment for controlling seizures and myoclonus seems to be beneficial.[3]

Toxic-Metabolic

Complete treatment history, occupational, and home environmental exposure history are important in analyzing the toxic causes of encephalopathy. Lithium (iatrogenic) can cause encephalopathy. Inorganic lead causes peripheral neuropathy and organic lead is more noxious and can cause cognitive and behavioral symptoms. Mercury (organic and inorganic forms) can cause psychological disturbances. Bismuth toxicity, due to inappropriate use for gastrointestinal disorders, can cause RPD and is reversible if detected early.[1] A few reversible causes like vitamin deficiencies, and endocrinological disorders should also be definitely ruled out. Niacin deficiency (vitamin B3) can cause subacute cognitive impairment and is encountered mostly in nutritionally deprived and in association with systemic disorders like diabetes mellitus, chronic malignancies, and chronic gastrointestinal disorders. Thiamine (vitamin B1) deficiency causes Wernicke encephalopathy and needs urgent thiamine replacement. Vitamin B12 deficiency, folate deficiency, etc. are other potentially reversible causes. Endocrine abnormalities involving thyroid, parathyroid, and adrenal should be screened in any case of rapid progression of dementia. Serum electrolyte levels including sodium, potassium, calcium, and magnesium should also be included in the diagnostic evaluation. Uremic encephalopathy, portosystemic shunt encephalopathy, acquired hepatocerebral degeneration, hypoxia or hypercarbia, hyperglycemia, or hypoglycemia are some other etiologies for RPD. Screening for porphyria and mitochondrial diseases should also be done.

Vascular

Vascular conditions like strokes, especially thalamic or callosal infarcts, multi infarcts, cerebral amyloid angiopathy, venous sinus thrombosis, dural arteriovenous fistulas, posterior reversible encephalopathy syndrome (PRES), CNS vasculitis, hypertensive encephalopathy account for other primary causes of RPD.[1,3] Diffusion-weighted imaging, and gradient echo MRI, vascular

imaging like CT angiography, magnetic resonance venography (MRV), magnetic resonance angiography (MRA) aid in the diagnostic workup of dementia.

Infections

Infectious causes for a rapid cognitive decline include herpes simplex encephalitis, AIDS, and its associated CNS conditions like (toxoplasmosis, primary CNS lymphoma, and progressive multifocal leukoencephalopathy), Lyme disease, Whipple's disease, fungal infections like CNS aspergillosis and rare local infections like Balamuthia mandrillaris and neuroleptospirosis. In endemic regions, neurosyphilis should also be considered as a close differential. Infectious causes usually present with specific symptoms like fever, pleocytosis, and meningeal signs and have relatively acute onset.

Malignancy

Neoplastic causes like primary CNS lymphoma and intravascular lymphoma may present with a sudden deterioration of cognition and may present a challenge for the physician. The clinical presentation may mimic Creutzfeldt-Jakob disease and imaging with MRI may not be yielding, as it may not always present with a space occupying lesion or mass lesion. Other metastases/neoplasm related causes that should be considered in the differentials include lymphomatosis granulomatosis, lymphomatosis cerebri, gliomatosis cerebri, metastatic encephalopathy, carcinomatous meningitis, etc.

Autoimmune Dementia

At present autoimmune encephalopathies are thought to be the cause for a relatively fair amount of RPDs.[3] A good number of these encephalopathies are treatable, and hence the importance of prompt diagnosis. The pathognomonic features include rapid and fluctuating course, presence of autoantibodies in the peripheral blood and inflammatory markers in CSF. Clinical presentation may be in the form of limbic encephalopathy with disorders of short-term memory behavioral alterations, depression, and temporal lobe seizures. Limbic encephalopathy may be often paraneoplastic, even preceding the diagnosis of the underlying malignancy, in many cases the neurological disorder is non-paraneoplastic. Anti-Hu antibody is the most common cause of limbic encephalopathy, associated with small-cell lung carcinoma, whereas Anti-CV2 antibodies can be associated with small cell lung carcinoma and thymoma. N-methyl D-aspartate receptor (NMDA) antibodies are usually associated with paraneoplastic encephalitis, occurring in young women with ovarian teratoma.[7] Autoantibodies against neuronal VGKC may be related to lung cancer or thymoma, but most cases are not paraneoplastic, especially in the absence of other paraneoplastic autoantibodies. The former has even shown association with acquired neuromyotonia (Isaacs' syndrome). The clinical spectrum may be of limbic encephalitis combined with neuromuscular hyperexcitability.

Antiglutamic acid decarboxylase (anti-GAD) antibodies are seen associated with conditions like type 1 diabetes and stiff person syndrome and occasionally, cause subacute encephalitis with RDP, ataxia, autonomic instability, and myoclonus, which responds well to immunosuppressive therapy.[8] Autoimmune RPDs can even mimic CJD, both clinically and radiologically, especially limbic encephalopathy with anti VGKC antibodies (LGI1 antibody subtype) exhibiting cortical ribboning in MRI scans. Hyponatremia due to SIADH is more common in VGKC antibody complex encephalopathy.

A steroid responsive encephalopathy with high-serum titers of antithyroid (anti-thyroglobulin antibodies [anti-TG] and anti-thyroid peroxidase antibodies [anti-TPO antibodies) brings into the picture of Hashimoto's encephalopathy. The disorder usually affects middle aged women and the presentation may be of stroke like relapsing and remitting episodes or of an RPD. There are reports of systemic autoimmune disorders like SLE and Sjogren's syndrome presenting as RPDs rarely in the literature.[3] The later may be due to antibody mediated vasculitis or direct antibody attack to the CNS parenchyma as in case of SLE. Despite its propensity for affecting the peripheral nervous system Sjogren's can present as RPDs with cognitive decline and mood disorders often mimicking multiple sclerosis with recurrent attacks and focal symptoms. The presence of antiphospholipid antibody can aid as a clue to the situation. Neurobechet's, neurosarcoidosis, and celiac disease worth mention as they present as RPDs rarely with cognitive decline, behavioral alteration, and spinal cord lesions. Primary or secondary vasculitis due to Wegener's granulomatosis and polyarteritis nodosa can cause encephalopathy resembling RPDs. These

conditions often prompt the requirement of extensive workup with inclusion of serum ACE levels, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies, antigliadin, antitissue transglutaminase, and anti-endomysial antibodies and even a cerebral angiogram in the armory of evaluation panel, depending on appropriate clinical picture.[3]

Secondary Causes of RPDs

Normal pressure hydrocephalus also rarely presents as RPD. The complete clinical gamut of memory loss, gait ataxia, and urinary incontinence may not always manifest. High-resolution structural MRI with orthogonal reconstructions will delineate the cause. Diagnosis can be confirmed by means of CSF pressure measurement and improvement following a drainage lumbar puncture. These patients benefit from a ventriculoperitoneal shunt.

Systemic disorders like sarcoidosis, mitochondrial disorders can clinically present with rapid cognitive impairment. Drugs also may precipitate a steep decline of cognitive function. Narcotics, anticholinergic medications, and benzodiazepines are commonly implicated.

Pseudodementia is a diagnostic possibility of exclusion. Patients with history of major depression may present with rapid decline of cognitive functions and often get misdiagnosed as RPDs. A thorough evaluation and ruling out of the neurological and systemic causes will aid in considering the possibility.

Conclusion

Considering the wide range of clinical conditions, which can present as RPDs, the clinician should always give emphasis on enquiring on the natural progression of the disease with particular attention in eliciting the relevant clinical signs. The exact pattern of the cognitive decline and association of psychiatric and neurological symptoms should be enquired in detail with an interrogation into the association of inherited familial conditions, systemic diseases, and causes including metabolic, drugs, and toxins.

The investigation armory should not be restricted to the routine panel of hemogram, electrolytes, liver, renal, and thyroid function testing, a screening for rheumatological disease and malignancy, CSF analysis including a search for oligoclonal bands and MRI, and rather it should be structured and staged. The use of a systematic approach in diagnosis like "VITAMINS" is often rewarding and aid in rapid diagnosis of reversible conditions. However, if the first stage of interrogation is absurd, one should always open eyes to wide array of differentials and impetuous enough to consider a second stage of investigation including a paraneoplastic workup, CT thorax and abdomen, whole body PET, or immunoassays for specific pathogens if required. A blind alley should prompt to consider even brain biopsy.

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CHAPTER

88 Approach to a Patient with Acute Muscular Weakness

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Rini George, Guhan Ramamurthy, Shrivarthan R

Abstract

The approach to a patient with acute muscular weakness chapter deals with the discussion of various causes of muscular weakness, its clinical features, recommended diagnostic testing, and management. Advancements in genetic testing,imaging studies and laboratory diagnostics offers better understanding about the disease pathogenesis and its course. New molecular markers developed in myopathy help in clinical prognostication and guide treatment. The care of the patients with acute muscular weakness can be challenging. Treatment must be individualized and effective patient participation is necessary for effective management.

Introduction

Acute onset paralysis of the limbs and bulbar musculature is a neurological emergency. It may be caused by a wide variety of disorders. Some of these conditions may have associated respiratory muscle involvement requiring mechanical ventilation. A detailed history, general physical and neurological examination demonstrating the pattern of involvement can help in narrowing the differential diagnosis. Salient features to be noted in history, physical and neurological examination are summarized in **Table 1**.

When evaluating a patient presenting with acute onset weakness of limbs, it is imperative that the following factors be considered. The **Flowchart 1** helps in providing a structured approach to a patient presenting with acute muscular weakness.

- The mental status of the patient should be ascertained—a depressed sensorium suggests central nervous system (CNS) pathology.
- The history of the temporal course and progression of the illness is noted—whether it is acute, subacute, chronic, progressive, relapsing, and remitting. Acute onset weakness occurs in Guillain-Barré Syndrome (GBS), porphyria, diphtheria, tick paralysis, inflammatory myopathy, periodic paralysis, to name a few. Fluctuating weakness is seen in myasthenia gravis and Lambert Eaton myasthenic syndrome. Episodic weakness occurs in periodic paralysis.
- On examination of the motor system we can determine the limbs involved—whether the weakness is symmetrical or asymmetrical. The involvement of all four limbs with a definite sensory level on the torso indicates the presence of a high-cord lesion.
- The presence of sensory symptoms or sensory level helps in diagnosis. The sensory symptoms can be attributed to early polyneuropathy. A definite sensory level on the torso is seen in myelopathy.
- The history of bowel, bladder involvement, and other autonomic signs should be enquired. Early bladder involvement occurs in myelopathy.
- It should be examined whether the weakness is proximal or distal: A proximal weakness occurs in myopathy. In polyradiculoneuropathy the weakness

TABLE 1 Assessment of a patient with acute muscle weakness

Assessment of a patient with acute muscle weakness
History
• Onset and progression and duration • Distribution of weakness • Presence of sensory symptoms • Recent history of fever and diarrhea • Exposure to drugs / toxins • Similar history of weakness in the past • Positive family history
Physical examination
• Look for the presence of skin findings of dermatomyositis (Gottron papules, heliotrope rash, shawl sign, holster sign) • Thyromegaly and thyroid eye disease • Eye signs in myasthenia - Curtain sign, see saw ptosis, peek sign, Cogan's lid twitch • Bulbar involvement • Evaluation of respiratory reserve—coughing ability, single breath count of 30, Forced vital capacity, negative inspiratory force
High yield - Neurological examination
• Pattern of weakness • Bulk, Tone, reflexes • Sensory examination

is initially proximal followed by distal weakness. The involvement of both proximal and distal muscles occurs in polyradiculoneuropathy.

- Early wasting points toward an axonal rather than a demyelinating etiology.
- Bulbar symptoms can occur in GBS, myasthenia gravis, inflammatory myopathy.
- The hereditary nature of illness is determined by associated family history.
- History of associated medical illness like thyroid disease, connective tissue disease.
- H/o drug/toxin exposure should be looked into. Arsenic poisoning, barium carbonate poisoning mimic GBS with systemic symptoms.

It is essential to localize to the most probable site in the motor unit and the possible etiology that has caused the acute muscle weakness. The various causes of acute muscle weakness are summarized in **Table 2**. The discussion of all the disorders presenting with bilateral muscular weakness is beyond the scope of this chapter. A few common conditions are elaborated below.

Guillain-Barré Syndrome

It is an immune-mediated, rapidly progressive, ascending, predominantly motor polyneuropathy leading to bulbar and respiratory compromise. It has a monophasic course. All age groups can be affected. Antecedent respiratory/gastrointestinal illness is found in 60% of cases. Campylobacter jejuni is the most common infection associated with the AMAN variant. Assisted ventilation may be required in up to 25% of cases.[1]

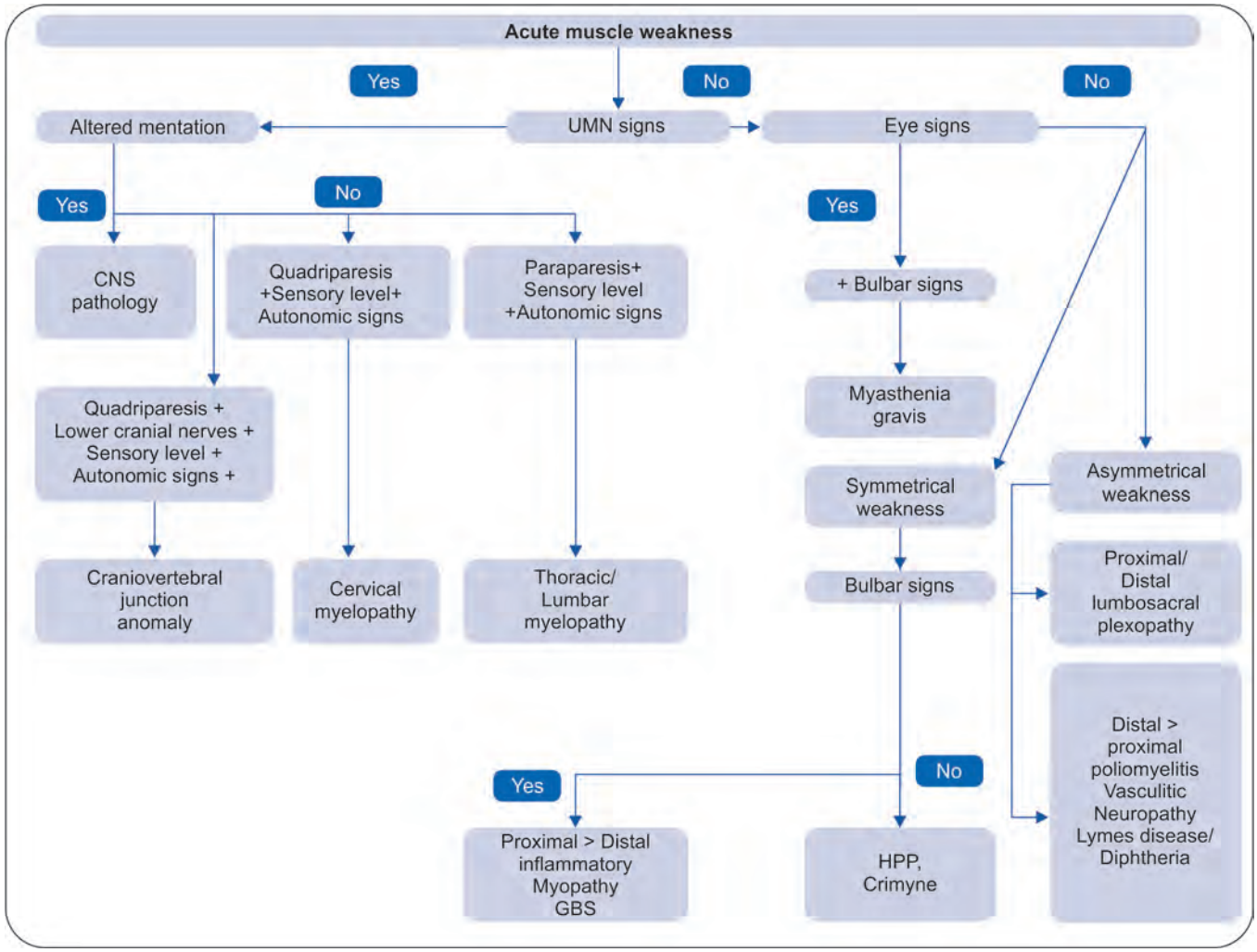
Clinical Features

- Acute flaccid symmetrical quadriparesis. Around one third of patients remain ambulant throughout the course of the illness.
- Early areflexia.
- Distal paresthesia involves the toes and fingers simultaneously (unusual in other causes of polyneuropathy).
- Bifacial weakness occurs in 50% of cases.
- Bulbar weakness with dysphagia and dysarthria are common.
- Back pain and radicular pain are seen in 25% of patients.
- Autonomic dysfunction can occur. It does not progress beyond 4 weeks. Most individuals have a peak deficit by the first week of illness.

The subtypes of GBS include:

- Acute demyelinating polyneuropathy (AIDP). Most common in North America and Europe (90%).
- Acute motor axonal polyneuropathy (AMAN)—Accounts for 30–47% of cases. It is now classified as a nodopathy.[2] It reaches nadir quickly. It is strongly associated with antibodies to GM1, GD1a. The binding of antibodies to the nodal axolemma leads to activation of complement and formation of membrane attack complex. The binding of antibodies alone leads to a functional disruption in conduction, whereas axonal degeneration occurs with the destruction of the nodal protein by the membrane attack complex. Recovery can occur at rates compatible with AIDP depending on the stage in pathogenesis, with functional disruption being associated with a better prognosis.
- Acute motor and sensory axonal polyneuropathy (AMSAN)—It is essential to screen these patients for porphyria. It is the most severe phenotype with rapid

Flowchart 1: Approach to a patient with muscle weakness



HPP, hypokalemic periodic paralysis; Crimyne, critical illness myopathy and neuropathy

TABLE 2 Causes of acute muscle weakness

Causes of acute muscle weakness
Acute conditions affecting the spinal cord – Infections (HIV, TB, Syphilis, CMV, EBV), Acute transverse myelitis, Vascular (Ischemia, hemorrhage)
• Anterior Horn cell—Poliomyelitis**,** West nile virus infection
• Polyradiculoneuropathy—GBS, HIV infection, Zika virus, COVID-19
• Polyradiculopathy—Disc disease, Cytomegalovirus infection, neoplasm, hematoma
• Plexus—Acute Brachial Plexopathy, Acute Lumbosacral Plexopathy
• Nerve—Mononeuritis multiplex, Diphtheria, Lyme disease, Acute intermittent porphyria, critical illness neuropathy, Paralytic seafood poisoning
• Neuromuscular Junction—Organophosphate poisoning, botulism, tick paralysis, myasthenia gravis
• Muscle—Inflammatory myopathy, infectious myopathy, acute periodic paralysis, toxic myopathy, critical illness myopathy

onset and complete paralysis. It is strongly associated with antiganglioside antibodies GM1 and GD1a.

Other variants and their associated antiganglioside antibodies.

- Miller Fischer Syndrome: GQ1b, GD1b, GT1a
- Acute sensory ataxic neuropathy: GD1b
- Pharyngo-cervical brachial variant: GD1a, GT1a, GD1b
- Multiple cranial neuropathies
- Facial diplegia with a parasthesias
- Paraplegic variant
- Acute pandysautonomia

Diagnosis

Lumbar puncture showing albuminocytological dissociation is the hallmark of Guillain-Barré syndrome. This is an elevated CSF protein with a normal cell count. This occurs mainly in the second week of illness.

Nerve Conduction Study

- It is normal early in the course of the illness.
- Abnormalities depend on the variant.
- AIDP: Prolonged distal latencies, reduced conduction velocity, prolonged F-wave latency, conduction block, temporal dispersion.
- AMAN/AMSAN: decreased motor and/or sensory amplitudes in the absence of demyelinating features.

The electrophysiological findings in AMAN can at times show a conduction block, which leads to misdiagnosis with AIDP. Conduction block occurs with functional disruption due to antibody binding to the nodal axolemma which is termed as reversible conduction failure. Serial electrophysiology is therefore required to differentiate between the variants.

Antiganglioside antibodies: Their role in diagnosis has not yet been established.

Serum potassium levels: Hypokalemia can mimic GBS.

Other blood tests: Sodium, potassium, phosphate, magnesium, CPK, white cell count, CRP.

MRI spine with contrast: Nerve root enhancement is visualized.

Treatment

- It requires a multidisciplinary approach.
- Intravenous immunoglobulin (IVIg) and plasmapheresis are FDA approved for the treatment of GBS.
- IVIg is administered at a dose of 2 g/kg over 5 days in patients with severe illness and presentation within 2 weeks of disease onset.
- Plasma exchange: From 5–6 cycles at 1–1.5 times the plasma volume.
- Regular monitoring is required for respiratory dysfunction, autonomic dysfunction.
- Prevention of complications like deep vein thrombosis, decubitus ulcers is important.

Inflammatory/Autoimmune Myopathy

It a heterogeneous group of disorders which include:

- Dermatomyositis
- Immune-mediated necrotizing myopathy
- Anti tRNA synthetase syndromes
- Polymyositis

They can be differentiated by characteristic clinical features, serological tests, and findings on muscle biopsy.[3]

Clinical Features

- Proximal muscle weakness of the upper and lower limb manifested clinically as difficulty in getting up from squatting position and difficulty in raising the arms overhead
- Distal muscles are relatively spared
- Truncal weakness
- Neck muscle weakness
- Dysphagia due to pharyngeal weakness

Dermatomyositis:

- *Gottrons papules:* Scaly erythematous lesions on the extensor surfaces of the fingers
- *Shawl sign:* Erythematous rash over the shoulders
- *Heliotrope rash:* Periorbital violaceous eruption
- *Holsters sign:* Poikiloderma of the upper outer thigh
- *Calcinosis:* Painful lumps on the skin surface
- There may be the development of malignancy like adenocarcinoma either before or after the onset of weakness.

Immune-mediated necrotizing myopathy:

- H/o statin exposure
- Progressive symptoms are noted despite stopping statins, thus differentiating it from statin-induced myopathy
- It is not associated with extramuscular features

Antisynthetase syndrome: Is associated with: Raynauds phenomenon, arthritis, mechanics hands (hyperkeratotic lesions on the radial and palmar surfaces), interstitial lung disease, myositis.

Polymyositis: These patients present with proximal muscle weakness without associated dermatological manifestations. Prior to biopsy, there is a probability for misdiagnosis with conditions like dermatomyositis sine dermatitis, inclusion body myositis, limb-girdle muscular dystrophy.

Extramuscular involvement:
- Interstitial lung disease
- Joint disease
- Cardiac involvement

Diagnosis
- Creatinine kinase, LDH, AST, ALT, aldolase are elevated
- *EMG:* Small polyphasic motor unit potentials are seen
- Spontaneous activity may reveal complex repetitive discharges in dermatomyositis

Muscle Biopsy
- *Dermatomyositis:* Perifascicular atrophy, perivascular infiltrate with B cells, plasmacytoid cells, dendritic cells.
- *Immune-mediated necrotizing myopathy:* Muscle fiber necrosis
- *Antisynthetase syndrome:* Perifascicular necrosis
- *Polymyositis:* Inflammatory infiltrates in the non-necrotic muscle fibers

Serological Tests
See **Table 3**.

TABLE 3 Serological markers in inflammatory myopathy

Type of myopathy	*Serological tests*
Dermatomyositis	Anti TIF1, anti MDA5, anti Mi-2, anti NXP2
Immune-mediated necrotizing myopathy	Anti SRP, anti HMG-CoA reductase
Antisynthetase syndromes	Anti tRNA synthetase anti jo 1 (histidyl)1, anti-threonyl, anti-alanyl, anti-alanyl, anti-glycyl, anti-phenylalanyl, anti-tyrosyl, anti-isoleucyl tRNA synthetase syndromes

HMG-CoA, 3-Hydroxy-3-methylglutaryl CoA; MDA, melanoma differentiation associated protein; NXP, nuclear matrix protein; SRP, signal recognition peptide; TIF, transcription intermediary factor.

Treatment
- IV/oral steroids are useful depending on the severity.
- Immunosuppressants: azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, tacrolimus as maintenance therapy.
- Refractory cases: IV immunoglobulin, Rituximab

Critical Illness Polyneuropathy
It is an acute axonal sensorimotor polyneuropathy leading to muscle weakness with difficulty weaning from the ventilator.[4] It is often associated with critical illness myopathy represented by the acronym CRIMYNE (critical illness myopathy and neuropathy). It is considered that both entities have a common pathophysiological mechanism. Around 70–80% of the patients admitted to ICU develop CIP. Difficulty in weaning the patient from the ventilator despite normal mental, pulmonary, and cardiovascular function, and correction of the metabolic, infectious causes of respiratory failure.

Risk Factors for Critical Illness Polyneuropathy
Sepsis/SIRS, multiorgan failure, female sex, prolonged illness, renal failure and renal replacement therapy, TPN, hypoalbuminemia, vasopressor use, hyperglycemia, hyperosmolarity.

Clinical Features
- It leads to symmetrical flaccid weakness.
- Proximal and distal weakness with hypotonia and areflexia.
- Muscle atrophy can occur.
- Cranial nerve involvement is very rare. Ophthalmoplegia has been reported in a few instances. If there is cranial nerve involvement, other causes of acquired muscle weakness like Guillain-Barré syndrome should be ruled out.

Treatment
Treatment is not effective.

Prevention

Nutritional intervention, antioxidants, testosterone derivatives, growth hormones, immunoglobulins, treatment of sepsis, intensive insulin therapy (maintaining blood glucose between 80–110 mg/dL; risk of hypoglycemia).[5]

Periodic Paralysis

They are a group of autosomal dominant disorders involving muscle ion channels. They are characterized by episodic muscle weakness and areflexia. These are triggered by changes in behavior and diet. Primary periodic paralysis includes hypokalemic periodic paralysis, hyperkalemic periodic paralysis, Andersen-Tawil syndrome. There is an overlap with other disorders causing myotonia and episodic weakness like paramyotonia congenita. Differences between hypokalemic and hyperkalemic periodic paralysis is given in **Table 4**.

Hypokalemic Periodic Paralysis

It is associated with mutations in the calcium channel (CACNA1S) in 60–80% or mutations involving the sodium channel (SCN4A) in 20%.[6]

Clinical Features

Symptoms occur at weekly/monthly intervals. There may be sensory symptoms prior to the onset of weakness—fatigue, myalgia. Usually, there are no cranial nerves or respiratory symptoms. Initial attacks are associated with complete recovery. With time, progressive muscle weakness develops.

Diagnosis

- It may be made clinically from the clinical history and associated features.
- The serum potassium levels are reduced, but never below 2 mM. With lower potassium levels, gastrointestinal, renal, adrenal causes should be ruled out.
- ECG: Features of hypokalemia such as prolonged PR interval, absent T waves and prominent U waves may be present.
- Thyroid function tests should be done in all cases to rule out thyrotoxic periodic paralysis.
- A glucose challenge test with 2–5 mg/kg of glucose may precipitate an attack.
- EMG during an attack reveals short polyphasic motor unit potentials.
- Genetic testing for calcium channel mutations has now largely replaced the need for biopsy.

Treatment

Acute attacks are treated with oral/IV potassium depending on the severity.

Prophylaxis

- Carbonic anhydrase inhibitors like acetazolamide can reduce the frequency and duration attacks. Dichlorphenamide can be used in cases not responding to acetazolamide.
- Other drugs like potassium-sparing diuretics, ACE inhibitors can also be used to prevent attacks.

Myasthenia Gravis

It is an autoimmune disorder with antibodies directed against the nicotinic acetylcholine receptor (AChR). The amount of acetylcholine released is normal, but the availability of acetylcholine receptors is reduced leading to smaller endplate potential.

Clinical Features

The patient presents with extraocular, bulbar, respiratory, and proximal limb weakness. Extraocular weakness may mimic III, IV, VI nerve palsy with sparing of the pupils.[7] Bulbar weakness may present with difficulty

TABLE 4 Distinguishing features of hypokalemic periodic paralysis and hyperkalemic periodic paralysis

	Hypokalemic periodic paralysis	*Hyperkalemic periodic paralysis*
Duration of symptoms	Hours to days	Minutes to hours
Precipitating factors	Rest after exercise, carbohydrate load	Post-exercise, fasting
Severity	Moderate to severe	Mild to moderate
Associated myotonia	Absent	Present

in swallowing, speaking, and nasal regurgitation. Limb weakness is proximal, resembling myopathy. These patients characteristically have diurnal variations with fatigue. Anti-MUSK (muscle specific kinase) myasthenia presents with ocular, bulbar, neck, and respiratory muscle weakness. Myasthenic crisis is when a respiratory failure occurs as a result of weakness. A precipitating event like an infection, surgery, and change in medications is often present.

Diagnosis

Repetitive nerve stimulation is abnormal in 50–70% of patients with myasthenia graves. In MG, there is a decremental response of 10% in the CMAP with slow RNS, which is not seen in normal subjects. The decremental response is the electrophysiological correlate of fatigable weakness.

Tensilon test: Edrophonium is short-acting acetylcholinesterase injected intravenously under cardiac monitoring. The patient is observed for improvement in symptoms, particularly of the extraocular muscles and ptosis.

Ice pack test: It is a nonpharmacological test. It can be used in patients in whom edrophonium is contraindicated. The placement of an ice pack over the ptotic lid leads to improvement.

Serological tests: Anti-acetylcholine receptor antibody

Anti MUSK antibody: Anti titin, actin, myosin, ryanodine receptor, and other striated muscle antibodies are positive in patients in early-onset thymomatous myasthenia gravis.

CT/MRI chest: To rule out the presence of a thymoma.

Treatment

- Symptomatic treatment with acetylcholinesterase inhibitors
- Rapid-acting immunomodulation with IVIG or plasmapheresis.
- Long-lasting immunosuppression with steroids and immunosuppressants.
- Surgical treatment in cases with thymoma.

Conclusion

Acute muscular weakness may be caused by a wide variety of etiologies. The pattern of weakness may vary depending on the etiology. The weakness may be proximal or distal, symmetrical, or asymmetrical. There are characteristic features that help in arriving at a diagnosis. Careful attention should be given to the presence of respiratory, bulbar weakness, which warrants intensive care since acute onset weakness is a neurological emergency.

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CHAPTER

89 The Art and Science of Thrombolysis in Acute Ischemic Stroke

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Abstract

Opening a blocked artery remains the prerequisite to ensure reperfusion of the critically perfused brain. The "science of thrombolysis" in acute ischemic stroke is built on robust twin pillars of good clinical practice and sound science. It is imperative that patients are immediately triaged, imaged, and judged whether they have viable tissue, which could recover with reperfusion. Thereafter, through the evidence gathered over time, it is identified whether the patients meet the strict criteria for thrombolysis. Patients often fall in grey areas, outside these strict established guidelines, who, however, may be salvaged with thrombolysis with expert clinical acumen. The "art of thrombolysis" is to identify these patients. Thrombolysis is the most validated and valuable tool for physicians in their arsenal against acute ischemic stroke and only smart patient selection can expand its repertoire further, providing best chances of a positive functional outcome.

Introduction

Acute ischemic stroke (AIS) is a heterogeneous disorder with varied etiology and complex pathology. Major trials have confirmed the benefit of thrombolysis in the acute stage, irrespective of the stroke subtype. Based on a very simple algorithm that "time is brain" and "unblocking" a "blocked" artery remains the quintessential prerequisite to ensure reperfusion of the critically perfused brain, the "science" of "thrombolysis" in AIS is built on robust twin pillars of good clinical practice and sound science. It is imperative that patients are immediately triaged, imaged, and judged whether they have viable tissue, which could recover with reperfusion.

The evidence gathered over several decades is used to identify patients who fulfill the current guidelines and inclusion criteria for thrombolysis. However, in clinical practice, patients are often encountered who fall "outside" established guidelines, those in whom thrombolysis is "absolutely" contraindicated, those who do not benefit with thrombolysis (failed thrombolysis) and those who lie within "grey areas" but may nonetheless be salvaged with thrombolysis with expert clinical acumen.

The "art" of thrombolysis is to identify patients in the above categories.

Approach

Precise history taking and proper structured evaluation are imperative for decision-making with regards to acute stroke management. The points that have to be noted include the time of symptom onset, age, baseline vitals and blood sugar and stroke severity (graded by NIHSS[1]) **(Table 1)**.

Neuroimaging is undertaken after clinical assessment, with the aim of establishing a clinical diagnosis as promptly as possible. The choices for the same include NCCT or MRI.[2] The former is frequently used because it distinguishes a hemorrhagic from an ischemic stroke and may reveal early ischemic changes. These are graded on the ASPECTS scale **(Fig. 1)** (Scores >7).

TABLE 1 NIHSS scoring

Tested item	*Title*	*Responses and scores*
1A	Level of consciousness	1-Alert 2-Drowsy 3-Obtunded 4-Coma/Unresponsive
1B	Orientation questions (2)	0-Answers both correctly 1-Answers one correctly 2-Answers neither correctly
1C	Response to commands (2)	0-Performs both tasks correctly 1-Performs one task correctly 2-Performs neither
2	Gaze	0-Normal horizontal movements 1-Partial gaze palsy 2-Complete gaze palsy
3	Visual fields	0-No visual field defect 1-Partial hemianopia 2-Complete hemianopia 3-Bilateral hemianopia
4	Facial movement	0-Normal 1-Minor facial weakness 2-Partial facial weakness 3-Complete unilateral facial palsy
5	Motor function (arm) • Left • Right	0-No drift 1-Drift before 10 seconds 2-Falls before 10 seconds 3-No effort against gravity 4-No movement
6	Motor function (leg) • Left • Right	0-No drift 1-Drift before 5 seconds 2-Falls before 5 seconds 3-No effort against gravity 4-No movement
7	Limb ataxia	0-No ataxia 1-Ataxia in one limb 2-Ataxia in two limbs
8	Sensory loss	0-No sensory loss 1-Mild sensory loss 2-Severe sensory loss
9	Language	0-Normal 1-Mild aphasia 2-Severe aphasia 3-Mute or global aphasia
10	Articulation	0-Normal 1-Mild dysarthria 2-Severe dysarthria
11	Extinction or inattention	0-Absent 1-Mild loss (1 sensory modality lost) 2-Severe loss (2 sensory modalities lost)

Total score- 42. Higher score corresponds to higher stroke severity.

Multimodal imaging (CT/MRI) **(Table 2)** provides added information about the vascular status (primary and collaterals), perfusion status, and extent of ischemic insult.[4,5] These take between 10–15 minutes to perform and are required in guiding thrombolysis decisions in special situations like unknown time of onset and wake-up strokes. Small infarct core with higher salvageable penumbra or DWI hyperintensities without corresponding ones seen on T2-FLAIR are usually taken as markers to thrombolyse patients in these situations.[5]

Treatment

The primary therapeutic goal of acute stroke treatment is the prompt restoration of blood flow in the occluded vessel. The following factors must be considered to guide patient selection for the same:

- Age
- Time of symptom onset
- Baseline:
  - NIHSS
  - ASPECTS

Within the Standard Guidelines

Intravenous alteplase (0.9 mg/kg body weight; 10% dose given as an intravenous bolus, with the remaining infused over 1 hour; maximum dose—90 mg) and tenecteplase (0.25 mg/kg body weight; given as a bolus dose) are the thrombolytics approved for use. They can be used up to 4.5 hours of stroke onset, the greatest benefit found with earlier treatment [The NNT increases from 2 (treatment 0–1.5 hours) to 7 (treatment 1.5–3 hours) to 14 (3–4.5 hours)].[6] The standard guidelines[7] for the same are discussed as follows.

Inclusion criteria:

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <4.5 hours since treatment initiation
- Age ≥18 years

Exclusion criteria:

- Significant head trauma or prior stroke in the past 3 months
- Symptoms suggestive of subarachnoid hemorrhage
- Arterial puncture at a non-compressible site in the past 1 week

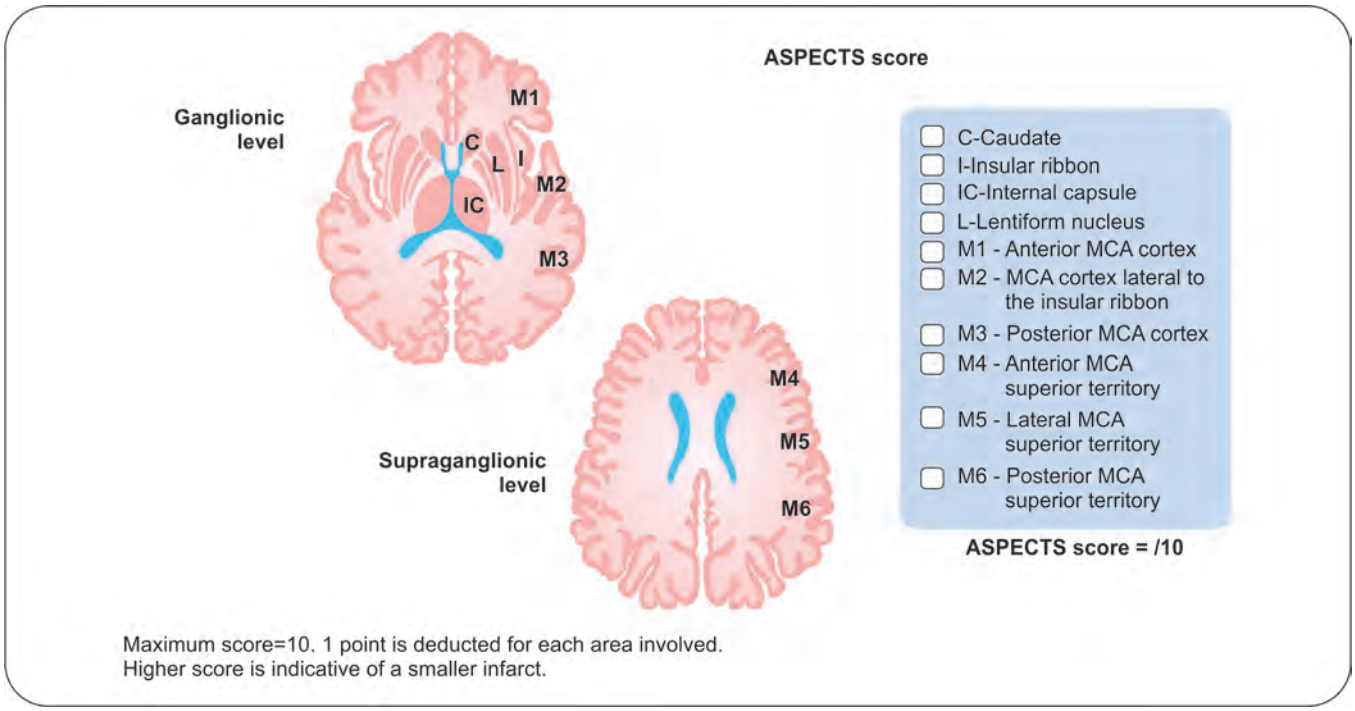

Fig. 1: ASPECTS score[3]

TABLE 2 Multimodal imaging

Imaging	*Functions*	*Advantages*	*Disadvantages*
CTP	Information about infarct core and penumbra	Quicker than multimodal MRI	Additional exposure to radiation and contrast agents
CTA	Extent and location of arterial occlusion/stenosis/dissection		
CTV	Detection of CVT		
Multimodal MRI • DWI • PWI • T2-FLAIR • MRA • MRV	• Location, age, and extent of ischemia • Location and extent of hypoperfused area • Exclusion of stroke mimics • Location and extent of arterial occlusion/stenosis/dissection • Detection of cerebral venous thrombosis	More accurate in determining posterior circulation stroke	Longer time to perform, not widely available, expensive, cannot be used in cases with ferromagnetic implants

- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation or aneurysm
- Recent intracranial or intraspinal surgery
- Active internal bleeding
- Elevated blood pressure (systolic >185 mm Hg, diastolic >110 mm Hg)
- Acute bleeding diathesis, including but not limited to:
  - Platelet count <100,000/mm^3
  - Heparin received in the past 48 hours resulting in abnormally elevated aPTT above the upper limit of normal
  - Current use of anticoagulant with INR >1.7 or PT >15 seconds
  - Current use of direct thrombin or direct factor Xa inhibitors

- Blood glucose <50 mg/dL
- CT demonstrates multilobar infarction (hypodensity in >1/3 of cerebral hemisphere)

Relative exclusion criteria:

- Minor or rapidly improving stroke symptoms
- Pregnancy
- Seizure at onset with post-ictal residual neurological impairments
- Major surgery or serious trauma within the previous 2 weeks
- Recent gastrointestinal or urinary tract hemorrhage in the past 3 weeks
- Recent myocardial infarction in the past 3 months

*Relative contraindications for thrombolysis between 3–4.5 hours:

- Age >80 years
- Diabetes mellitus
- NIHSS >25
- History of oral anticoagulant intake irrespective of INR

Outside the Standard Guidelines

The standard guidelines for thrombolysis were set based on the findings of the pivotal trials (NINDS, ECAS III, and ATLANTIS).[8] These trials excluded many patients to limit complications, who could potentially benefit from thrombolysis. These include patients mentioned under the relative contraindications section.

Delayed Thrombolysis

The patient selection for this subgroup is largely dependent on the multimodal imaging techniques mentioned previously. With the advent of these, the era of exclusively time-based thrombolysis may finally be over.

The WAKE UP trial[9] enrolled patients with wake-up strokes or strokes whose time of stroke onset was not known, but were last seen normal more than 4.5 hours ago. This was based on the premise that stroke in these patients usually occurs closer to waking up/found not to normal unlike traditional teaching where it was taken from when they were last seen to be normal. Inclusion criteria required the presence of ischemic lesion visible on DWI but no parenchymal hyperintensity on FLAIR (indicating that the stroke had probably occurred in the past 4.5 hours). They found that this approach was associated with a significantly better functional outcome as compared to placebo.

The EXTEND trial[10] enrolled ischemic stroke patients for thrombolysis in the extended window period (4.5–9 hours after stroke onset or wake-up stroke between 4.5–9 hours of sleep), guided by perfusion based imaging. Those patients who were found to have hypoperfused, yet salvageable brain regions by the same were randomly assigned either to receive intravenous alteplase or placebo. Patients were eligible if they had a mismatch between the core of infarction and potentially salvageable brain tissue in the penumbra. They found a higher likelihood of better functional outcome in thrombolysed patients as compared to placebo.

Minor Nondisabling/Recovering Strokes

The AHA/ASA recommend the administration of intravenous alteplase for patients with mild disabling strokes but are indecisive about mild strokes with nondisabling symptoms.[7] This has posed a therapeutic dilemma: treat because they might worsen or do not treat because of risk of sICH? The PRISMS trial[11] helped define the role of intravenous rTPA in this setting. Apart from the excellent outcome in the aspirin group, the overall similar outcomes between the two groups make it unlikely that thrombolysis in patients with NIHSS scores ≤5 with nondisabling deficits would significantly improve their functional outcome. However, the trial does not address the issue of what constitutes a "non-disabling" deficit in its entirety. Ambiguity and lack of consensus in this regard will continue to raise concerns regarding "missing" eligible patients for thrombolysis on the grounds of the deficits being "nondisabling."

Patients with Seizure at Onset

Post-stroke seizures are classified as early (within 1 week of stroke) and late (>7 days post-stroke).[12] Occasionally, these early seizures occur at stroke onset. The inherent difficulty in differentiating Todd's palsy from ischemic stroke associated weakness makes this situation a relative contraindication for thrombolysis.[13] However, with the advent of multimodal imaging techniques described previously, the decision for thrombolysis can be made with more certainty if there is an ischemic penumbra that can be salvaged.[14] Both AHA/ASA and ESO recommend thrombolysis, if it can be ascertained with confidence that the focal deficit is due to ischemic stroke, and not a post-ictal phenomenon.[2]

Patients on Anticoagulation

All patients on vitamin K activity based anticoagulation (warfarin/acitrom) need to undergo INR testing prior to anticoagulation, and can be safely thrombolysed if INR <1.7. All patients with an INR above that range cannot be thrombolysed as the risk of bleeding negates the benefit of thrombolysis.[7]

Ideally, patients on novel non-vitamin K based anticoagulants (direct thrombin inhibitors/factor Xa inhibitors) should not be thrombolysed if the last dose has been taken within the past 48 hours. However, it can be considered if all appropriate laboratory tests: aPTT, PT, clotting time, thrombin time, and factor Xa assay are normal.[7]

Pregnancy

Ischemic strokes in pregnancy and puerperium are rare and usually of cardioembolic origin (secondary to rheumatic heart disease) in our country. Treatment is challenging because of the potential risks to the mother and teratogenicity to the fetus. The former include antepartum hemorrhage due to abruption placentae, peri-, or postpartum hemorrhage and premature labor.[15]

No RCTs on thrombolysis have been conducted in this patient population both due to ethical reasons and paucity in numbers. Some case reports/case series have shown beneficial results. The afflicted patient is thrombolysed based on the inclusion and exclusion criteria mentioned previously as the maternal health takes precedence over the fetal health. Also, rTPA does not cross the blood-placental barrier and animal studies till date have not shown any evidence of teratogenicity.

Therefore, the decision regarding thrombolysis should be taken on a case-to-case basis balancing the benefits against potentially unknown harms.

Dementia

Thrombolysis in individuals with dementia remains unaddressed and does not find mention in either inclusion or exclusion criteria for thrombolysis. The higher burden of small vessel disease and/or amyloid angiopathy in this patient population makes most physicians reluctant toward thrombolysis due to the presumed added risk of post-thrombolysis hemorrhage.[16,17] However, studies revealed that white matter disease was associated with increased risk of post-thrombolysis hemorrhage but not for poorer outcome at 3 months.[18] Another study found no difference in the rates of mortality and intracranial hemorrhage in this patient population compared to those without dementia.[19]

Caution may be exercised in individuals who are no longer independent for activities in daily living (mRS >3) as not much might be gained from thrombolysis, but should be actively contemplated in the remainder.

Malignancy

There is limited data available on the safety and efficacy of thrombolysis in patients with a malignancy. The presumed risk of symptomatic intracranial hemorrhage makes it a relative contraindication for the same.[20] However, a few case series found that it was not a significant independent risk factor for post-thrombolysis morbidity or mortality. Therefore, thrombolysis may be safely considered in patients with malignancies, provided an absence of an intracranial neoplasm or brain metastasis.

Abbreviations

AHA, American Heart Association
ASA, American Stroke Association
ASPECTS, Alberta Stroke Programme Early CT Score
CT, Computerized Tomography
CTA, CT Angiography
CTP, CT Perfusion (study)
CTV, CT Venogram
CVT, Cerebral Venous Thrombosis
DWI, Diffusion Weighted Imaging
ESO, European Stroke Organization
FLAIR, Fluid Attenuated Inversion Recovery
INR, International Normalized Ratio
MRI, Magnetic Resonance Imaging
NCCT, Non-Contrast Computed Tomography
NIHSS, National Institute of Health Stroke Scale
NNT, Number Needed to Treat
PWI, Perfusion Weighted Imaging
RCT, Randomized Controlled Trial
rTPA, recombinant Tissue Plasminogen Activator
sICH, symptomatic Intra-Cranial Hemorrhage

Conclusion

Thrombolysis with rTPA and tenecteplase has dramatically revolutionized acute stroke treatment due to their availability as an effective means of treatment. There is mounting evidence of their benefit not only within but also beyond the standard treatment guidelines. The benefit of thrombolysis can be further extended through smart selection of patients based on a clinico-imaging criterion, which improves response rates and decreases the complication risk. Evidence-based exclusion criteria are invaluable but should be adaptable in the acute setting as stringent additional testing will be counter-productive wasting precious time.

The selection of patients for thrombolysis is both an art and a science. The "art" is dependent on the clinical acumen and experience of the treating physician. This art reassures him that a benefit is expected from the treatment and is not being done for the lack of other better alternatives. The "science" part arises from the analysis of predictive markers determining the response to therapy.[21]

Thrombolysis is the most validated and valuable tool for physicians in their arsenal against ASI and only smart patient selection can expand its repertoire further, providing best chances of a positive functional outcome.

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CHAPTER

90 Imaging in Stroke

Justin C

Abstract

Stroke imaging is growing by leaps and bounds with every passing year.Since mechanical thrombectomy has become the standard of care in large vessel occlusions. Its imperative that every physician is equipped with the knowledge of stroke imaging to keep up with the latest trends. This chapter briefly outlines the important signs of stroke in imaging starting from non contrast ct brain to advanced imaging evaluations done before a patient is undertaken for mechanical thrombectomy.

Introduction

A clinical diagnosis of stroke even when it is largely accurate by an experienced clinician warrants mandatory neuroimaging. Imaging in stroke patients is the quintessential step before any step in the management of these patients. Furthermore, in stroke there is a rapid shift from time-based approach to tissue-based approach during interventions. Before doing MR imaging, a non contrast CT brain in stroke window will be a cost effective, time saving, and logical first step and in many cases the only investigation that will ever be needed in stroke patients. With the advent of extended stroke interventions with endovascular techniques, CT angio, and CT perfusion imaging will be needed to assess the risk benefit ratio before intervening.

Acute Stroke

Ischemic strokes contribute to almost 85% of stroke cases with hemorrhagic strokes contributing to 10% of cases and the rest by subarachnoid hemorrhage (SAH). Transient ischemic attack is a transient neurological deficit due to focal brain, spinal cord or retinal ischemia that rapidly recovers usually within 1 hour with no infarction or tissue injury.

Intracerebral Hemorrhage (ICH)

Even though MRI brain is the most specific investigation for identifying bleeds in brain, non-contrast CT is the gold standard investigation for ICH. The density of bleed declines by 1.5 HU/day. The location of the bleed may offer some clue to the etiology of the bleed **(Table 1)**.

Hematoma clot expansion in hypertensive patients can be halted by effective blood pressure management and if necessary by rFactor VII administration.[1] Hemorrhage extending into ventricles worsens the clinical outcome in all patients (except in thalamic hemorrhage). Hence, early CT brain helps charter the course in ICH patients and not merely excludes hemorrhage for acute ischemic stroke patients. Some of the important signs of ICH in both NCCT and CT brain are listed in **Table 2** and depicted in **Figures 1A to C**.

Vascular Imaging

Vascular imaging may be necessary in patients with suspected arteriovenous malformation (AVM) induced superficial bleed that can be surgically evacuated or in aneurysmal SAH.

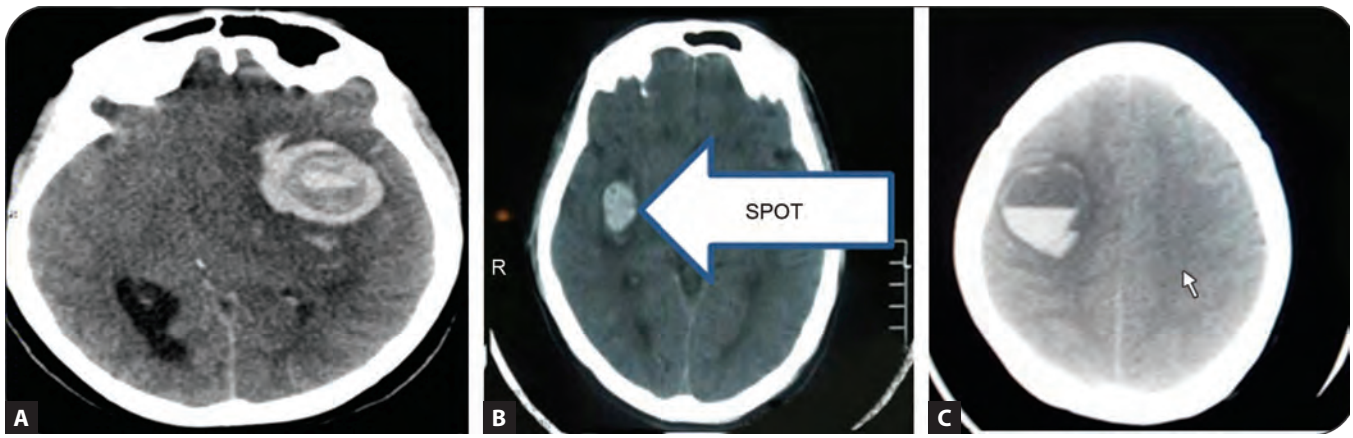
TABLE 1 Location of bleed and its etiology

Location	*Etiology*
Striatocapsular & striatothalamic	Hypertension
Lobar—(more in occipital)	CAA
Lobar—(large irregular shaped from cortex to ventricles)	AVM
Lobar—with blood fluid level	Coagulopathy
Lobar—parietal or temporal	Vein of Trolard or Labbe thrombus
Lobar -Frontal with SAH (dissecting Jet of bleeding aneurysm)	Aneurysms
Cisternal bleed/sulcal bleed	Aneurysms
Parasagittal bleeds/Meningeal based bleed with edema	Dural venous thrombosis/CVT
Subdural bleed	Coagulopathy or trauma
EDH	Trauma
Primary IVH	Cavernoma, AVM, coagulopathy, HT, tumors
Convexity SAH/ICH	RCVS

AVM, arteriovenous malformation; CAA, cerebral amyloid angiopathy; CVT, cerebral venous thrombosis; EDH, epidural hemorrhage; HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

TABLE 2 Signs in CT brain indicating active bleed

ICH signs in CT	*Comments*
CTA Spot *sign*—contrast extravasation into hematoma	Active bleed with poor outcome
Swirl sign (in NCCT) akin to CTA Spot sign	Acute extravasation of blood into hematoma
Island sign—multifocal bleed around main bleed	Active hematoma expansion
Blend sign—blending of hypodense and hyperdense area	Active hematoma expansion
Black hole sign (hypoattenuating within hyperdense)	Active hematoma expansion



Figs. 1A to C: Some important ICH signs in Plain CT Brain. (A) Plain CT brain Showing central Swirl sign and peripheral island sign. (B) CT brain demonstrating central spot sign. (C) Plain CT brain demonstrating blood fluid level

MR Imaging

MR imaging remains as the most accurate investigation for detecting very small hemorrhages. The transition of oxyhemoglobin (diamagnetic) in blood to later derivatives starting from deoxyhemoglobin (paramagnetic) causes local T2 dephasing of the protons from its precessional path and induces rapid signal loss in GRE and susceptible weighted imaging, manifesting as blooming. Whether thrombolysis can be safely done in patients with microbleeds due to hypertensive vasculopathy is a topic of controversy with many deferring thrombolysis when there is more than 10 microbleeds.

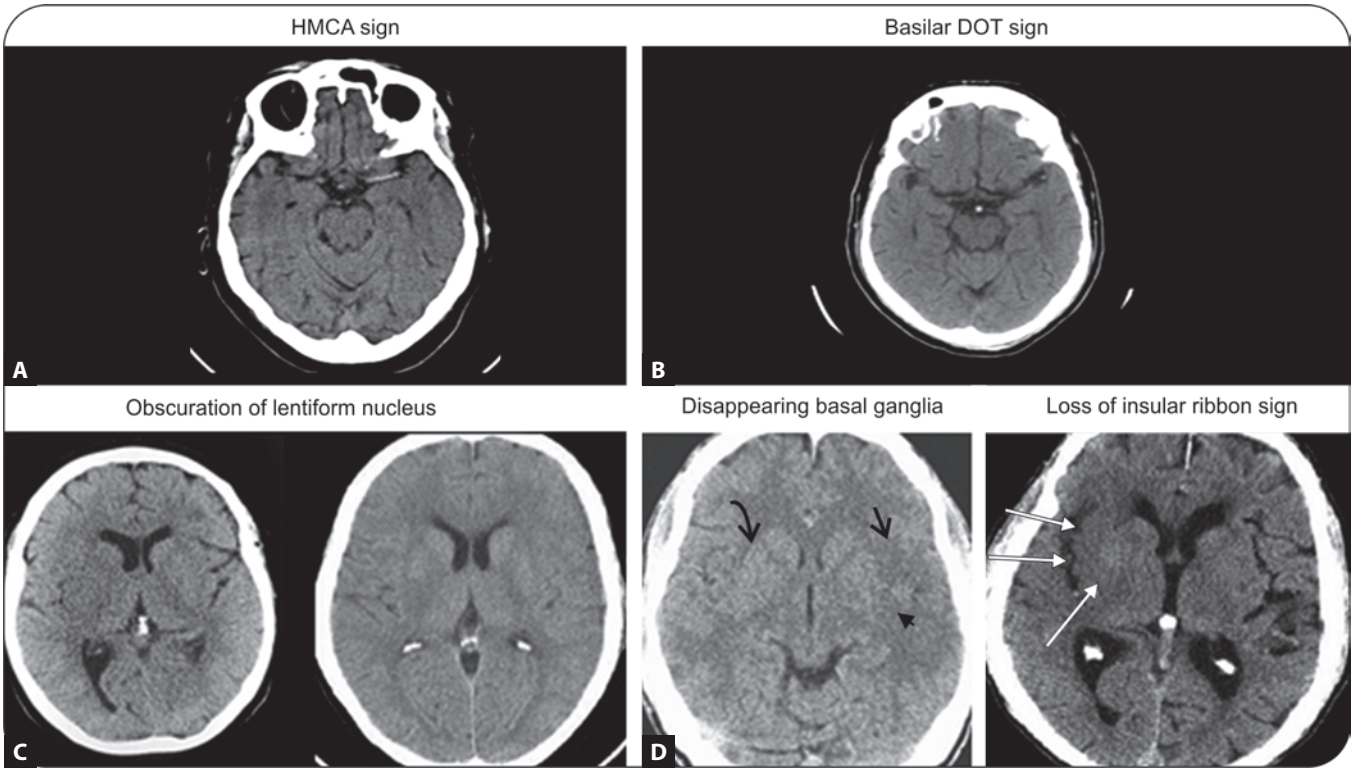
Acute Ischemic Stroke (AIS)

Aided with an accurate history, an NCCT is the ideal emergency investigation in AIS patients. It conveniently rules out hemorrhage and many of the stroke mimics. Ischemic tissue due to cytotoxic edema appears hypodense on NCCT. Reversible ischemic tissue may appear hypodense and swollen in CT. Very large hypodense lesion portends poorer outcome and high risk of hemorrhagic transformation.

Even in an acute setting almost half the patients with AIS have a normal CT brain. A well trained eyes can pick out some of the early ischemic signs **(*see* Figs. 2A to D)** in plain CT **(Table 3)** so that thrombolysis can be undertaken without delay.

TABLE 3 Signs of early ischemia in NCCT

Early ischemic changes in NCCT	***Comments***
Hyperdense arteries (MCA, PCA, ACA)	Highly sensitive, less specific
M2 Dot sign	Highly specific, less sensitive
Basilar artery Dot sign	Very high mortality
Striatal and lentiform hypodensity	
Loss of insular ribbon sign	One of the earliest changes
Cortical gray-white differentiation loss	
Hemispherical sulcal effacement	
Focal compression of lateral ventricles	



Figs. 2A to D: Early Ischaemic signs in Plain CT brain. (A) Showing hyperdense left MCA in the sylvian cistern (HMCA sign). (B) Showing Hyperdense Basilar artery in suprasellar cistern (Basilar Dot sign). (C and D) Showing blurring of margins of basal ganglia & Right insular ribbon sign respectively

ASPECTS Scoring

The *Alberta stroke programme early CT score (Anterior ASPECTS)* is a 10-point scoring system with CT imaging done in patients with MCA strokes **(*see* Fig. 3)**.

Anterior ASPECTS

- Two slices are chosen for the analysis—thalamic level (M1 to M3) and just above basal ganglia (M4 to M6) **(*see* Fig. 3)**.
- Ten segments located within mca distribution. Caudate head, insula, lentiform nucleus, internal capsule, and M1–M6.
- Normal segments—0 point. Ischemic region—1 point. Points are deducted from an initial score of 10 for every region involved
- Maximum is 10 points. Lower scores denotes larger regions of mca infarct. A score of 7 or less indicates 1/3 of mca territory infarct and increased chance of poor clinical outcome.
- Score 7 = 1/3 mca infarct. Score 0 = full mca

Posterior ASPECTS

The posterior ASPECTS just like anterior aspects is the 10-point scoring system where points are lost for each region affected. The pons and the midbrain are worth 2 points each (unilateral or bilateral) **(*see* Fig. 4)**.[2]

- Thalamus (1 point each)
- Occipital lobes (1 point each)
- Midbrain (2 points)
- Pons (2 points)
- Cerebellar hemispheres (1 point each)

Many accredited stroke centers follow an individualized stroke image algorithm. One such highly recommended algorithm adopted by Massachusetts General Hospital, USA is shown in the **Flowchart 1**.

Massachusetts General Hospital acute stroke imaging algorithm for triage of patients with severe ischemic

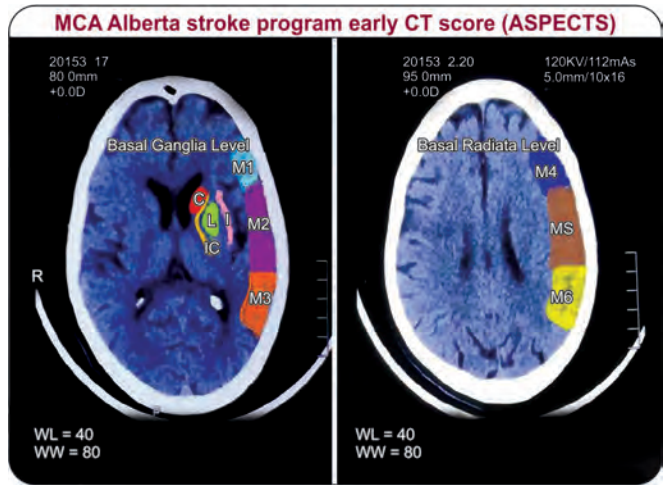


Fig. 3: Plain CT brain demonstrating MCA segments (Thalamic Level-M1 to M3 and level above basal ganglia-M4 to M6) used to calculate ASPECTS Score
C: caudate; IC: internal capsule; L: lentiform nucleus; I: insular Cortex.

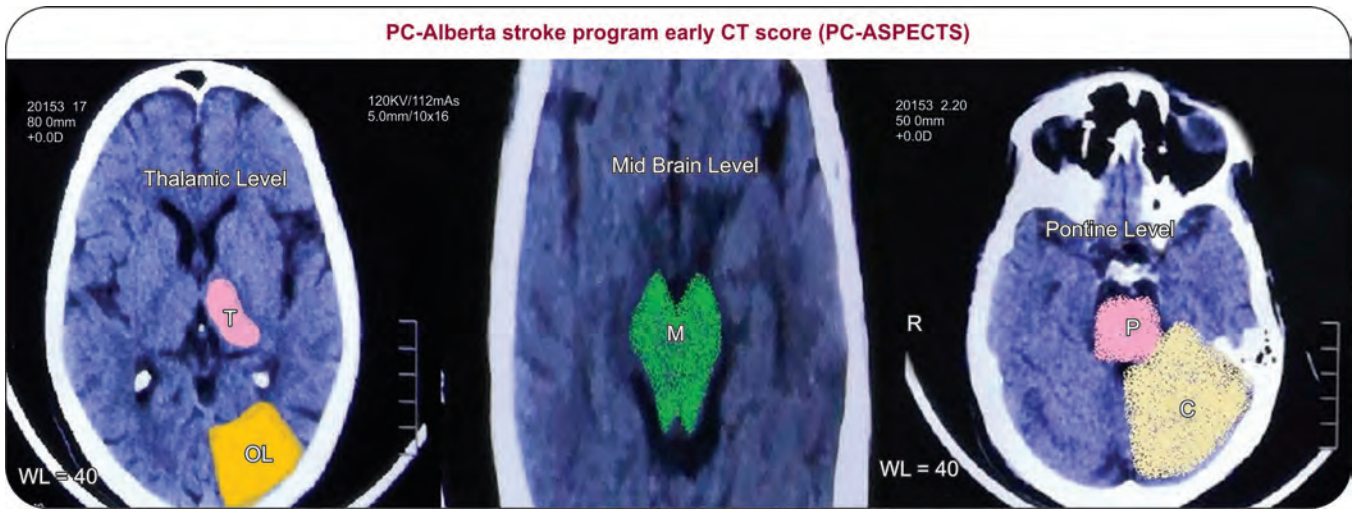
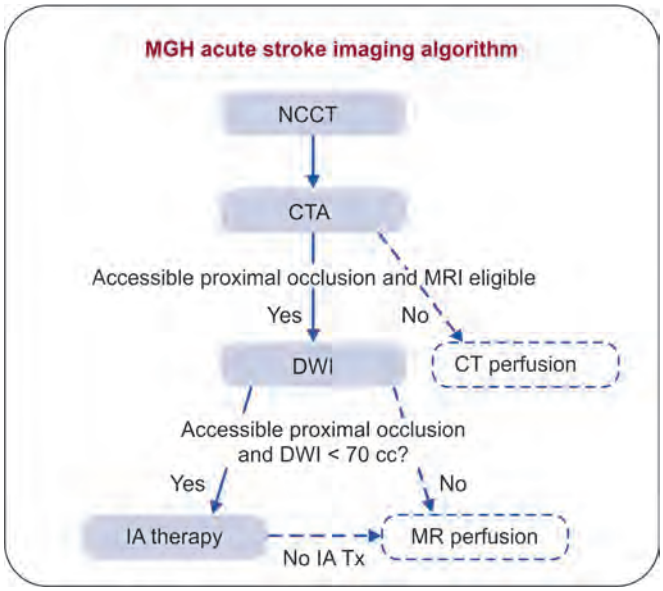


Fig. 4: Plain CT brain demonstrating posterior circulation. Segments used to calculate posterior ASPECTS
T, thalamus; OL, occipital lobe; M, any part of the midbrain; P, any part of the pons; C, cerebellar hemispher.

Flowchart 1: Flowchart depicting stroke imaging algorithm adopted in Massachusetts General Hospital, USA



strokes caused by anterior circulation occlusions dictates a Plain CT Brain for all patients followed by CT angiography. The patient is further evaluated with DWI if the patient has an NIHSS score of 10 or above with an occlusion identified at distal ICA and Proximal MCA with accessibility to microcatheter. If the size of core infarct is less than 70 mL in DWI the patient is taken up for endovascular therapy. If the patient is unfit for endovascular therapy, perfusion studies can be done for further guidance of therapy.

Goals of Acute Stroke Imaging-4Ps

- Parenchyma—assess early signs of acute stroke, rule out hemorrhage
- Pipes—assess extracranial and intracranial arteries
- Perfusion—assess CBV, CBF, MTT
- Penumbra—assess tissue that can be salvaged

CT Angiography

Contrast enhanced CT offers substantial additional value in assessment of cerebral blood volume, CT perfusion studies and in CTA. One of the most important objectives is location of the clot in the distal ICA or proximal MCA so as to undertake intra-arterial therapy. Volume of infarct is an important parameter deciding the use of IAT, with

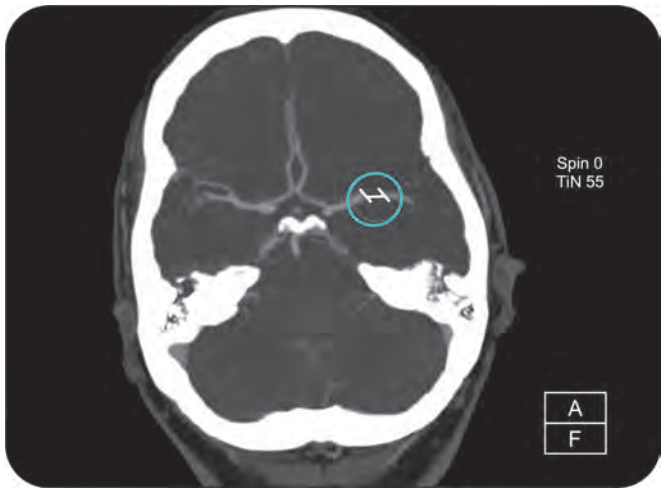


Fig. 5: CT brain angio showing flow a void due to a clot in MCA. The entire length of the flow void from distal to proximal (blue circle) is taken as clot length

volume greater than 70–100 mL having high chances of hemorrhage.

CT angiography may offer great insights into the nature of the thrombus by following assessments.

- *Length of clot:* In MCA strokes, studies have shown that the IVT has no potential to recanalize if the clot length exceeds 8 mm **(*see* Fig. 5)**. Such patients may greatly benefit from endovascular interventions (Provided with good collaterals). Surprisingly many basilar artery occlusions (BAO) even with high NIHSS scores obtain very good recanalization with IVT even comparable to intra-arterial thrombolysis.
- *CTA source image ASPECTS:* For ASPECTS scoring and collateral assessments. CTA SI being more sensitive offers a distinct advantage in early ischemic strokes when compared to NCCT **(*see* Fig. 6)**.
- *Residual flow assessment:* Succesful thrombolysis and outcome depends upon the ability of the thrombolytic agent to permeate the entire length of the clot . This can be assessed in CTA by means of residual flow grade with residual grade 1 and 2 offering greater chances of opening up of vessels by means of either allowing thrombolytic agent to permeate the clot or by means of good collaterals **(*see* Fig. 7)**. Another way of analysing residual flow includes calculating proximal and distal clot interface HU ratio. With ratio greater than 2 having poor chances of recanalization.

- *Terminal Internal carotid artery occlusions:* Carotid T and L shaped occlusions theoretically may have less chance of recanalization when compared to Terminal I shaped occlusion because of collateral MCA flow,higher density of the clot and increased lepto meningeal collaterals in the later. Shape of the thrombus also helps interventionalists to plan and decide approach to thrombectomy. **(*see* Fig. 8)**.
- *Clot burden score:* It is a scoring system to determine the extent of thrombus in proximal anterior circulation by location with scores ranging from 0–10. A score of 10 is normal and a score of 0 indicate multi segment occlusion with a score greater than 6 having greater recanalization rates **(*see* Fig. 9)**:
  - 10-total patency. 0-occulsion of major vessel
  - 2-absence of contrast opacification m1
  - 2-distal m1/supra clinoid ica
  - 1-each m2
  - 1-a1 segment
  - 1—infra clinoid ica
  - lower cbs—larger, proximal thrombus, large infarct, worse collaterals
  - >6 higher recanalization. <6 less rate of recanalization **(*see* Fig. 9)**
- *Collateral score:* collaterals that supports the penumbral tissue during ischemia includes convexity leptomeningeal vessels and circle of willis. Decreased flow leads to increased progression of ischemia and absent collaterals is associated with worse clinical outcome.

A modified Tan **(*see* Fig. 10)** or Miteff scoring systems is used for angiographic collateral assessment determining the course of AIS.

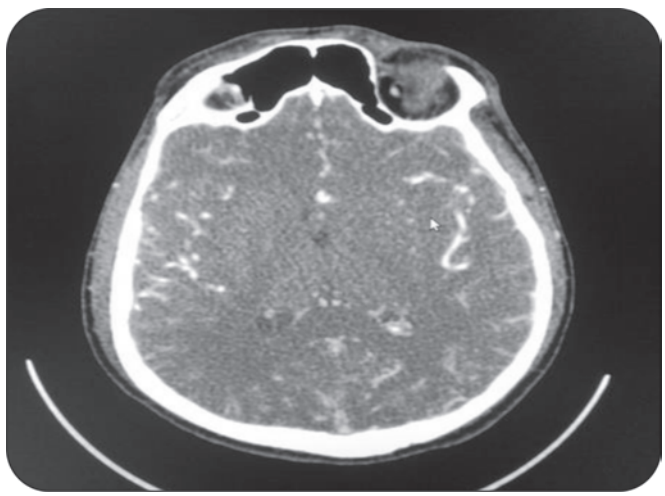


Fig. 6: A normal CTA source image

CT Perfusion (CTP) Imaging

CTP is sensitive to capillary and tissue level blood flow and provides insight into delivery of blood to brain parenchyma. Typical parameters assessed are the following:

cbv: total volume of blood in a given unit volume of brain (mL/100 g)

cbf: volume of blood moving through a given unit volume of brain/unit time (mL/100 g/mt)

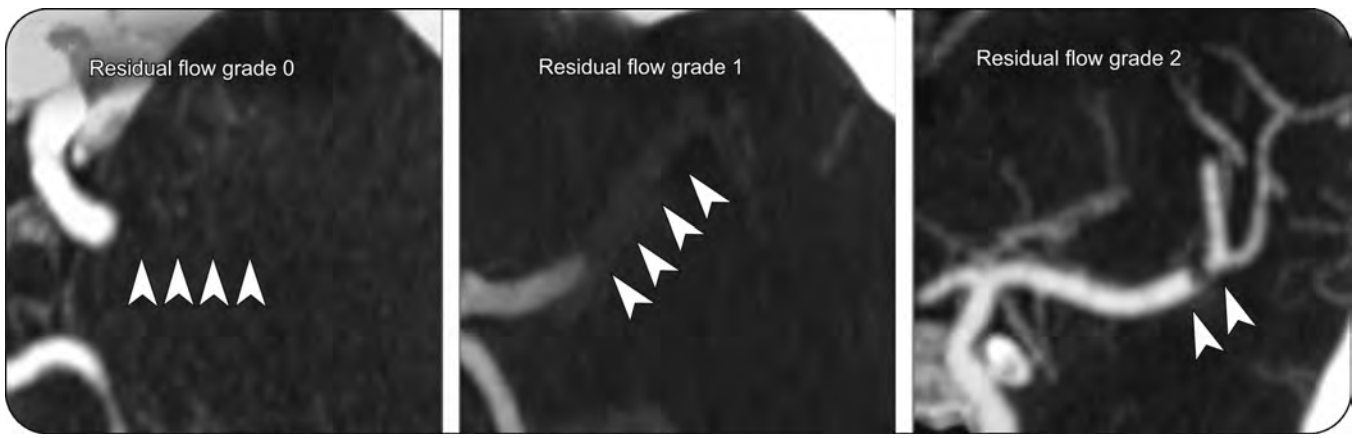


Fig. 7: CTA showing different grades of residual flow in MCA

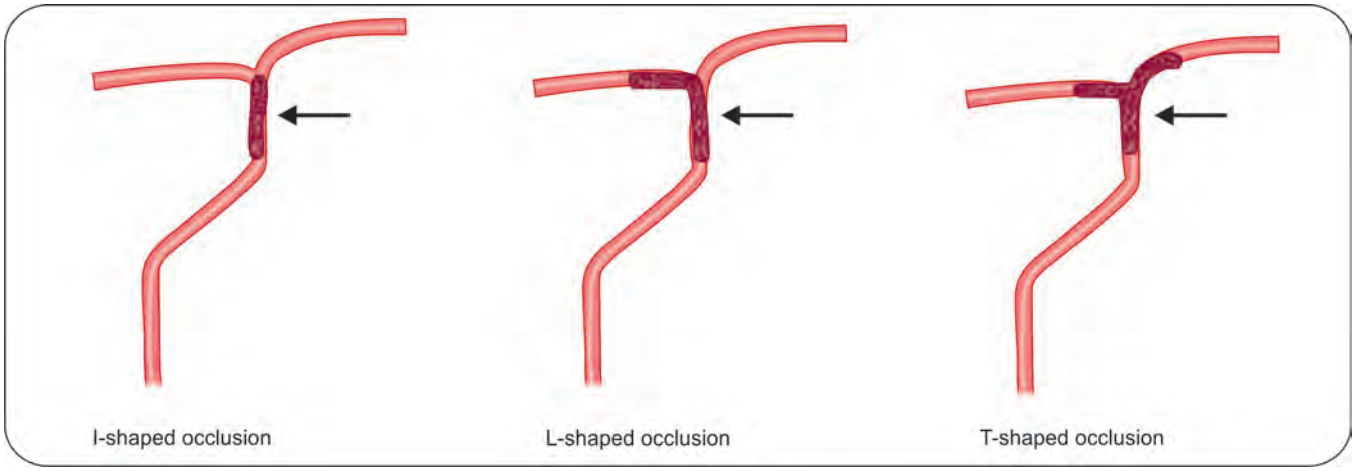


Fig. 8: Illustration of right ICA showing different shapes of carotid occlusions (depicted through black arrows)

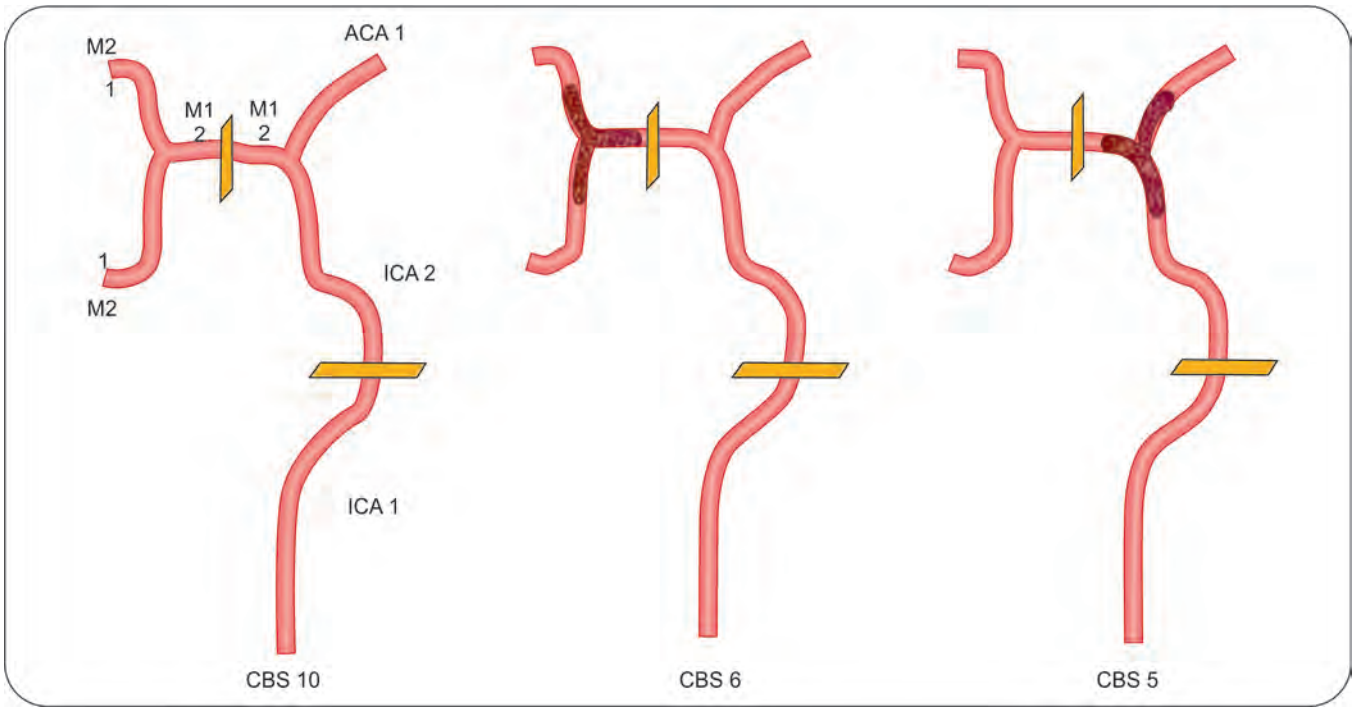


Fig. 9: Illustration of right ICA showing values of vessel segments to calculate clot burden score (values of involved segments are subtracted from the total score)

mtt: average of transit time of blood through a given brain region

$$mtt = cbv/cbf$$

In the first few hours after stroke, the final infarct volume in absence of reperfusion is predicted by MTT and TTP. Tissue infarction is represented by reduced CBV due to failure of autoregulatory responses. Ischemic penumbra is then the difference between CBV and MTT and TTP, which in turn denotes viable tissue at risk for infarction.

All three perfusion CT parameters can be depicted either visually—on a color scale—or numerically, using selected regions of interest.

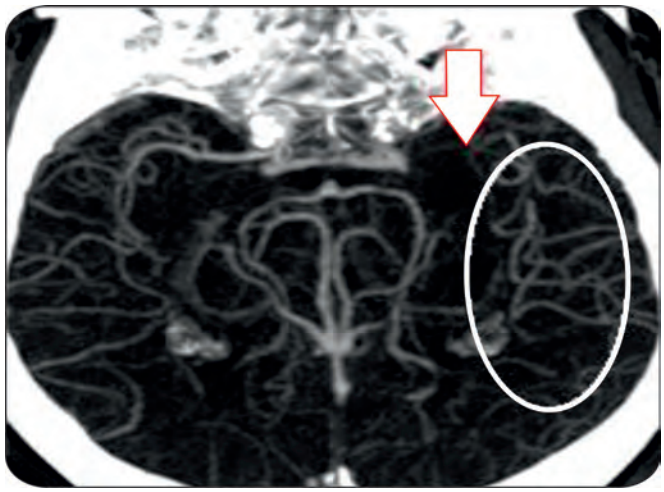


Fig. 10: CTA showing left MCA occlusion (arrow) with good collaterals

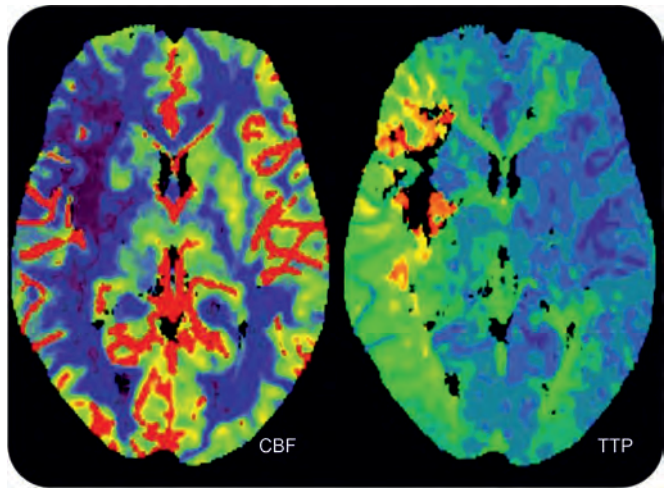


Fig. 11: CT perfusion imaging showing right MCA territory abnormal perfusion with increased T max

The standard color scale is graded from shades of red and yellow to blue and violet.

With CBV and CBF, perfusion is portrayed in red/yellow/green (highest) to blue/purple/black (lowest).

Normally there is equal symmetric perfusion in the cerebral hemispheres with higher CBF and CBV in gray matter (cortex, basal ganglia) compared to white matter.

MTT shows the most prominent regional abnormalities. Color scales are reversed to emphasize the abnormally prolonged transit time in the ischemic brain. The slower the transit time, the closer to the red end of the scale. Brain with normal transit time appears blue ***(see* Fig. 11)**.

Important ancillary finding like Luxury perfusion and crossed cerebellar diaschisis may be seen.

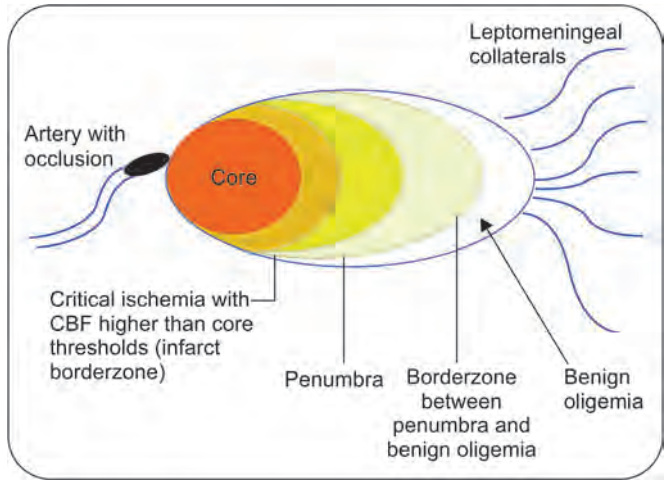


Fig. 12: Illustration demonstrating core, penumbra and Zone of benign oligemia in AIS

MR Imaging

Diffusion weighted imaging is one of the most sensitive technique for ischemic core estimation. Studies have shown that a DWI abnormality volume of more than 70 mL is highly specific for a poor outcome.

Diffusion and perfusion weighted imaging offers vast information regarding tissue viability in stroke. Perfusion MRI is applied as a bolus tracking during gadolinium administration (same as CTP) or instead of using an intravascular contrast agent, CASL magnetically labels the blood entering the brain allowing measurement of TTP, MTT, CBV, and CBF. CASL imaging within 24 hours of stroke symptom onset can depict perfusion defects and diffusion-perfusion mismatches.

DWI/PWI Mismatch

Ischemic penumbra is depicted as DWI/PWI mismatch in MR imaging. The errors in calculation of core infarct size is because diffusion imaging overestimates core volume by causing restriction in regions of penumbra whereas perfusion imaging overestimates penumbra by including regions with benign oligemia **(*see* Fig. 12)**.

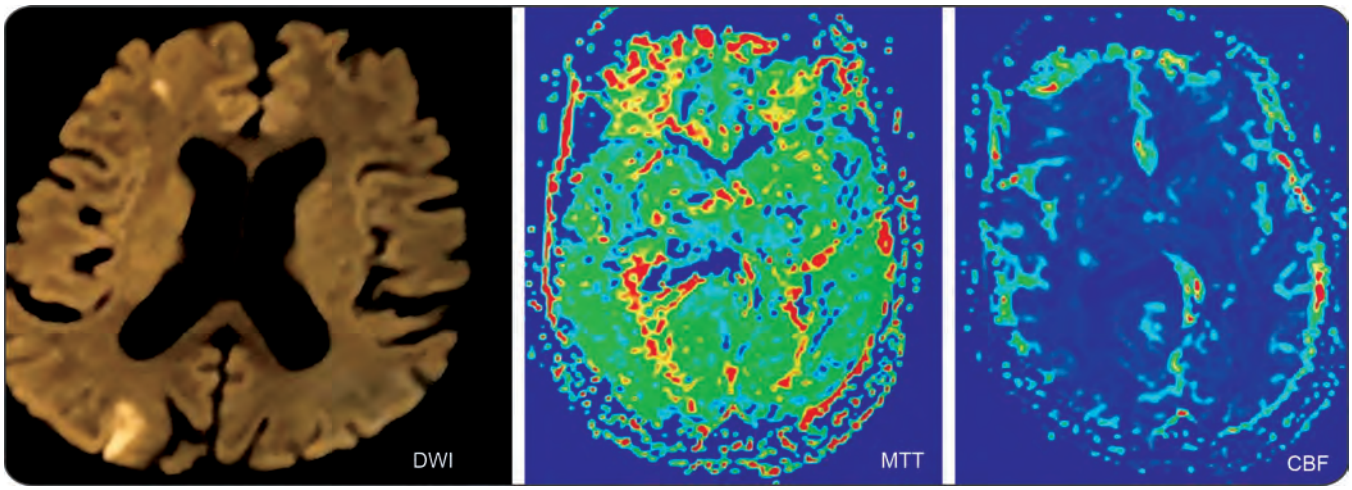


Fig. 13: MRI brain showing right occipital diffusion restriction with right temparo-occipital perfusion mismatch (raised MTT and reduced CBF)

"Classic" mismatch pattern is where the ischemic core on DWI is embedded within a hypoperfused penumbral brain region on PWI ***(see* Fig. 13)**.

"Nonclassic" fragmented mismatch pattern is where part or all of the ischemic regions on DWI are dissociated from the hypoperfused region on PWI.

It is very clear that proximal MCA and distal ICA has to have a small core infarct with a disproportionately large penumbra, nearing a DWI/PWI mismatch of 100%. This is also confirmed clinically with the clinical/diffusion mismatch, for example, NIHSS score (≥8) with a small core infarct (≤25 mL).

DWI Negative Stroke

- Lacunar infarcts
- Brainstem infarcts
- Clot lysis with recanalization
- Moderately reduced or fluctuating hypoperfusion that is not severe enough to restrict water movement

MR Angiography

There are three types of MR angio techniques:

- Time of flight
- Phase contrast
- Gadolinium contrast

Only CE MRI has any use much like CTA in acute ischemic stroke patients.

MRS

The use of MRS in AIS patients apart from showing reduced NAA peak and a raised lactate peak does not offer much information and remains to be validated.

PET/SPECT Imaging

SPECT has application only in presurgical epileptogenic foci mapping and has negligible role in neuroimaging much less in strokes and is largely superseded by the superior PET imaging in every possible way. PET imaging has research application in strokes patient and is currently out of focus in strokes because of the complexities in metabolic activity of the ischemic tissue.

Xenon Inhalation CT

Xenon is inhaled and based on the tissue concentration the CBF data is obtained. The anesthetic properties and difficulty in administration has precluded its routine use.

Transcranial Doppler Ultrasound/TCCD

TCD and TCCD are rapidly evolving as auxiliary investigations in stroke patients. Operator dependence and high expertise are the major limiting factor for its routine use.

TCD and TCCD have a role in stroke following settings:

- Continuous monitoring and identify recanalization during or after thrombolysis

- Detection of right to left shunt
- Monitor flow velocities in sickle cell patients to prevent stroke
- Cerebral VMR measurement
- Vasospasm in SAH

Conclusion

Imaging in stroke has grown by leaps and bounds and much exciting developments await in the horizon. Both CT and MRI are complementary in stroke imaging and in many patients a detailed evaluation will require both these investigations.

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CHAPTER

91 Movement Disorders: Can We Apply Break to It?

Pradeep K Maheshwari, Anjana Pandey, Akanshi Agarwal

Abstract

Movement disorder encompasses large number of neurological disorders that share the common clinical feature of involuntary movements of either hypo- or hyperkinetic character. Movement disorders are classified first phenomenologically and then etiologically. In terms of phenomenology, hypokinetic movement disorders include Parkinson's disease, several other conditions with Parkinsonian features, and rare disorders like stiff-person syndrome. A large number of hyperkinetic movement disorders are divided in several categories including tremors, chorea, dystonia, tics, stereotypies, and myoclonus. The ataxias and movement abnormalities associated with cerebellar system disorders and the large category of gait disorders also fall within this category. This chapter deals with the clinical approach and management of common movements disorders.

Introduction

The term "movement disorder" denotes an abnormality of the form and velocity of movements of the body and is often equated with disorders of basal ganglia. Although some movement disorders are present in pure isolation, many clinical syndromes take form of "mixed movement disorder." Thorough clinical examination should take front seat in diagnosis rather than adopting a scattergun approach to investigations is critical which in turn is time consuming and costly.

Movement disorders are defined as neurologic syndromes that cause interruption of motor activities by either production of excessive, unwanted and involuntary movements or paucity of normal free flowing movements.

Classification

Broadly, movement disorders can be classified into:

- *Hypokinetic Disorders*
  - Parkinsonism
- *Hyperkinetic disorders*
  - Tremors
  - Myoclonus
  - Chorea
  - Ballism
  - Dystonia
  - Tics
  - Athetosis

Parkinsonism

Parkinson's disorder results from dopaminergic neuronal degeneration in the nigrostriatal pathway. It affects about 1% of population over the age of 50 and is the second most common movement disorder.[1]

Differential Diagnosis of Parkinson's Disease

- PD
- Parkinsonian syndromes
  - Progressive supranuclear palsy
  - Multisystem atrophy (MSA)

  - Diffuse Lewy body disease
  - Corticobasal degeneration
  - Drug induced
- Other Non-Parkinson's akinetic-rigid syndromes
- Wilson's disease
- Depression
- Arthritis, polymyalgia, fibromyalgia

Cardinal Features

- *Tremors:* The commonest presentation is rest tremor in one hand which is often accompanied by decreased arm swing and shoulder pain. The tremor is a coarse "pill rolling" movement, fairly rhythmic, from 2–6 Hz.
- *Bradykinesia and rigidity:* More commonly visible on symptomatic side, and midline signs such as reduced facial expression or mild contralateral bradykinesia may already be present. Patients typically develop stooped posture. Poor balance, tendency to fall, and difficulty in walking is seen in patients with Parkinson's disease.

Other Motor Features:

- Micrographia
- Masked facies
- Reduced eye blinking
- Soft voice
- Dysphagia
- Freezing
- Bradylalia

Non-Motor Features:

- Sensory disturbances
- Mood disorders
- Sleep disturbances
- Autonomic disturbances—orthostatic hypotension, gastrointestinal disturbances, sexual dysfunction
- Cognitive impairment (dementia)

Treatment

Drugs commonly used:

- Management of motor complications **(Table 1)**
- Management of non-motor complications **(Table 2)**:
- Neuroprotective therapies: *See* **Table 3**
- Deep brain stimulation (DBS): DBS is functional neurosurgical approach used to treat motor fluctuations. Indications are:
  - Levodopa responsive Parkinson's disease
  - Motor fluctuations
  - Age < 70–75 years
  - Adequate trial of dopaminergic medications given

TABLE 1 Management of motor complications[2]

Medication	*Starting dose*	*Target dose*	*Adverse effects*	*Main benefit*
Carbidopa-L-Dopa	25/100 mg tid	Up to 50/250 mg	Dyskinesia, hallucination, nausea, confusion	Bradykinesia and tremors controlled
Anticholinergics				
Trihexyphenidyl	0.5 bid	Up to 2 mg tid	Atropinic effects	Tremor reduction
MAO- inhibitors				Potential neuroprotection
Selegiline	5 mg	5 mg bid	Cheese effect	Reduced off time
Rasagiline	0.5 mg	1 mg daily	"	"
Dopamine agonists				
Ropinirole	0.25 mg tid	9–24 mg/day	Orthostatic hypotension, confusion, sleepiness	Reduced motor fluctuations
Pramipexole	0.125 mg tid	0.75–3 mg/day	"	"
COMT inhibitors				
Entacapone	200 mg		Diarrhea, dyskinesia	Prolonged effect of L-Dopa
Also- Tolcapone and newer acting Opicapone				
Glutamate antagonists				
Amantadine	100 mg/day	100 mg bid-tid	Confusion, hallucination, congestive heart failure	Smoothing of motor fluctuations

TABLE 2 Management of non-motor complications

Symptom	*Medication*
Depression	SSRIs—Mirtazapine, TCAs
Psychosis	Anti-psychotics like quetiapine
Dementia	Cholinesterase inhibitors like donepezil, rivastigmine
Sleep disturbances	Low dose clonazepam
Bladder disturbances	Oxybutynin, tolterodine
Orthostatic Hypotension	Low dose fludrocortisone, midodrine[3]

TABLE 3 Neuroprotective approaches and their mechanism of action

Mechanism	*Potential neuroprotective approach*[4]
Oxidative stress and mitochondrial dysfunction	Antioxidants (monoamine oxidase inhibitors, coenzyme Q10), glutathione promoters, inhibitors of α synuclein aggregation[5]
Excitotoxicity	Glutamate antagonists (e.g., riluzole)
Apoptosis	Antiapoptotic agents (e.g., mixed lineage kinase inhibitors)
Trophin deficiency	Neurotrophins
Caspase activation	Caspase inhibitors as minocycline

- Ablative surgeries:
  - Thalamotomy
  - Pallidotomy
- Newer drugs in development:
  - *Istradefylline*: Adenosine A2a antagonists which improve motor fluctuations as an add-on drug
  - *Remacemide:* NMDA channel antagonist delays the absorption of L-dopa

Hyperkinetic Disorders (Table 4)

Overview of examination of hyperkinetic disorders:

- The site or location of the movements
- The distribution or extent of the movement
- The rhythmicity, regularity, uniformity, multiformity pattern, and recurrence of movements
- The speed, frequency, and course of particular movement
- The movement's force and amplitude
- What is the relationship of movement to rest, activity, posture, exertion, or temperature?

TABLE 4 Classification of hyperkinetic disorders

Regular/predictable	*Intermediate*	*Fleeting/unpredictable*
• Tremor • Hemiballismus • Palatal myoclonus	• Dystonias • Myokymia • Athetosis • Tic • Stereotypy • Myorhythmia	• Fasciculations • Myoclonus • Chorea • Dyskinesias

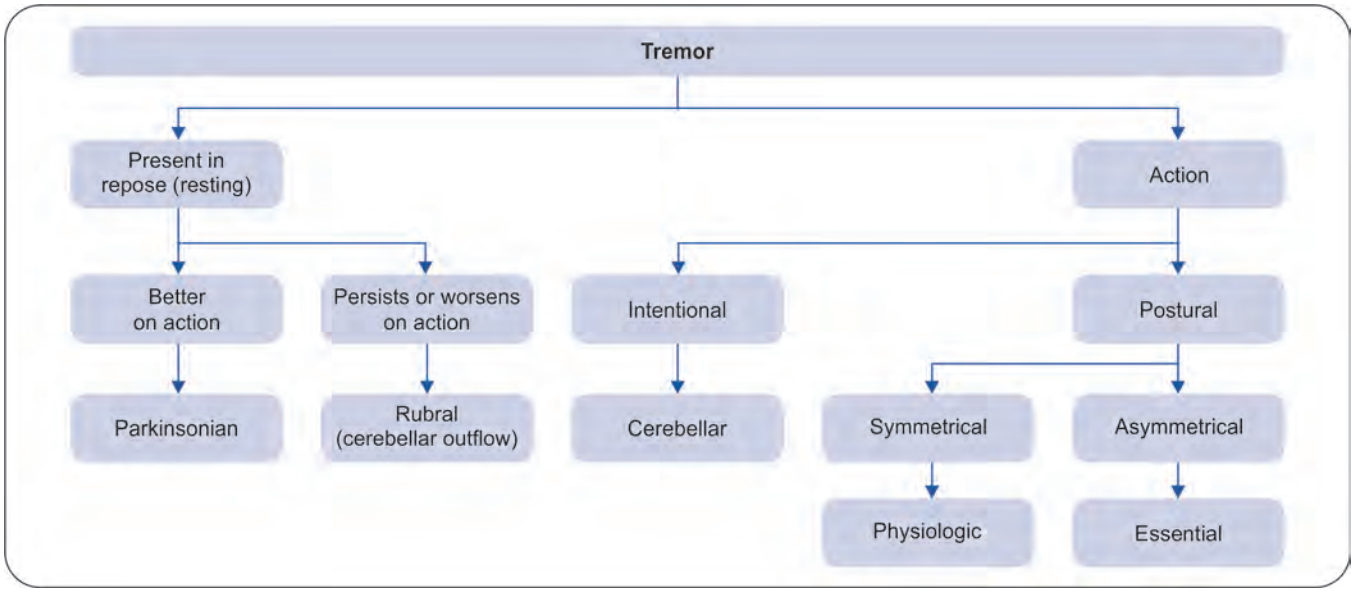
- Whether the movement is suppressible by attention or sensory tricks?
- Whether the movement is present or absent during sleep?

Tremors

Rhythmic, oscillatory, and involuntary movement produced by alternating, synchronous contractions of reciprocally innervated muscles **(Flowchart 1)**.

- *Essential tremors (ET):* It is commonest of all movement disorders. ET is often familial. It is an action tremor that affects head, hands, and voice, worsened by anxiety. The neurological examination is otherwise normal.
- *Parkinsonian tremors:* The tremor is slow, coarse, and compound, rate averaging 4–5 Hz. Causes include idiopathic Parkinson's disease, drugs induced like antipsychotic agents, HIV/AIDS, neurosyphilis, toxoplasmosis, PML or chronic head trauma.
- *Orthostatic tremors:* Orthostatic tremor consists of a high-frequency (14–18 Hz) tremor in the legs during standing. Unaware of the tremor, the patient may complain of unsteadiness or discomfort in the legs that are relieved by leaning against a stationary object, by walking, or by sitting down.
- *Cerebellar tremors:* Cerebellar tremors are slow, absent at rest, and progressively increase with amplitude of movement. A variant known as Holmes tremor is typically present during rest, posture holding, and movement.
- *Hereditary geniospasm:* It is characterized by involuntary vertical movement of the tip of the chin with quivering and mouth movements.
- *Neuropathic tremor:* These are associated with neuropathy diagnosed when other tremorgenic neurologic disorders have been rules out. The neuropathic tremors are kinetic, usually postural 4–7 Hz in frequency.

Flowchart 1: Main types of tremors[6]



Management of Tremor

See **Table 5**.

Chorea

Chorea is swift, graceful, semi-purposeful, dance-like non-patterned, involuntary movements involving proximal or distal muscle groups. They are present at rest but are increased by emotional stress, tension, activity, and self-consciousness.

Huntington's disease: It is an autosomal disorder which is progressive and fatal. It is characterized by:

- Involuntary choreiform movements which advances to dystonia, rigidity, myoclonus.
- Cognitive dysfunction: depression with suicidal tendencies, psychosis, and aggression.
- Gait abnormality.
- Oculomotor involvement: Characterized by slowness of both pursuit and saccadic movements and patient is unable inability to make a volitional saccade without movement of the head.

Management: Dopamine blocking agents like Tetrabenazine have been approved. More recently, deuterated tetrabenazine has also been approved. Recently, an experimental anti-sense drug successfully lowered the level of mutant huntingtin protein in spinal fluid of affected patients.[9]

TABLE 5 Medical management of tremors[7,8]

Tremor syndrome	*Medication*
Essential Tremor	First line: Propranolol (up to 320 mg) and Primidone Second line: Topiramate, Gabapentin Third line: Clonazepam, Botulinum toxin
Parkinson's Disease	Levodopa and/or Dopamine agonists
Orthostatic tremor	Clonazepam, Gabapentin
Dystonic tremor	Clonazepam, Baclofen
Palatal tremor	Phenytoin, Carbamazepine
Cerebellar tremor	Propranolol, Clonazepam
Neuropathic tremor	Propranolol, Primidone

Sydenham's chorea (aka Saint Vitus Dance): It is acute in onset, self-limited choreiform movements seen mostly in patients with rheumatic fever.

Paroxysmal chorea is seen in hyperglycemia and hypoglycemia, infections, and vascular diseases.

Athetosis

In athetosis (Hammond's disease), the movements are involuntary, coarse, rhythmic and writhing in character. Movements are slower but more sustained and have larger in amplitude than those in chorea. Any combination of flexion, extension, pronation, supination, and abduction in variable degrees can be seen. The movements are

intensified by voluntary activity (overflow phenomenon) and disappear in sleep. Athetosis is usually congenital following perinatal injury but can also be acquired following disease, trauma, or drug toxicity. Treatment is exactly like chorea.

Dystonias

Dystonia is defined as involuntary, sustained patterned, or repeated muscle contractions often associated with twisting movements and abnormal posture. Voluntary actions worsen dystonia and it is because of overflow muscle activation.[10] Factors that aggravate dystonia are stress and fatigue and relieving factors are relaxation and sensory tricks (geste antagoniste). Classification of Dystonia is given by European Federation of Neurological Sciences (EFNS-2011)[11] **(Table 6)**.

Management

- Anticholinergic is the most successful oral medication for the treatment of dystonias, particularly trihexyphenidyl.
- Baclofen: This drug has good response in young patients less than 20 years of age and with mild to moderate dystonia.[12]
- Benzodiazepines: Mainly used for blepharospasm and cervical dystonia with predominant head tremor.

TABLE 6 Classification of dystonia by European Federation of Neurological Sciences (EFNS-2011)[11]

Classification by	*EFNS Guidelines*
Age of onset	• Early onset • Late onset
Distribution	• Focal- – Blepharospasm – Laryngeal – Cervical torticollis – Oromandibular – Limb—writer's cramp, foot dystonias • Segmental • Multifocal • Generalized hemidystonia
Aetiology	• Primary – Primary Pure (DYT 1,6) – Primary Paroxysmal (DYT8,10,18) – Primary Plus (Dystonia Plus syndromes) • Secondary (stroke, trauma, demyelinating, degenerative disease) • Herodegenerative

- Botulinum toxin: Treatment of choice for patients with focal or segmental dystonia, like spasmodic dysphonia, blepharospasm, oromandibular, cervical, and lingual dystonia. It can also be used to treat occupational dystonias, like writer's cramp.
- Physical and occupational therapy.

Hemiballismus

Here the movements are wide, flinging, incessant that occur unilaterally. It classically occurs due to hemorrhage or infarction in contralateral subthalamic nuclei. The movements occur incessantly during awake state and disappear only with deep sleep. It is difficult to treat situation, extremely disabling and occasionally fatal too.

Myoclonus

It can be defined as single or repetitive, sudden, brief, jerky, arrhythmic, lightning-like, involuntary movement involving part of muscles, entire muscles, or groups of muscles. It appears symmetrically on both sides. Such synchrony is unique to myoclonus. The distribution of myoclonus can be localized, diffuse, segmental, or generalized. On the basis of etiology, myoclonus can be classified into physiological myoclonus (e.g., hypnic jerks), epileptic myoclonus, essential myoclonus (idiopathic or hereditary), myoclonus is secondary to an underlying disorder or psychogenic or symptomatic myoclonus.[13]

It arises in the CNS from cortical, subcortical, and spinal cord levels. Can be provoked by various stimuli like noise or touch but disappears during sleep.

Clonazepam may be helpful in all types of myoclonus. Other drugs that can be used for cortical myoclonus are antiepileptic drugs such as valproate, levetiracetam, and piracetam, but ineffective in other forms of myoclonus.

Tourette's Syndrome

Neurobehavioral disorder which predominately affects males and characterized by multiple motor tics and vocalizations. Such tics may be suppressed for short periods of time or even totally abolish for days to weeks. Onset occurs before the age of 15 years and incidence decreases or even nil during adulthood. Tourette's syndromes are associated with anxiety, attention deficit hyperkinetic disorder (ADHD), depression, and obsessive compulsive disorder (OCD). Onset in adults is

associated with Parkinson's disease, dystonia, drugs (e.g., neuroleptics, levodopa), and trauma.

Tics

It is a brief stereotyped irresistible repetitive purposeful movement. It can be voluntarily suppressed for a short period.

Drug-induced Movement Disorders

Acute

They include akathisia, acute dystonic reactions, serotonin syndrome, tremor, neuroleptic malignant syndrome. It occur within minutes to days of drug ingestion.[14]

Subacute

It occurs within days to weeks of drug ingestion.

Tardive syndromes: These are drug induced and occur either during exposure or within weeks of stopping a drug and these are present for at least 1 month.[15]

- *Tardive dyskinesia (TD):* It develops months to years after ingestion of antipsychotic treatment. Characterized by choreiform movements of the mouth, tongue, and lips.
  - Lower risk of TD is conferred by youth and use of atypical antipsychotics. Increased risk is conferred by advanced age, toothlessness, and organic cerebral dysfunction.
  - Roughly one third of TD cases resolve within 3 months of discontinuing the offending drug. Most other patients slowly improve over a course of years.
- *Tardive dystonia:* Chronic neuroleptic exposure leads to this condition and is characterized by rocking motion and axial muscle involvement. Tardive dystonia often persists even after offending medication is weaned off and is often refractory to treatment.
- *Tardive akathisia* and *Tardive Tourette's syndrome* are much less common but still associated with chronic antipsychotic exposure.

Neuroleptic malignant syndrome is characterized by hyperthermia, rigidity, tachycardia, and renal failure. It usually occurs days to weeks after exposure to medication. It might also be precipitated by discontinuation of antiparkinsonian medications.

Conclusion

Movement disorders can manifest in numerous ways, with symptoms ranging from subtle to disabling. In recent years, there has been tremendous increase in new diagnostic information, pharmacological, and neurosurgical treatments for movement disorders, as well as a greater understanding of impaired motor control function. The most important for anyone affected by movement disorder is a dedicated team of specialists who can monitor the progress and support optimal health with the latest therapeutic options available.

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CHAPTER

92 Migraine—Difficulties in Diagnosis

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Abstract

Headache poses diagnostic challenges to the physicians for many reasons. It is an extremely common complaint which may be associated with acute illness or serious pathology such as brain tumor or cerebral aneurysm. The majority of patients experiencing recurrent headache in the population suffer either from a variant of tension type headache or migraine. Migraine is more likely to be disabling and becomes the most likely diagnosis for any patient presenting with recurrent headache interfering with function. It is the surround of migraine—the aura, prodrome, and postdrome that can be most challenging and confused with other pathologies.

A basic working knowledge of the common primary headaches and a rationale manner of approaching the patient with these conditions allow a specific diagnosis of migraine to be made quickly and safely. This article discusses about the approach for diagnosis of migraine.

Introduction

Migraine is the most incapacitating disorder of brain, which presents as more severe form of headache with recurrent attacks. The incidence of migraine in women is 15% and whereas in men it is 6%. Approximately 20% of the population experience migraine during their lifetime.[1] Migraine is highly prevalent and is the 7th leading cause of time spent disabled worldwide, yet it has received relatively little attention as a major public health issue. According to "waiting room" survey, 29% of patients encountered at least one migraine headache in a primary care setting within the preceding year.[2] Unfortunately, only 48% of individuals with migraine have received the appropriate diagnosis.

There are many barriers to the diagnosis of migraine, approximately one third of the migraineurs fail to consult the medical care, relaying largely on treatment with over the counter analgesics.[3] This may reflect inadequate access to medical care, ignorance of the availability of the excellent treatment of headache, or reluctance to present with a symptom that society often labels as "benign or nuisance." Even with the evidence of neurological basis of migraine, the stigma of a psychiatric element persists widely in society. Under appreciation by the physician's acts as a barrier for effective diagnosis in clinical settings, magnified by undue emphasis on the serious, but much more uncommon, causes of headache.

Definition

Migraine is defined as intermittent attacks of headache lasting 4–72 hours, with the pain exhibiting two of four specific characteristics (unilateral, throbbing, moderate-severe, worse with activity) and requiring either nausea or photophonophobia.[4]

Migraine may begin early in childhood, but its prevalence increases at 10–14 years of age and continues to increase until 35–39 years of age, after which it gradually decreases, particularly women after menopause. Migraine affects three times more commonly in women than men.

Classification of Migraine

See **Box 1**.

Clinical Features

Migraine, which often begins in childhood, adolescent, or early adulthood, can progress through four stages, not everyone who has migraines goes through all stages.

- Premonitory (Prodromal) Phase (50–80%)—A day or two before the onset of migraine, the changes that alert upcoming migraine attack includes mood changes, neck stiffness, frequent yawning, food cravings, increased thirst, micturation, and constipation.
- Aura (15–20%)—Some people experience aura before or during migraines, which are reversible symptoms of the nervous system, that includes visual symptoms such as flashes of light, scintillations, bright spots, hemianopsia, scotoma, vision loss, auditory phenomena, like hearing noises, pins, and needle sensation of arm or leg, numbness in the face or one side of the body. Each symptom usually begins gradually and progress with time, lasting over 20–60 minutes.
- Headache—If untreated, this phase usually lasts from 4 to 72 hours. Headache characterized by unilateral throbbing/pulsatile headache occasionally affecting both sides, associated with nausea, vomiting, sensitivity to light and sound.
- Post Drome (80%)—This phase lies between resolution of headache and normalization of patient symptoms, during which the patient experiences non-headache symptoms such as limitation of normal functions, which includes easy tiredness, difficulty in concentration, neck stiffness, and irritability.

BOX 1 International Classification of Headache Disorders, Third Edition BETA (ICHD-3 BETA)[5]

- Migraine without aura
- Migraine with aura:
  - Migraine with typical aura
  - Migraine with brainstem aura
  - Hemiplegic migraine
  - Retinal migraine
- Chronic migraine
- Complications of migraine:
  - Status migrainosus
  - Persistent aura without infarction
  - Migrainous infarction
  - Migraine aura-triggered seizure
- Probable migraine:
  - Probable migraine without aura
  - Probable migraine with aura
- Episodic syndromes that may be associated with migraine:
  - Recurrent gastrointestinal disturbance
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis

Triggers of Migraine

Glare, bright light, sound, hunger, physical exertion, hormonal fluctuations during menses, lack or excess of sleep, alcohol intake, barometric pressure changes.

Diagnosis

Why Diagnosis of Migraine is Difficult?

Migraine headaches can be easily diagnosed, but aura may mislead the diagnosis, migraine aura is positive phenomenon, hallucinations associated with migraine are usually elementary instead of complex, but the most common one is unformed visual aura and is characteristic feature of the disease. Investigations in these patients turns out to be normal, even if abnormalities are detected they may be incidental.

Migraine can be differentiated from autonomic cephalgias, but overlap syndromes such as cluster headache also seen, and diseases simulating migraine such as headache from hypertension, giant cell arteritis, reversible cerebral vasospastic syndrome, carotid artery disease, acute glaucoma, intracranial mass lesions, raised intracranial pressure, meningitis and reversible cerebral vasospastic syndrome must not be missed.

Borderline conditions include mitochondrial cytopathies, migralepsy, and migrainous stroke. Importantly migraine is often misdiagnosed for other paroxysmal events mainly cerebrovascular disease and seizures, but also peripheral nervous system disorders, syncope, multiple sclerosis, vestibular disorders, gastrointestinal and cardiac disease, functional and psychiatric illness.

The diagnosis becomes even more difficult when the patient is in transitional or intermediate or having mixed

features of both tension type headache and migraine, in such patients a headache diary or headache notebook is useful to get necessary information in diagnosing the migraine.

Diagnostic Evaluation

When to Suspect a Migraine?

It will be most accurate and most efficient, to consider migraine simply as the most common episodic headache presenting to clinician. Acute sinusitis is an easily recognized source of headache, but chronic sinus dysfunction rarely acts as independent source of recurrent headache.[6] Migraine should be the first thought for those patients describing episodic headache that is severe, disabling, or interfering with normal function. A stable pattern, an absence of daily headache or daily analgesic use and a normal neurologic examination will help in diagnosis of migraine. Typical symptoms and signs can be used to provide additional support to the diagnosis. Fundamentally we should "think migraine first" with any clinical presentation of episodic headache, particularly when it is disabling.

Patients with a stable pattern, normal general physical and neurological examinations and a typical migraine presentation do not require further diagnostic evaluation. However, progressive patterns, abnormal examination findings, or atypical presentations including those with daily headaches will need further evaluation.

The "Nasty Nine" (listed in **Box 2**) outlines the nine specific situations necessitating neuroimaging, electroencephalography, lumbar puncture, or serum studies.[7]

The IHS criteria are helpful in diagnosis of the migraine, and it has made migraine a positive diagnosis rather than a diagnosis of exclusion. Careful questioning of the patient and application of the diagnostic criteria and to carry out a brief, but sensitive and highly focused neurological examination is very helpful.

An abbreviated version of IHS diagnostic criteria is shown in **Box 3**.

There are two main types of migraine:

- migraine without aura
- migraine with aura.

Migraine without aura is three times common than migraine with aura.

BOX 2 Indications for diagnostic evaluation of headache: "Nasty Nine"

- First/worst severe headache
- Abrupt-onset headache
- Progressive or changing headache pattern
- Headache with neurologic symptoms >1 hour
- Abnormal examination findings in headache patient
- Headaches associated with syncope or seizure
- Headaches in children <5, adults >50 years of age
- Headaches in immunocompromised patients
- Headaches that increase on Valsalva, exertion, and sexual activity

BOX 3 IHS diagnostic criteria for migraine from Headache Classification Committee of The International Headache Society[8]

- Migraine without aura—lasts 4–72 hours
- Has at least two of the following characteristics:
  - unilateral
  - pulsating
  - moderate or severe intensity
  - aggravated by exertion
- Associated with one or more of the following:
  - nausea, vomiting, phonophobia, photophobia

- Migraine with aura—Two or more headache preceded by aura:
  - Aura symptoms usually involving:
    - blurred vision
    - flashing lights
    - missing area of visual field
  - Aura symptoms fully reversible, lasting less than 1 hour. Headache follows aura within 1 hour

Migraine without Aura

Migraine without aura previously known as common migraine, where patient complains of episodic headache lasting from hours to days, disabling type accompanied by gastrointestinal symptoms or by increased sensitivity of special senses. With exercise or hard work, tension type headache can be easily distracted but same is not possible in migraine without aura. The duration and frequency of migraine plays vital role in differentiating headache due to medication overuse (MOH) or tension type headache (TTH) where the frequency is more than twice a week, but the same frequency is unlikely seen in migraine without aura (MO).

Migraine with Aura

Migraine with aura previously known as focal or classic migraine, aura progress over time and lasts for several minutes, improves at one aspect and at other it worsens. It is difficult to distinguish between migraine with aura from thromboembolism and epilepsy because here aura sometimes affects sensation, movement, cognition, vestibular function, or consciousness. Sometimes in migraine with aura of recent onset is usually preceded by long standing history of MO, which should be differentiated from "bilious attacks," "sinusitis" or "normal headaches."

In middle age group migraine with aura without headache is most common, sudden onset of MA episodes without headache is mistaken as transient ischemic attacks (TIA). In contrast, sudden episodes of MA with headache need to be distinguished from thromboembolism as it is associated with headache of abrupt onset with non-evolving impairment, which is restricted to single vascular territory.

Take a Detailed History

From diagnosis point of view, history taking remains the most important aspect. It is important to allow patients for proper description regarding their attacks and also for clarifying the history by proper questioning with the aim to fill the gaps in the history that the patient has told you spontaneously. The mainstay of diagnosis of migraine depends completely on history, thorough examination of a patient helps to identify other associated problems, which may exacerbate an underlying tendency to migraine.

The questionnaire should begin by asking about the pattern of the pain, including when, and how headaches begin, duration and frequency of episodes with associated exacerbating or triggering factors. The questionnaire should also include nature of pain, its location, character, and severity, and the symptoms, which accompany pain suggesting other primary or secondary headache disorders such as epiphora, nasal and conjunctival hyperemia, ptosis, edema of eyelids, fever, neck stiffness, and sweating.

It is important to know about present and previous treatments that have been tried and on what basis these treatments are taken and the reason for their discontinuation if any and regarding patient's previous medical history (anxiety, depression, and sleep disorders), current treatment for non-headache diseases, family history (of headache), and social history (regarding occupation, smoking, alcohol, and caffeine consumption).

If structured approach to history taking is strictly followed and proper headache diary is maintained then necessary information that is needed for most probable diagnosis can easily be gathered and gaps in patient's history can be easily filled without specifically asking patient.

Examination

The main aim of examination is to consider regarding organic brain disease and to screen for accompanying comorbid diseases such as hypertension, depression, etc., and also to reassure the patient and their family regarding disease. A thorough neurological examination assessing cognitive, sensory, motor system along with the fundoscopy for the pappilledema is must.

Investigate Appropriately

Decision about investigation done on migraine patients are driven by two most common cultural myths. The first myth being the brain tumor common cause of headache followed by abnormal blood tests or scan results based diagnosis of migraine. The goal of investigation is to

TABLE 1 Investigations to rule out other pathologies of headache

Tests	*Reason*
CBC with ESR	Temporal arteritis
CSF analysis	For fever with headache patients
X-ray PNS	For sinusitis
X-ray chest	Consider in smokers or with metastatic cancers
X-ray cervical spine	Cervical spondylosis
Brain MRI	Due to its greater sensitivity and capability of visualizing intracranial structures it is preferred for all subacute and chronic presentations of headache
CT	Useful in patients presenting with abrupt onset of headache and to find rare brain tumors, subarachnoid hemorrhage, and chronic subdural hematomas
EEG	Useful in evaluation of patients with headache, loss of consciousness and to diagnose basilar migraine in addition to differentiation of organic headache

exclude other causes of migraine like symptoms not to confirm migraine. The following are the investigations required for those headache patients with unusual signs and symptoms are CBC with ESR, Chest X-ray, X-ray PNS, X-ray C spine, CSF fluid analysis, CT/MRI brain, and EEG **(Table 1)**.

Differential Diagnosis

- Tension type headache
- Cluster headache
- Idiopathic stabbing headache
- Medication overuse headache

Conclusion

Migraine presents a major diagnostic and therapeutic challenge to general physicians and neurologists. Patients with unstable or progressive pattern headache, an abnormal examination or an association with features unusual for migraine should trigger further evaluation. According to studies there is a general disenchantment of migraine patients with their physician[9] and a widespread problem of analgesic overuse.[10]

These problems may be overcome by programs of education for the public, physicians, and neurologists, patient should be made aware of the dangers of the analgesic abuse and of the availability of appropriate and more effective migraine treatments.

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CHAPTER

93 Vascular Dementia—Current Concepts

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Abstract

Vascular dementia is a disease, carrying a great history of understanding, dates back to 19th century, when pathologists identified arteriosclerotic changes in the brain vessels, supplying the gray and white matter of the brain, was contemplated as senile dementia. The main problem was the identification of vascular dementia was submerged in the wide understanding of Alzheimer's disease (AD), which was dominating the understanding of dementia, along with identification of frontotemporal dementia. In the elderly citizens, who are prone for atherosclerotic changes in the vessels offer great contribution to the development of dementia. Vascular dementia (VAD) is now understood along with vascular cognitive impairment (VCI) not only includes VAD, but also AD with ischemic cerebral lesions and VCI without dementia. The identification of VAD is essential, in the concept of management of dementia, which in other conditions are progressive. The therapeutic amenability of VAD makes it as a distinctive entity in the early stage of the disease. Subcortical vascular ischemia with dementia (SIVD) is identified by the severe degree of occlusion of small vessels that ramify into the white matter, causing occlusion, resulting in multiple lacunar infarctions in the subcortical structures. The differentiating issues with AD and SIVD may by difficult by assessing the cholinergic deficits, but the recent progress of in vivo amyloid imaging studies could relatively identify the separate entity of SIVD, from AD, where in the amyloid plaques are absent in SIVD. The upcoming concepts between VAD/VCI and their clinical concepts give wonderful idea about the management of the SIVD.

Introduction

SIVD is widely identified disease of slowly progressive dementia, in contrast to the classical Alzheimer's disease and frontotemporal dementia, which are due to development of degeneration and infiltration of amyloidal plaques into the gray matter of the brain, causing shrinkage of the brain matter. There are some distinct identifiable clinical observations between these diseases, and the main benefit of understating the SIVD is its amenability to the treatment. Hence, identification of SIVD become mandatory, and excluding it from other forms of dementia, since other forms of dementia are difficult for management. The identification of subcortical white matter lacunes becomes one of the major components of identification of SIVD, which depending on its location makes the clinical manifestations, as well its volume of affected brain matter. Vascular dementia (VAD), due to CVD, that directly or indirectly damages the neurons associated with cognitive activity.[1] It is also identified that in majority of AD cases, vascular lesions becomes a coexisting factor, contributes heavily in the pathogenesis of dementia, with the existing degenerative brain parenchyma.[2,3] The recent postulation of vascular cognitive impairment (VCI), which embraces both VAD, AD with CVD—sometimes labeled as mixed dementia. More so, another entity also identified as VCI with no dementia (VCIND). VCI becomes a larger term that would include all the stages of cognitive impairment associated with CVD.

Indian Scenario of Vascular Dementia

VAD is a complex presentation in clinical practice. Varied presentations are observed in clinical practice. Its symptoms are not homogenous, but highly variable. The incidence of VAD is ubiquitous in India, but still now exact incidence is not clearly available, even though quite an amount of data is available in the literature. In a cohort study, where in NINDS-AIREN criteria were used to diagnose VAD. Patients were subtyped into subcortical, cortical, cortical-subcortical, and infarct may be quite tiny, but in a strategic location, may present as dementia. In a study by Suvarna Alladi et al., dementia in developing countries: Does education play the same role in India as in the West? over 42 patients with VAD, subcortical dementia was the most common type (52.4%), followed by cortical-subcortical (26.2%), strategic infarcts (14.3%), and cortical dementia (7.1%). Stroke (81%), hypertension (71.4%), and diabetes (35.7%) were principal risk factors. Small artery disease was the elementary vascular mechanism in 42.9%; intracranial large artery disease, in 16.7%; extracranial disease, in 2.3%; cardioembolism, in 2.3%; multiple mechanisms, in 19%; and unknown, in 16.7%. Subtypes were similar in associated risk factors and neuropsychological features but differed in clinical corelates and vascular mechanisms. The results and clinical presentations is highly dependent on the underlying mechanism, pathology, extent and location of the infarct, which may differ in different ethnic groups.[4,5]

Pathophysiology

The main issue involving VAD is generated from vascular lesions. These lesions may be large like a major artery occlusion or tiny perforators, causing lacunar infarcts. These lacunar infarcts, even though they are tiny, when happens in multiple areas, and constitute a major brain volume affection, the dementia evolves. More so, tiny infarcts in strategic locations like frontal lobe, temporal lobe, or brain stem do affect the higher mental function critically. Hence, the deciding factors are volume of infarction, or location of the infarction. Once the ischemic process begins, axonal degeneration results, from the neuronal damage, Wallerian degeneration results, especially more in the white matter subcortical lesions. Neuronal interconnections become a gross impediment in the thought process, ranging from minimal cognitive impairment to a progressive dementing illness.

Recent Concepts in VAD and VCI

The following classification is widely adopted among neurologists across the world:

- Multi-infarction dementia,
- Strategic infraction dementia,
- Hemorrhagic dementia,
- Mixed dementia,
- SIVD, and
- Other forms of vascular dementia.[6,7]

Strategic infarction dementia, hemorrhagic dementia, does develop in a rapid fashion clinically due to acute cerebrovascular diseases. A stepwise progression, inherent fluctuation of clinical presentation of symptoms, and focal neurological signs are suggesting the development of acute VAD. With SIVD, cognitive impairments are often sneaky in its onset, while later decline progressively, like in classical AD.[8]

Classical motor symptoms is not most often demonstrable clinically, sometimes unnoticeable, further confusing clinicians. Existence of pure SIVD has been reported in studies related to amyloid imaging, where significant subcortical white matter ischemic changes were evident with no trace of deposition of amyloid plaques. Pure SIVD is distinct from AD or mixed dementia, which demonstrate fibrillar forms of amyloid deposition in the brain.[9]

Various other types of VAD include dementia where in the etiologies are heterogeneous, for example, cerebral amyloid angiopathy, hereditary diseases (such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) [CADASIL]) and vasculitis.[10-12]

On the issues of mild cognitive impairment (MCI) due to AD or early phase of AD, it is observed that accumulation of amyloid beta (Aβ) plaques and neurofibrillary tangles (NFT) in the brain. These deposits and NFT do hinder the neuronal transmission, interfering with the thought process of the patients suffering from AD. But, the understanding of VCI identifies potentially treatable and preventable components of dementia. It is worth observing that after the establishment of cognitive impairment, the vascular potential risk factors, can be clinically intervened, and there is a chance of rectification of clinical symptoms, and mostly it prevents secondarily in the newly occurring ischemic zones, toward worsening of symptoms in contrast to AD.[13]

It is also observed that small vessels which are deeper in the brain do have multiple changes due to atherosclerosis,

and also due to various small vessel diseases, causing SIVD, in senior citizens, very commonly which is a finding recently observed, by many workers.[14]

Pathophysiology of SIVD

- Marked ischemic change in the brain, due to discrete and incomplete infarctions which may be tiny in character.
- Hypo or diminished perfusion of blood into the white matter, due to critical occlusion of the perforators and medullary branches of the cerebral vasculature.
- There is a typical white matter lesions resulting in ischemia of neurons, oligodendrocytes, Wallerian degeneration of the myelin sheath and axons. The lacunar infarctions (étatlacunaire) are a result of perforating arteriolar occlusions within the subcortical structures, including basal ganglia, thalamus and external and internal capsules. It is observed that there are decreased auto regulation, BBB disruption, endothelial dysfunction, resistance to blood flow, and dilatation of perivascular spaces.[15]
- Consequent these vessel changes and subclinical infarctions there is gross disruption of the prefronto-subcortical circuits and thalamocortical circuits due to white matter ischemic lesions and lacunar infarctions.
- These disruptions are the causative factors for the ongoing dementia and cognitive impairment in SIVD. There are some evidences that A-beta plaques, neurofibrillary tangles are visualized in the SIVD, which is also thought to be a consequent issue due to ischemia of the brain structures.[16]

Clinical Manifestations of SIVD and Its Associations with Structural and Functional Brain Images

The mainstay in the SIVD is the cognitive impairment of varying degree, its stepwise development along with the neurological deficits is common. Abnormal behavior disorders like disinhibition and akinetic mutism are common if the prefronto subcortical circuits are damaged directly or as a secondary effect of ischemia.[17]

Other findings are uncommonly hemiparesis, peripheral speech disorders, pseudobulbar palsy, urinary incontinence, and features of extrapyramidal involvement when the ischemia is in basal ganglia especially in putamen. Impairment of attention, poor verbal fluency may manifests in early phase of SIVD **(Table 1)**.[18,19]

Still there are studies in progress which can differentiate SIVD from mixed dementia by establishing the clinical, imaging studies, especially from studies available with amyloid PET imaging.

SIVD Biomarkers

So far various studies have been observed, without any conclusive evidence of any biomarkers. Many of the recent longitudinal studies have met with results that they proceed ultimately to AD. In VAD, the novel genetic variants discovered could be presumably used as potential biomarker for diagnosis and treatment.

The field of pharmacogenetics is a beacon of hope in VAD for improving drug efficacy and safety. Causal gene identification is highly limited to monogenic form of VAD, while by evidence VAD of sporadic form is less probable. For future research, more homogenous subgroups with a larger and heavier sample sizes are essential. For further genetic investigations in VAD, endophenotypes look as a promising research tool. Apart from genome wide association studies (GWAS) and gene analysis studies, focus on epigenetic modifications and microRNAs are also increasing. The therapeutic implications of the same have to be evaluated in future, depending on the evidences available time of time. BBB (blood brain barrier) disruption is one of the beneficial situations for future analysis. Significant, biodegradation products are

TABLE 1 Differential diagnosis clinical features between SIVD and AD

Higher cognitive functions	*Vascular dementia (SIVD)*	*AD*
• Attention	• Grossly impaired	• Mildly impaired
• Language and understanding	• Decreased output and fluency	• Poor recalling and naming
• Visuospatial orientation	• Fair and mild affection	• Gross affection
• Memory functions all types	• Moderate loss	• Gross and severe loss
• Frontal lobe executive functions	• Severe loss	• Moderate loss

identified, which include increased albumin leakage in CSF. It is also observed that certain metalloproteinases are observed to be available as markers of neuroinflammation, as they disrupt the basal lamina, tight junctions of blood vessels, with disruption of myelin. The levels of metalloproteinases-9, in CSF, are observed to be increased in VAD. The concentration of the neurofilament cytoskeleton, which may give hall mark for white matter disruption of large meylinated axons, observed to be higher in patients with SIVD.[20]

Several different results have been reported with biomarker studies on VAD/VCI patients. A recent study compared the biomarkers from CSF of four groups, namely MCI group that remained stable as MCI (MCI-MCI); SIVD (MCI-SIVD); mixed dementia (MCI-MD); and MCI group that finally progressed to AD (MCI-AD). It was reported that the levels of phosphorylated and total tau (T-tau) were lower, while that of Aβ were higher in the MCI-SIVD than the MCI-AD group. In the MCI-MD group, biomarker levels in the CSF were between those levels of MCI-SIVD and MCI-AD group. CSF levels of MDI-SIVD were closer to the levels of control group and the MCI-MCI group. The intermediate levels of CSF biomarker levels of tau and Aβ in the SIVD group as compared to MCI-MD and control groups indicate a common pathology of SIVD with AD. The biomarker levels in the CSF of VAD and AD patients when compared, it is observed that Aβ levels are lower, while tau levels are higher in AD patients as compared to VAD patients. However, overlaps have been observed between the two. No such differences were observed between the biomarker levels in non-elderly individuals, who had mild, moderate, or severe white matter hyperintensities.

Alternative biomarkers associated with SIVD include those related to BBB breakdown. Albumin leakage can result following BBB breakdown, increasing the protein concentration in the CSF as a result. In view of this, increased albumin levels are supportive as evidence of SIVD. MMPs are attributed as neuroinflammatory markers, as they attack the blood vessel tight junctions and basal lamina, apart from disrupting the myelin. MMP-9 levels were increased in CSF of VCI patients as compared to AD patients. Neurofilament is another important white matter disruption marker. Neurofilament acts as a cytoskeleton in large myelinated axons. In individuals with higher neurofilament levels, SIVD is prominent. In non-demented individuals with severe white matter lesions, similar findings were reported. As described previously, advanced imaging techniques can help serve as potential biomarkers, enabling understanding of underlying pathophysiology of SIVD.

Imaging in SIVD

One of the promising diagnostic identification of SIVD is done in imaging studies. MRI imaging appears to be a superb identification tool, than CT of higher resolution, along with the MR angiography to identify the affected territory. Tiny infarcts in common locations like cortical, subcortical, exceeding a volume of more than 50 cc, or any small tiny insignificant volume of infarct in a strategic location, results in high degree of clinical manifestations (***Refer* Figs. 1 and 2**). Hence, it is observed by MRI studies, that it is not the multiplicity, but its location and total volume of gray matter involvement or white matter connect ions, manifests in clinical syndromes. PET scan also observed to be quite useful in identifying ongoing infarct, or preimaging status of the infarcts, which would be useful in assessment of management of the disease. It is almost emphasized as on current state of affairs, more than bio markers, imaging studies are highly efficient in identifying the diseases at an early state.

- Large areas of infarction or hemorrhage post stage with severe brain substance damage, both gray and white matter.
- Decreased diffusion anisotropy in the places of white matter hyperintensities, amyloid PET imaging for routine diagnosis of AD, myloid PET imaging can be clinically useful for differentiating pure SIVD and mixed dementia, which sometime can be challenging to distinguish and would give rise to diagnostic dilemmas.

Role of Neurophysiological Studies

It is not the issue that neurophysiological studies like cortical evoked potentials, EEG, and BAER also play an important role in identifying the interrupting pathways well in advance to imaging studies. But it needs heavy and careful scrutiny to identify such subtle changes, to inform the clinicians about the development of SIVD.

Strategies for Treatment of SIVD

- Major treatment strategies include improving the obvious clinical symptoms at the same time mitigating the underlying small vessel disease progression.

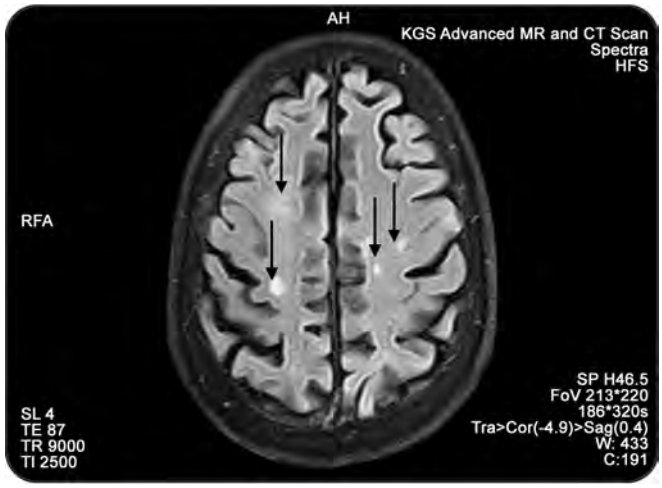

Fig. 1: Multiple tiny infarcts, constituting more volume of infarct and also multiple hyperintese areas in the strategic location of the brain

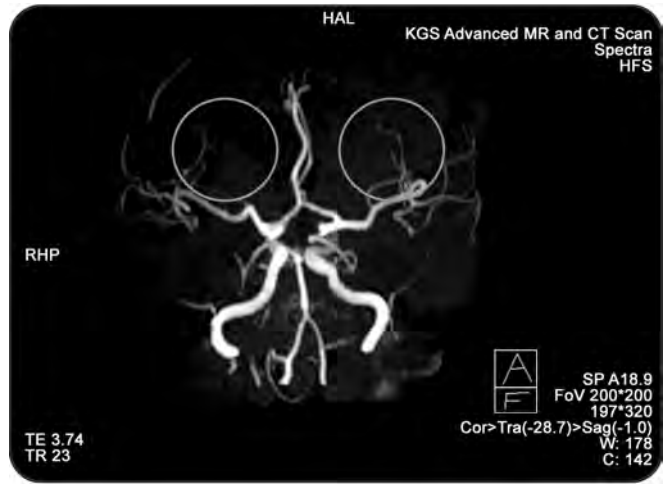

Fig. 2: Left side denotes fair vascularity of penetrating arteries, right side shows avascular component, MR angiogram

- An important significant factor contributing to cognitive impairment and brain atrophy is microinfarct pathology. By regulating small vessel disease, once can administer antiplatelets agents as a means of secondary stroke prevention.
- For the primary prevention of VCI, antiplatelet agents as a means of therapy are not established yet. Due to its vasodilatory effect, nimodipine, a calcium channel blocker, has been found as a potential agent for SIVD treatment. In early clinical trials for VAD, nimodipine was found to be successful, following which an "intention to treat" trial with 230 patients was conducted. The set primary end point was not achieved in the trial, although, positive results were obtained in the mini mental state examination and global deterioration scale, along with improvement in language production.
- For managing cognitive symptoms, the uses of cholinesterase inhibitors have been implicated. SIVD associated cholinergic deficits are well defined from the findings that perforating arterioles supply the basal forebrain cholinergic nuclei and that hippocampal CA1 region is highly vulnerable to ischemia.
- Deficits in the cholinergic fibers have been identified in CADASIL patients. In view of which, cholinesterase inhibitors have brought in for the treatment of cognitive impairments of VAD, which are linked with deficits of the cholinergic fibers. Beneficial effects on cognitive functioning of cholinesterase inhibitors were observed in a randomized controlled drug trial on CADASIL patients. In another CADASIL study, donepezil, a cholinesterase inhibitor did not show improvement in the primary endpoints. A subgroup analysis on the other hand indicated improvement in the treatment group in executive functions. Associated behavioral changes can be managed by use of atypical neuroleptics while depression can be managed by the use of antidepressants such as selective serotonin reuptake inhibitors (SSRIs). For preventing AD and VCI, modification of cardiovascular risk factors has been suggested. The risk factors include diabetes, hypercholesterolemia, and hypertension. Associated lifestyles changes in diet, physical activity, smoking, obesity, alcohol consumption, etc. may also help manage VCI.
- Nimodipine 30 mg once daily, donepezil 10 mg, maintain till the higher cognitive functions become stable.

Abbreviations

AD, Alzheimer's disease
SIVD, subcortical ischemic vascular disease
VAD, vascular dementia
VCI, vascular cognitive impairment

Conclusion

VAD is a diverse condition encompassing various conditions. SIVD can imitate AD, and as like AD, SIVD also demonstrates a slow progression in cognitive decline. Changes in mood and behavior, along with impairments in frontal executive symptoms can be revealed by carrying out neuropsychological tests and extensive medical histories. Dementia from other causes can be differentiated from SIVD by the help of neuroimaging studies and identifying specific CSF biomarkers. Proper management and early treatment of SIVD along with secondary stroke prevention can be accomplished effectively by clinicians by reviewing carefully a patient's medical history, his test reports obtained following neurological examinations, structural/functional neuroimaging, biomarker analysis, etc. Means of making the treatment and diagnosis of SIVD more effective and efficient include development of diverse experimental SIVD model for thorough understanding of the pathology. Identifying and corroborating the specific biomarkers will also assist in improving treatment strategies. Maintaining a database of extensively collected details from longitudinal studies, data from imaging and biomarker studies for subcortical vascular MCI and SIVD is required, which can be shared with fellow scientists and researchers for ensuring better management of the disease condition. Standardization methods for vascular lesions in neuroimaging and neuropathologies are underway. However, miles are to be covered before the concept of SIVD can be incorporated in clinical practice and be accepted widely.

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CHAPTER

94 Chronic Inflammatory Demyelinating Polyradiculoneuropathy

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Abstract

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated disorder of peripheral nerves and radicles. It is usually a symmetrical, non-length-dependent hyporeflexic neuropathy, involving both proximal and distal limbs, with motor and sensory deficits, progressing over at least 08 weeks. Although a rare entity, it is thought to represent about one-fifth of all initially undiagnosed neuropathies, and is one of the commonest treatable neuropathies worldwide. Pathophysiologically, it is characterized by immune-mediated loss of myelin, resulting in slowed/blocked nerve conduction. Many new paranodal proteins, which may be specific targets of immune attack in some subsets of CIDP, have been described. Clinically, it differs from Guillain-Barre syndrome (GBS) with respect to the onset and duration of symptoms, as well as prominent involvement of sensory nerves. In contrast to GBS, which is monophasic, CIDP is a chronic, relapsing-remitting illness, and requires long-term immunosuppression. Corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIg) are the recommended first-line therapies, and 50–90% patients respond to one of these. Apart from this, many atypical variants of CIDP have also been described. The EFNS/PNS Criteria 2010 are used to diagnose CIDP on the basis of clinical and electrophysiological data. After the first-line treatment, long-term immunosuppression is usually given in the form of either oral drugs such as azathioprine, methotrexate, mycophenolate, or biologicals such as rituximab. Subcutaneous IVIg has been recently approved as a maintenance therapy for CIDP. Few validated scoring systems are available for objectively documenting the response to therapy. The aim, in the long term, is to balance risk of early relapse with the need to avoid overtreatment and immunosuppression. Overall, CIDP remains one of the few chronic neuropathies that are readily treatable, and early diagnosis and appropriate treatment are crucial to improve the patient's quality of life.

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated disorder of peripheral nerves and radicles. It is a symmetrical, non-length-dependent hyporeflexic neuropathy, involving both proximal and distal limbs, with motor and sensory deficits, progressing over at least 8 weeks. It was first described by Austin in 1958, and later identified as a separate entity—"Chronic Inflammatory Polyradiculoneuropathy," by Dyck in 1975.[1,2] It has an estimated incidence of 0.7–1.6 cases per 100,000 per year, and prevalence varying 1.2–8.9 per 100,000 persons.[3] Although a rare entity, it is thought to represent about one-fifth of all initially undiagnosed neuropathies, and is one of the commonest treatable neuropathies worldwide.[4] Corticosteroids, plasmapheresis and intravenous immunoglobulin (IVIg) are the recommended first-line therapies,[4] and 50–90% patients respond to one of these.[5]

Epidemiology

CIDP is a disease of adulthood, and its prevalence increases with increasing age. In patients less than 19 years of age, the prevalence is 0.23–1.26 per 100,000; while it increases up to 5.74–14.37 per 100,000 in ages above 60 years.[3] It is 1.6–2.9 times more common in males.[3] It is also more common among diabetics, though exact figures are debatable.[6]

Pathophysiology

CIDP is characterized by immune-mediated loss of myelin, predominantly in the spinal roots, proximal nerve trunks, and major plexuses, but it can also be disseminated throughout the peripheral nerves. This causes slowing of nerve conduction and/or conduction block.[7]

Myelinated axons only allow action potentials at the nodes of Ranvier between the myelinated internodes (saltatory conduction), and they propagate the action potential at rates significantly higher (70–150 m/sec) than in unmyelinated neurons (0.5–10 m/s) **(Fig. 1)**.

Both cell-mediated and humoral mechanisms are involved in pathogenesis of CIDP. It is considered an autoimmune response against some unidentified Schwann cell/myelin antigen. The trigger for this autoimmune response is also unknown.[7]

Cellular mechanisms are implicated on the basis of inflammatory infiltrates in nerve biopsies, changes in the frequencies/function of T-cell subsets, altered expression of cytokines in blood and CSF of patients, and the role of T-cells in experimental autoimmune neuritis (EAN) model.[7,8]

Deposition of immunoglobulins and complement on the surface of Schwann cells and myelin in sural nerve biopsies, and rapid response to plasmapheresis indicate the role of humoral immune-system.[7]

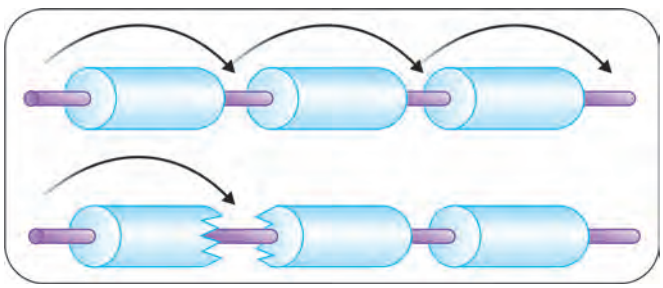

Fig. 1: Upper panel: Normal saltatory conduction along myelinated nerves; Lower panel: Breakdown of saltatory conduction due to demyelination

Proteins in and around the node of Ranvier are also involved. The paranode consists of contactin-1/CASPR-1(contactin associated protein-1) complexes, which bind to Schwann cell neurofascin-155 (NF155). They are vital for the initial clustering of sodium (Na^+) channels, and maintenance of clustering at the node,[9] acting as a membrane barrier to limit diffusion of ion channels essential for saltatory conduction. They undergo immune-attack in several anti-ganglioside-mediated "nodoparanodopathies."[9] Antibodies against NF155 have been identified in 4% of CIDP cases.[10] An additional subset of CIDP has been identified with autoantibodies against contactin-1/CASPR-1 complex.[11]

Clinical Features

Typically, patients have relatively symmetric proximal and distal weakness (non-length dependent), along with sensory dysfunction in the form of paresthesias, numbness, sensory ataxia, and uncommonly pain. By definition, these symptoms must progress for at least 8 weeks. On examination, profound hyporeflexia/areflexia is characteristic.[4,8]

Though motor weakness is often more prominent and disabling, sensory loss occurs in up to 90% of patients, and is greater for vibration and proprioception than pain and temperature. Pain is rare initially, but is present in up to 70% of patients in the long term.[8]

Uncommon features:

- Cranial neuropathy—up to 20% cases: facial nerve (10–15%) or oculomotor nerve (5%)[8]
- Back pain—lumbar canal stenosis or cauda equina syndrome can occur rarely if there is marked nerve root swelling or hypertrophy[12,13]
- Distal neuropathic tremors—up to 50% of patients[13]
- Dysautonomia—mild, limited distribution[13]
- Respiratory failure—extremely rare (<5%), must prompt search for alternate diagnosis[13]

There are also variations in onset and course of CIDP **(Table 1)**.[14]

Acute onset and relapsing forms are difficult to distinguish from Guillain-Barré syndrome (GBS) **(Table 2)**. Patients with GBS-like presentation who progress beyond 8 weeks, or relapse beyond 2 months or more than twice, are considered to have CIDP.[15]

TABLE 1 Variations in onset and course of CIDP

Onset (duration between onset to worst weakness)		*Course*	
Acute (<4 weeks)	2–16% cases	Chronic progressive	Around 2/3rd
Subacute (4–8 weeks)	17–35%	Relapsing-remitting	Between 18–33% (more common in younger patients)
Gradual (>8 weeks)	>50%	Monophasic	Between 10–25% (more common in children)

TABLE 2 Differences between GBS and CIDP

Features	*GBS*	*CIDP*
Onset	Acute	Insidious
Nadir of weakness (from onset)	<4 weeks	>8 weeks
Antecedent events (infections, vaccination, etc.)	>70% cases	<30%
Sensory features	Less prominent	More prominent
Dysautonomia	65%, may be severe	25%, may be mild
Respiratory failure	Common	Rare
Response to steroids	Absent	Present

Apart from this, there are many other clinical variants of CIDP, which are syndromically distinct **(Table 3)**.

Some clinical conditions may predispose a patient to CIDP. They should be investigated in all patients, because treatment of the primary underlying disease may sometimes lead to improvement of neuropathy **(Box 1)**.[17]

Diagnosis

Currently, EFNS/PNS criteria-2010 are the most widely accepted diagnostic criteria **(Table 4)**.[18] Maximum emphasis is placed on clinical and electrophysiological evidence of demyelination. All other investigations are supportive. The second revision of these criteria has just started, and further changes are expected.[19]

Differential Diagnosis

Immune mediated: GBS, MMN, drug-induced demyelinating neuropathy [TNF-alpha inhibitors-(infliximab, etanercept, adalimumab), tacrolimus, checkpoint inhibitors, bortezomib].

Metabolic: Diabetic and rarely, uremic neuropathies.

Systemic diseases: Amyloidosis, sarcoidosis, lymphoma, paraproteinemia-associated neuropathy, POEMS.

Infections: Neuroborreliosis, diphtheria, leprosy, HIV-associated neuropathy or radiculopathy, CMV-radiculopathy.

Hereditary: Hereditary neuropathy with pressure palsy, Charcot Marie Tooth disease, Fabry disease, Refsum disease, mitochondrial neuropathies.

Treatment

Corticosteroids, plasmapheresis and IVIg are approved first-line therapies for the treatment of CIDP.[4,5]

Steroids: Treatment is initiated with high dose/pulse of oral or injectable steroids. Regimens proven in trials include daily prednisolone (1–1.5 mg/kg), dexamethasone pulses, methylprednisolone intravenous or oral pulses. High dose should be maintained for at least 3–6 months, when the disease plateaus, after which gradual taper may be attempted. Relapse rates are unacceptably high; so, a steroid-sparing agent should be added with the initial regimen, so that by the time steroid taper is started, the other immunosuppressant is effective.[4,20]

IVIg: The ICE study established the role of IVIg as a first-line therapy.[21] Dose—2 gm/kg divided over 5 days. Maintenance doses may be required every 4–8 weeks.[22]

TABLE 3 Clinical variants of CIDP

Lewis-Sumner syndrome *[Also called multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)]*	Strikingly asymmetrical sensory and/or motor deficits in individual nerve distributions, clinical and electrophysiological motor and sensory involvement, (distinguishing it from multifocal motor neuropathy), steroid responsive[13,16]
Chronic Immune Sensory Polyradiculopathy (CISP)	Sensory ataxia due to inflammation restricted to dorsal roots—progressive numbness, ataxia, hyporeflexia, normal power. Nerve conduction studies (NCS) usually normal, but somatosensory evoked potentials (SSEP) shows prolongation. MRI may show enhancing radicles[13,16]
Sensory-Predominant CIDP (*Chronic sensory demyelinating neuropathy)*	Prominent sensory ataxia, pain, and paresthesias. Despite the lack of weakness, NCS shows significant motor conduction slowing 10% of CIDP, responds well to IVIg[13,16]
Distal Acquired Demyelinating Symmetric Neuropathy (DADS)	Symmetric, sensory, or sensorimotor starting distally in the lower limbs, without proximal involvement (length-dependent). Slowly progressive, frequently (nearly 2/3rd) associated with IgM paraprotein. Approximately 50% DADS with IgM also have anti-MAG antibodies. Tends to be resistant to standard therapies for CIDP[4,16]
Pure Motor CIDP	Rare (2–5%)—involvement of motor and sparing of sensory fibers. Non-segmental pattern of weakness, lack of bulbar involvement, demyelinating electrophysiologic abnormalities, and response to immunotherapy distinguish it from motor neuron disease[16]
Neurofascin antibody-mediated CIDP	IgG4 autoantibodies to neurofascin-155(NF155). Younger age at onset, more common sensory ataxia and tremor. Often responsive to B cell depletion therapy (e.g., rituximab), less response with IVIg[10]
Contactin-1 antibody-mediated CIDP	Clinical phenotype not well established, often characterized by advanced age, rapid onset and severe, predominantly motor, and early axonal involvement. May also be responsive to B cell depletion, and refractory to IVIg[11]
CANOMAD (Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies)	Similar to the Miller Fisher variant of GBS, though chronic in nature (disialosyl ganglioside is GQ1b). Other associated IgM antibodies include GD1a and GD1b, which cause a sensory-predominant disorder
Localized variants	Limited chronic focal upper limb variant and chronic inflammatory lumbosacral polyradiculopathy (considered a regional lower extremity variant of CIDP), responsive to IVIg[12]

BOX 1 Conditions associated with CIDP

- Hepatitis C
- Lymphoma
- Monoclonal gammopathy of undetermined significance (MGUS)
- HIV/AIDS
- Organ transplant recipients
- Connective tissue disorders (notably SLE and Sjogren's syndrome)
- Inflammatory bowel disease
- Melanoma
- Diabetes mellitus

Plasmapheresis (PLEX): In a rapidly deteriorating patient, PLEX is the best treatment.[4,5] Usually, 5–7 cycles are performed over 2–4 weeks. Improvement begins within days, but relapse rates after stopping are very high (70%, 14 days after stopping PLEX). Therefore, additional immunosuppressive medication must be used. It is preferred, if patients are very weak, rapidly deteriorating, or unresponsive or intolerant to steroid or IVIg.[4,8,12,13,18]

Subcutaneous immunoglobulin (SCIG): PATH study (2018) comparing low-dose SCIG (0.2 g/kg), high-dose SCIG (0.4 g/kg), and placebo, showed absolute risk reduction (for relapse) of 25% for low-dose, and 30% for high-dose SCIG compared to placebo.[23] Therefore, SCIG seems to be a promising agent, but requires further large-scale studies to establish dosing protocols.

Biological agents: Rituximab was shown to be effective in a small retrospective Italian study.[4,5] In refractory CIDP, and patients with NF-155 or CASPR-1 associated disease, it has been stated to be an effective drug.[10,11] The RECIPE trial, started recently, hopes to shed more light on its role in CIDP.[24]

TABLE 4 EFNS/PNS 2010 criteria for CIDP

Clinical criteria

- **Inclusion criteria**
  - ***Typical CIDP***
    - Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities
    - Duration ≥2 months
    - Absent/reduced DTRs in all extremities
  - ***Atypical CIDP***
    - Predominantly distal (DADS)
    - Asymmetric (MADSAM)
    - Focal (e.g., involvement of the brachial or lumbosacral plexus, or of one upper or lower limb)
    - Pure motor
    - Pure sensory (including CISP)
- **Exclusion criteria**
  - Neuroborreliosis, diphtheria, drug, or toxin exposure probable to have caused neuropathy
  - Hereditary neuropathy
  - Prominent sphincter disturbance
  - Multifocal motor neuropathy (MMN)
  - Other causes—POEMS, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, peripheral nervous system (PNS) lymphoma, amyloidosis
- **Supportive criteria**
  - Elevated CSF protein with leukocyte count <10/mm^3
  - MRI: Gd-enhancement and/or hypertrophy of cauda equina, nerve roots, or brachial or lumbosacral plexuses
  - Abnormal sensory electrophysiology in at least 1 nerve:
    - Normal sural with abnormal median or radial sensory nerve action potentials (SNAP)
    - Conduction velocity <80% of lower limit of normal (LLN) (<70%, if SNAP amplitude <80% of LLN)
    - Delayed SSEP without CNS disease
  - Objective clinical improvement following immunomodulation
  - Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis

Electrophysiological criteria

- **Definite:** At least one of the following:
  - Motor distal latency ≥50% above upper limit of normal (ULN) in two nerves (excluding median neuropathy at the wrist), or
  - Reduced motor conduction velocity ≥30% below LLN in two nerves, or
  - Prolonged F-wave latency ≥30% above ULN in two nerves (≥50%, if motor amplitude <80% LLN), or
  - Absent F-waves in two nerves if these nerves have distal motor amplitudes ≥20% of LLN + ≥1 other demyelinating parameter in ≥1 other nerve, or
  - Partial motor conduction block: ≥50% proximal motor amplitude reduction relative to distal, if distal amplitude ≥20% LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve, or
  - Abnormal temporal dispersion (>30% duration increase between the proximal and distal CMAP) in ≥2 nerves, or
  - Distal CMAP duration increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) + ≥1 other demyelinating parameter in ≥1 other nerve
- **Probable:** ≥30% amplitude reduction of the proximal CMAP relative to distal, excluding posterior tibial nerve, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve
- **Possible:** As in "definite" but in only one nerve

TABLE 5 Overall disability sum score

Arm disability scale – function checklist	***Not affected***	***Affected but not prevented***	***Prevented***
Dressing upper part of body (excluding buttons/zips)	○	○	○
Washing and brushing hair	○	○	○
Turning a key in a lock	○	○	○
Using knife and fork (/spoon—applicable if the patient never uses knife and fork)	○	○	○
Doing/undoing buttons and zips	○	○	○
Arm grade 0 = Normal 1 = Minor symptoms or signs in one or both arms but not affecting any of the functions listed 2 = Moderate symptoms or signs in one or both arms affecting but not preventing any of the functions listed 3 = Severe symptoms or signs in one or both arms preventing at least one but not all functions listed 4 = Severe symptoms or signs in both arms preventing all functions listed but some purposeful movements still possible 5 = Severe symptoms and signs in both arms preventing all purposeful movements			
Leg disability scale – function checklist	***No***	***Yes***	***Not applicable***
Do you have any problem with your walking?	○	○	○
Do you use a walking aid?	○	○	○
How do you usually get around for about 10 metres?			
Without aid	○	○	○
With one stick or crutch or holding to someone's arm	○	○	○
With two sticks or crutches or one stick or crutch and holding to someone's arm	○	○	○
With a wheelchair	○	○	○
If you use a wheelchair, can you stand and walk a few steps with help?	○	○	○
If you are restricted to bed most of the time, are you able to make some purposeful movements?	○	○	○
Leg grade 0 = Walking is not affected 1 = Walking is affected but does not look abnormal 2 = Walks independently but gait looks abnormal 3 = Usually uses unilateral support to walk 10 metres (25 feet) (stick, single crutch, one arm) 4 = Usually uses bilateral support to walk 10 metres (25 feet) (sticks, crutches, two arms) 5 = Usually uses wheelchair to travel 10 metres (25 feet) 6 = Restricted to wheelchair, unable to stand and walk few steps with help but able to make some purposeful leg movements 7 = Restricted to wheelchair or bed most of the day, preventing all purposeful movements of the legs (e.g., unable to reposition legs in bed)			
Overall disability sum score = arm disability scale (range 0–5) + leg disability scale (range 0–7); overall range: 0 (no signs of disability) to 12 (maximum disability). For the arm disability scale: Allocate one arm grade only by completing the function checklist. Indicate whether each function is "affected," "affected but not prevented," or "prevented." For the leg disability scale: Allocate one leg grade only by completing the functional questions.			

TABLE 6 CDAS classification scheme for disease activity

Cute: > 5 years off treatment	• Normal examination • Abnormal examination, stable/improving
Remission: < 5 years off treatment	• Normal examination • Abnormal examination, stable/improving
Stable active disease: > 1 year, on treatment	• Normal examination • Abnormal examination, stable/improving
Improvemet: > 3 months < 1 year, on treatment	• Normal examination • Abnormal examination, stable/improving
Unstable active disease: abnormal examiation with progressive or relapsing course	• Treatment naïve or < 3 months • Off treatment • On treatment

Other immunosuppressive agents: Methotrexate, azathioprine, and mycophenolate mofetil are common steroid-sparing agents. Cyclosporine and cyclophosphamide are also used as second-line agents.

Strength-training exercises and gradual weight bearing, along with orthotics (when required) are also extremely important for recovery. Symptomatic treatment for neuropathic pain, dysesthesias, tremors, and dysautonomia is given as clinically indicated.

Most patients show maximum benefit from IVIg or steroids by 3rd month. If a clear treatment response is not documented by 3–6 months, the drug, dosage, or diagnosis should be reconsidered.[8] Once maximum benefit is achieved, structured dose reduction or optimization may be attempted.[19] However, the strategy to best taper treatment is unknown. Objective documentation of treatment response may help in such decision-making. INCAT-ODSS (Inflammatory Neuropathy Cause and Treatment-Overall Disability Sum Score) scale for disability assessment,[25] and CDAS (CIDP Disease Activity Status)[26] scheme for disease activity are two such scoring systems **(Tables 5 and 6)**. The aim is to balance risk of early relapse with the need to avoid overtreatment and immunosuppression.

Prognosis

Overall, CIDP is a treatment-responsive neuropathy, and 50–90% patients respond to one of the first-line therapies.[4,5] Lack of response must prompt search for alternative etiology. Poor prognostic factors are rapidly progressive disease, early axonal changes on NCS, advanced age, delayed initiation of therapy, and high proportion of fibers showing demyelination on biopsy.[27] A recent study also identified certain patterns on nerve ultrasound at the time of diagnosis, which may predict good response to treatment.[28] In the original series by Dyck et al. (1975), 60% were ambulatory, 25% wheelchair or bed-bound, and 10% died.[2] This figure has significantly improved with advances in diagnosis and treatment, and in a recent 14-year study of Danish patients, 53% could discontinue treatment, only 6% had severe morbidity, and 1% died.[29] However, CIDP is a lifelong disease that invariably results in some residual disability even with effective therapies.[5]

Conclusion

CIDP is a treatable immune-neuropathy with variable clinical presentation. Diagnosis is based on clinical phenotype and electrophysiological features. Early and effective immunotherapy can prevent long-term disability accumulation. Regular follow-up with objective monitoring can help in therapeutic decision-making.

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CHAPTER

95 Autoimmune Encephalitis

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Abstract

Autoimmune encephalitis is an upcoming cause of altered mental status with a subacute onset. The most common presentation is limbic dysfunction in patients of autoimmune encephalitis. However, other areas like hindbrain, spine, neocortex, striatum, and peripheral nervous system can also be variably involved depending upon the antibody involved. Paraneoplastic and non-paraneoplastic are the two broad categories of antibody dependent CNS disorders. Anti-NMDA Receptor Encephalitis is the most well defined autoimmune encephalitis syndrome. Detection of specific autoantibodies helps in establishing a definitive diagnosis of autoimmune encephalitis. Treatment is aimed at removal of the antibodies and suppression of the immune system. first line therapy includes intravenous methylprednisolone along with IVIG/plasma exchange. Second line therapy includes rituximab, cyclophosphamide, azathioprine, MMF.

Introduction

Autoimmune encephalitis is an upcoming cause of altered mental status with a subacute onset. It is only a recent addition to the medical literature. However, it is still not considered in the differential diagnosis outside of large tertiary care hospitals.

The term "autoimmune encephalitis" includes a group of disorders that present with closely related clinical features and MRI findings, but can be differentiated by the specific antibody.

The most common presentation is limbic dysfunction in patients of autoimmune encephalitis. However, other areas like hindbrain, spine, neocortex, striatum, and peripheral nervous system can also be variably involved depending upon the antibody involved. Prominent extralimbic involvement can also be seen in a few subtypes.

Subacute onset of impaired memory and cognition is generally seen.[1-5]

Pathophysiology

Paraneoplastic and non-paraneoplastic are the two broad categories of antibody dependent CNS disorders.

Paraneoplastic disorders are associated with antibodies acting against intracellular antigens. They are associated with cancer and involve T-cell mediated attack against the neurons. This leads to an irreversible neuronal damage. These antibodies act as useful tumor markers.

The other group involves antibodies against extracellular antigens of ion channels and the receptors. The association with cancer tends to be variable. The prognosis in this group is much better. The antibodies are directly pathogenic and cause reversible damage to the neurons without neuronal death.

Clinical Features

Autoimmune encephalitis can have varying manifestations. The typical presentation is altered cognition along with

TABLE 1 Autoimmune encephalitis syndromes

Antigen	*Clinical features*	*Tumor association*
NMDAR	Psychosis, insomnia, memory impairment, seizures, dyskinesias, autonomic disturbances	Ovarian teratoma
LGI1	Myoclonus, hyponatremia, dystonic seizures	Thymoma in 5% cases
Contactin-associated protein-like 2	Limbic encephalitis, neuromyotonia, memory loss and confusion, sleep disturbances, autonomic instability, neuropathic pain	Thymoma
AMPAR	Psychiatric disturbances	70% (various solid tumors)
GABA-A receptor	Rapidly deteriorating encephalopathy, status epilepticus, epilepsia partial continua	Thymoma (40%)
GABA-B receptor	Seizures, limbic encephalitis	SCLC
IgLON5	REM and non-REM sleep disturbances, obstructive sleep apnea	No association with cancer
DPPX	Encephalopathy, CNS hyperexcitability, hyperekplexia	Rarely B cell neoplasms
GlyR	Encephalomyelitis, muscle spasms, rigidity, myoclonus, hyperekplexia	H/O carcinoma
Metabotropic glutamate receptor 5	Encephalitis	Hodgkin's lymphoma* or no tumor
Metabotropic glutamate receptor 1	Ataxia	Hodgkin's lymphoma or no tumor
Neurexin 3-alpha	Confusion, seizures, encephalitis, dyskinesias	No cancer association
D-2 receptor	Involvement of basal ganglia	No cancer association

*Limbic encephalitis and Hodgkin's lymphoma are together known as Ophelia syndrome.
AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2, contactin-associated protein-like 2; CNS, central nervous system; DPPX, dipeptidyl-peptidase-like protein 6; FLAIR, fluid-attenuated inversion recovery; GABA, gamma-aminobutyric acid; GlyR, glycine receptor; LGI1, leucine glioma inactivated 1; mGluR, metabotropic glutamate receptor; MRI, magnetic resonance imaging; NMDAR, N-methyl-D-aspartate receptor; REM, rapid eye movement.

subacute progressive decrease in consciousness. Memory involvement occurs early in the disease **(Table 1)**.

Anti-NMDA Receptor Encephalitis

It is the most well defined autoimmune encephalitis syndrome. The pathogenesis involves IgG autoantibodies acting against the GluN1 portion of the NMDAr. The neuronal dysfunction is reversible initially but may become permanent if untreated due to persistent inflammation and glutamate excitotoxicity mediated by NMDA.

Clinical features:

- Prodromal symptoms like headache, fever, malaise
- Psychiatric symptoms such as bizarre, agitated, anxious behavior, hallucinations[6]
- Insomnia, seizures, memory deficits, decreased consciousness, stupor with catatonic features
- Dyskinesias, autonomic dysfunction

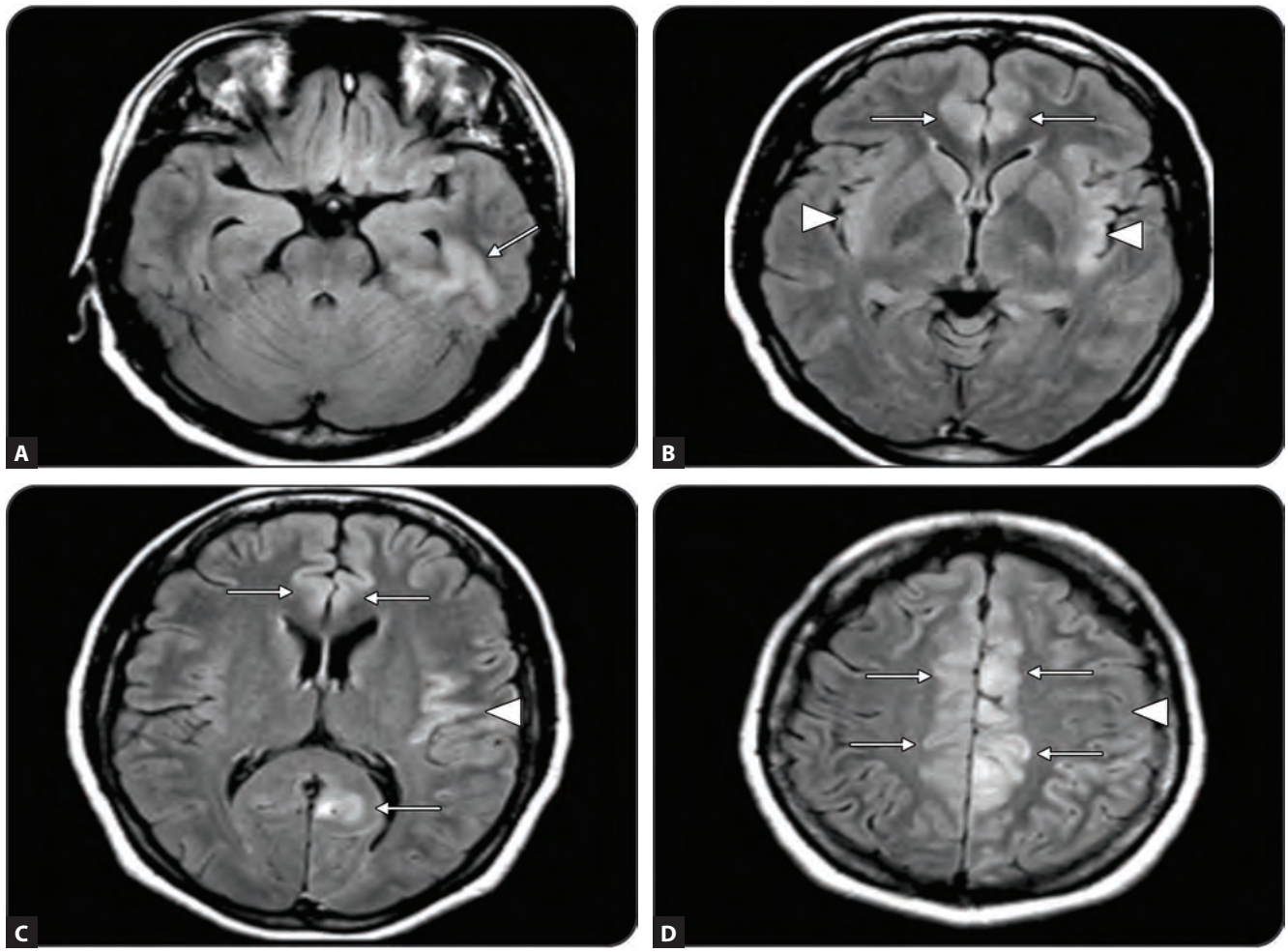
Diagnosis and differential diagnosis **(Table 2)**:

- Cerebrospinal fluid (CSF) analysis shows:
  - lymphocytic pleocytosis or
  - oligoclonal bands
- Electroencephalography (EEG) shows infrequent epileptic activity and frequent slow, disorganized activity
- MRI is usually normal or may show transient abnormalities in cortical or subcortical regions. Medial temporal symmetric hyperintensities are most frequent findings **(Figs. 1A to D)**
- PET scan demonstrates an increased gradient of cerebral glucose metabolism in the frontal-occipital region
- The detection of IgG antibodies against the GluN1 portion of the NMDA receptor is confirmatory of anti-NMDA encephalitis[7]

TABLE 2 Anti-NMDA receptor encephalitis diagnostic criteria

Probable anti-NMDA receptor encephalitis
All three criteria must be present: • Subacute onset (<3 months) of 4 out of 6 major groups of symptoms:* – Psychiatric manifestations or cognitive decline – Speech involvement – Involvement of the autonomic system – Seizures – Movement disorder – Depressed level of consciousness • One of the following: – Abnormal EEG (epileptic activity, slow/disorganized activity, extreme delta brush) – Oligoclonal bands or pleocytosis on CSF examination • Exclusion of other differentials
Definite anti-NMDA receptor encephalitis
• Positive IgG antibodies against GluN1 with 1 or more of the 6 major groups of symptoms, along with exclusion of other differentials

*Diagnosis can be made by presence of three groups of symptoms in the presence of ovarian teratoma



Figs. 1A to D: MRI showing T2 hyperintensity in the left inferior temporal lobe (A), cingulate gyrus (B–D), insular cortex (B and C)

Association with tumors: The occurrence of ovarian teratoma is dependent upon the age at which the patient presents. Female patients who are older than 18 years have ovarian teratomas in 50% of the cases, while girls who are younger than 14 years have a teratoma in 9% of the cases. Detection of a tumor is rare in male patients.

Association with HSVE: Herpes simplex viral encephalitis (HSVE) is associated with Anti-NMDA receptor encephalitis. MRI features like asymmetry of temporal lobe hyperintensities may be subtle findings, which may differentiate between the two diseases.

Treatment and prognosis: Treatment options include:

- *Immunosuppression:* Immunosuppression in form of IV methylprednisolone (1 g/day for 5 days) and either IVIG (400 mg/kg per day × 5 days) or PEX (plasma exchange)
- Tumor resection

Second-line therapies: Rituximab (375 mg/m^2 once a week × 4 weeks, or 1 g twice given two weeks apart) and cyclophosphamide (750 mg/m^2 once a month × 4–6 months). Other agents include Azathioprine and MMF.[8]

Anti-LGI1 Encephalitis

Hyponatremia, myoclonus and fasciobrachial dystonic seizures are most common presentations.[9-12]

This is a usual cause of rapidly progressive dementia in elderly. Recurrent hyponatremia is also common.

MRI shows features typical of limbic encephalitis. CSF is often normal or only shows oligoclonal bands.

Around 5–10% of cases are associated with thymoma.

Treatment includes glucocorticoids, IVIG, *mycophenolate* mofetil, and/or plasma exchange.

Anti-Caspr2-Associated Encephalitis

Anti-Caspr2 (contactin-associated protein-like 2) associated encephalitis commonly presents as limbic encephalitis, as Morvan syndrome (neuromyotonia, memory involvement and confusion, sleep disturbance, autonomic disturbance), or it can even present as isolated neuromyotonia referred to as Isaacs syndrome.[13] The progression of the disease is slower than other autoimmune encephalitis syndromes. It is usually not associated with cancer.

The target antigen, Caspr2, is involved in the normal functioning of voltage-gated potassium channels (VGKC).

Patients with thymoma are more likely to develop Morvan syndrome.

Immunotherapy remains the mainstay of treatment.

Anti-AMPA Receptor Encephalitis

Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAr) encephalitis presents with purely psychiatric symptoms.

It has a high association with cancer, more commonly in lung, breast, or thymic tumors.

Treatment consists of management of underlying tumor and/or immunotherapy.

Anti-GABA-A Receptor Encephalitis

It is characterized by a rapidly progressive encephalitis along with seizures which are refractory to the usual treatment, status epilepticus, or may even present with epilepsia partialis continua.

Tumors, most commonly thymoma, occur in 40% of patients.

Immunotherapy is the mainstay of treatment. Pharmacologic-induced coma may be required for prolonged seizures.

Anti-GABA-B Receptor Encephalitis

It is characterized by antibodies against the B1 subunit of the gamma-aminobutyric acid B (GABA-B) receptor. The patients commonly present with limbic encephalitis. Approximately 50% of the cases are associated with small cell carcinoma of lung.

Treatment includes immunotherapy and tumor treatment.

Anti-IgLON5 Encephalopathy

Patients present with sleep disorders (REM and non-REM) along with abnormal movements during sleep and features of obstructive sleep apnea.[14]

Video-polysomnography is essential to define the complex sleep disorder. CSF and imaging studies are normal aside from the presence of IgLON5 antibodies in CSF and serum. Response to immunotherapy is poor.

Anti-DPPX Encephalitis

Patients with antibodies against dipeptidyl-peptidase-like protein-6 (DPPX) present with prodromal symptoms of

weight loss and diarrhea, followed by encephalitis with features of central hyperexcitability (agitation, myoclonic seizures, tremors, hyperekplexia).

Treatment consists of immunotherapy.

Anti-GlyR Encephalopathy

Antibodies to the α-1 subunit of the glycine receptor (GlyR) have been associated with a syndrome of PERM, acquired hyperekplexia, and stiff-person syndrome.

Most patients respond to immunotherapy.

Anti-mGluR5 Encephalitis

Antibodies against the metabotropic glutamate receptor 5 (mGluR5) are associated with features suggestive of limbic encephalitis.

Hodgkin lymphoma (Ophelia syndrome) and SCLC are the tumors most commonly associated with this syndrome.

Treatment consists of immunotherapy and management of the underlying tumor.

Anti-mGluR1 Encephalitis

Anti-metabotropic glutamate receptor 1 (mGluR1) encephalitis presents commonly with ataxia (cerebellar).

There is usually no association with cancer. The patients improve with early immunotherapy.

Anti-Neurexin-3 Alpha Encephalitis

The common presenting features are severe encephalitis, progressively worsening consciousness, dyskinesias, and hypoventilation.

Treatment consists of immunotherapy.

Diagnostic Approach

Detection of specific autoantibodies helps in establishing a definitive diagnosis of autoimmune encephalitis.

Characteristic MRI findings in such patients include hyperintensities on FLAIR or T2-weighted images in affected brain regions commonly medial temporal lobes and/or brainstem.

Nonspecific EEG abnormalities are common and include focal/generalized slowing, epileptiform activity, and periodic lateralized epileptiform discharges (PLEDs). Patients with N-Methyl-D-aspartate (NMDA) receptor encephalitis have a characteristic EEG pattern called extreme delta brush.

CSF findings include modest elevation of protein usually less than 100 mg/dL, lymphocytic pleocytosis, elevated immunoglobulin G, and/or oligoclonal bands.

The patient should also be evaluated for occult malignancy, with the tumor location being guided by the presenting syndrome.

Antibody testing: Paraneoplastic and autoimmune antibody testing should be performed on both serum and CSF.[15]

General principles to be followed are:

- Test for antibodies in serum and CSF. Testing serum and then, if negative, testing CSF delays diagnosis and can lead to false positive results and is therefore not recommended.
- If the CSF is negative but the serum antibody is positive, the serum result should be considered as a false-positive diagnosis.
- If the clinical findings do not correlate with the antibody identified, the antibody identified may be a false-positive, particularly if the antibodies were identified only in serum.

Diagnostic Criteria[16]

See **Table 3**.

Treatment Approach (Flowchart 1)[17]

Treatment for autoimmune encephalitis when suspected clinically should be started prior to results of antibody testing after infectious etiology has been ruled out. The results of antibody testing can then be used to refine treatment strategy.

Treatment is aimed at removal of the antibodies and suppression of the immune system.

First-line therapy includes intravenous *methylprednisolone*, for example, 1 gm daily for 5 days in an adult and either intravenous immunoglobulin G, for example, 400 mg/kg per day × 5 days or PEX (plasma exchange) and tumor removal as and when indicated.

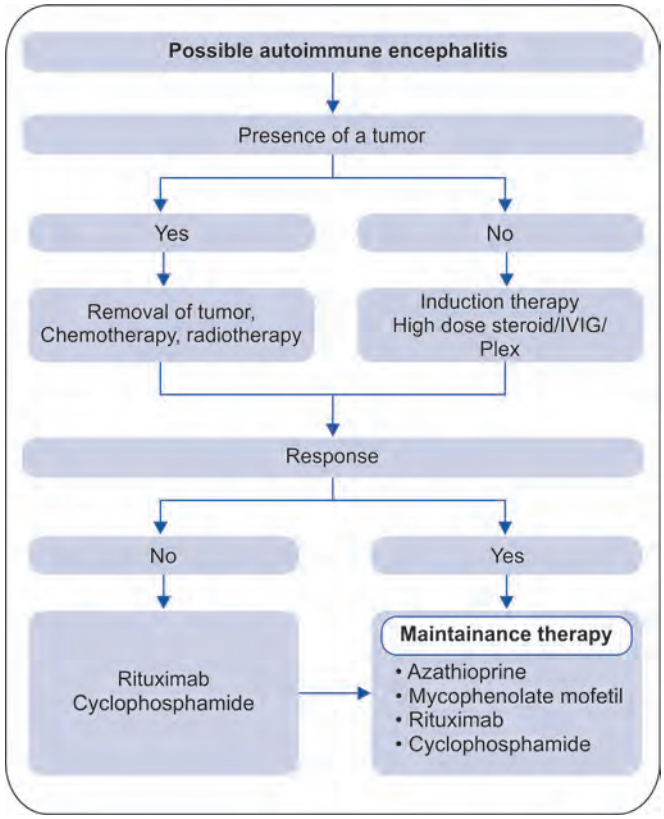
Second-line therapies include *rituximab* (either 375 mg/m^2 weekly × 4 weeks, or 1 gm given twice 2 weeks apart) and *cyclophosphamide* (750 mg/m^2 once a month × 4–6 months depending on results). Other agents include Azathioprine and MMF.

Seizures should be treated aggressively with antiepileptic drugs.

TABLE 3 Autoimmune encephalitis diagnostic criteria

Possible autoimmune encephalitis
All three following criteria should be met: • Subacute onset (<3 months) of memory disturbances, alteration in sensorium, or psychiatric signs and symptoms • At least one of the following features: – New onset focal neurological deficit – Seizures unexplained by a previous seizure disorder – Raised CSF cell count (>5 white blood cells per mm^3) – MRI showing features suggestive of encephalitis • Exclusion of other differentials
Definite autoimmune limbic encephalitis
All four following criteria must be met: • Subacute onset (<3 months) of features suggestive of limbic system involvement (memory disturbances, seizures, or psychiatric signs and symptoms) • MRI showing bilateral brain involvement of medial temporal lobes • At least one of the following: – Raised CSF cell count (>5 white blood cells per mm^3) – EEG showing epileptic/slow-wave activity restricted to temporal lobes • Exclusion of other differentials

Flowchart 1: Approach to autoimmune encephalitis



Conclusion

Autoimmune encephalitis is an important differential in patients presenting with altered sensorium of a subacute onset. The two main groups (intracellular directed antibodies and cell-surface directed antibodies) have a considerable overlap. Limbic structures are most commonly involved on neuroimaging. A small percentage of patients have no findings on neuroimaging in spite of profound neurological dysfunction, but antibody testing can ultimately lead to the diagnosis of autoimmune encephalitis in such patients.

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CHAPTER

96

Benign Paroxysmal Positional Vertigo: Diagnosis and Management by Physical Therapy and Repositioning Maneuvers

Ajay Kumar Vats, Atulabh Vajpeyee, GD Ramchandani, Jugal Kishor Sharma

Abstract

Benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular disorder worldwide. It is of paramount importance to understand the pathophysiology of this purely mechanical vestibular disorder. This is because the treatment involves physical therapy and/or repositioning maneuvers, which are dependent on the elicited positional nystagmus that localizes as well as lateralizes the involved semicircular canal. The chapter discusses the pathophysiology, clinical subtypes, diagnostic oculomotor patterns (positional nystagmus), and therapeutic repositioning maneuvers, and physical therapy for the treatment of different subtypes of the BPPV. The YouTube link of videos of diagnostic positional tests and the therapeutic repositioning maneuvers are presented in a tabular form.

Introduction

Benign paroxysmal positional vertigo (BPPV) is a mechanical disorder of the membranous labyrinth and is the most frequent cause of vertigo worldwide. It is caused by vestibular lithiasis, which exists in two forms:

- *Canalolithiasis:* The degenerative otoconial debris gets detached from the utricular matrix and inappropriately enters one of the three semicircular canals namely posterior, horizontal, and anterior in that order of frequency.[1]
- *Cupulolithiasis:* The otoconial debris becomes inappropriately adherent to the cupula, making it heavy and gravity sensitive.[2] Cupulolithiasis exists in two forms, with the otoconial debris getting attached to either canal (Cup-C) or utricular (Cup-U) side of the cupula.[3]

The chief symptom of BPPV is severe rotational vertigo triggered by changes in the position of head relative to the gravity. The typical situations during which attacks occur are lying on the bed, getting up from supine to sitting, assuming lateral recumbent positions, bending forward (e.g., to tie shoelaces), and pitching the head up (e.g., keeping an object on a high shelf). The associated autonomic symptoms like perspiration, nausea, and vomiting are more common in the horizontal semicircular canal benign paroxysmal positional vertigo (HSC-BPPV).[4] The head motion normally moves endolymph in the appropriate semicircular canal, bending the cupula to generate the nerve impulse in the vestibular nerve: the latter apprises the brain (via the vestibulo-ocular reflex) in which plane and at what angle the head has moved. Consequently, the brain reflexely generates the corrective eye movements equal in angle but in the opposite direction so that the point of fixation falls on the fovea centralis. If otoconial particles inappropriately enter any of the semicircular canals, they continue to drag endolymph for few seconds (maximum 30 seconds in canalolithiasis[5] and longer in cupulolithiasis[6]) even after the head movement has ceased, thus causing a sudden severe asymmetry in the resting vestibular tone and a transient severe vertigo. By a similar mechanism, a sudden severe asymmetry of the resting vestibular tone results from a cupula that has been rendered abnormally heavy and gravity-sensitive by the adherent otoconial debris and the consequent positionally triggered vertigo.

TABLE 1 Relative frequencies of the different BPPV subtypes presenting to a specialty clinic

Authors	No. of patients	PSC-BPPV (%)	HSC-BPPV (%)	ASC-BPPV (%)	Multiple canals (%)
De la Meilleure et al.,[7] 1996	287	78.05	16.38	-	5.57
Honrubia et al,[8] 1999	292	85.62	5.14	1.37	7.87
Macias et al,[9] 2000	259	93.02	1.94	-	5.04
Korres et al,[17] 2002	122	90.16	8.2	1.64	-
Sakaida et al,[10] 2003	50	56	38		6
Imai et al,[11] 2005	108	64.82	33.33	-	1.85
Nakayama & Epley JM,[12] 2005	833	66.39	10.08	2.28	21.25
Cakir et al,[13] 2006	169	85.21	11.83	1.18	1.78
Moon et al,[14] 2006	1692	60.9	31.9	2.2	5.0
Jackson et al,[15] 2007	260	66.9	11.9	21.2	-
Chung et al,[16] 2009	589	61.8	35.3	2.9	-

PSC-BPPV, Posterior Semicircular Canal Benign Paroxysmal Positional Vertigo; HSC-BPPV, Horizontal Semicircular Canal Benign Paroxysmal Positional Vertigo; ASC-BPPV, Anterior Semicircular Canal Benign Paroxysmal Positional Vertigo

Table 1 shows the relative frequency of all patients diagnosed with BPPV at any specialty clinic.[7-17] Due to its peculiar anatomy, which facilitates the sequestrated degenerative otoconial debris to gravitate into the canal, the posterior semicircular canal BPPV (PSC-BPPV) is the most prevalent variant of the disorder. The relatively higher location of the anterior semicircular canal (ASC) within the bony labyrinth restricts the upward movement of the otoconial debris as well as facilitates self-clearance of any debris' through its non-ampullary arm, that inadvertently enters it. Therefore, the anterior semicircular canal BPPV (ASC-BPPV) is the least prevalent variant of the disorder.[17] In the upright positions, the horizontal semicircular canal (HSC) is inclined 30-degrees relative to the horizontal plane, its cupular barrier is at a higher location, and it becomes vertical in the supine position. Therefore, any free-floating debris that enters the HSC tends to leave the canal through the utricular exit in its non-ampullary long posterior arm during lateral recumbent positions. The spontaneous remissions of HSC-BPPV reported in a few studies are perhaps responsible for its modest frequency.[11,18]

Classification of BPPV

BPPV can be classified as under:

Monocanalicular

- *Posterior Semicircular Canal BPPV (PSC-BPPV):*
  - Geotropic variant (*geo*-PSC-BPPV)—Otoconia either free-floating in the ampullary arm in the juxtacupular location or adherent to the cupula.
  - Apogeotropic (*apo*-PSC-BPPV)—Due to free-floating otoconia in the non-ampullary arm.
- *Horizontal Semicircular Canal BPPV (HSC-BPPV):*
  - Geotropic variant (*geo*-HSC-BPPV)—Due to free-floating otoconia in the long non-ampullary posterior arm (long posterior arm horizontal semicircular canalolithiasis).
  - Apogeotropic Variant (*apo*-HSC-BPPV)—Either due to free-floating otoconia in the short ampullary anterior arm of the HSC (short anterior arm horizontal semicircular canalolithiasis) or due to cupulolithiasis. The latter exists in two forms with otoconial debris getting adherent to either canal (Cup-C) or utricular side (Cup-U) of the cupula.
- *Anterior Semicircular Canal BPPV (ASC-BPPV):* The ASC-BPPV is due to canalolithiasis, as per the consensus statement of the committee for the classification of vestibular disorders of the Bárány Society.[19] The otoconial debris in the ampullary arm of ASC results in positional downbeating nystagmus during the provocative positional tests. The cupulolithiasis of the ASC and the non-ampullary arm ASC canalolithiasis are not convincingly known to exist.

Multicanalicular

- *Single-canal bilateral* involving the same semicircular canal in either of the labyrinths.

- *Multicanal unilateral* involving at least two different semicircular canals (posterior, lateral, or anterior) in one of the labyrinths.
- *Multicanal bilateral* involving two or more different semicircular canals in both labyrinths.

Diagnosis

The clinical features of the BPPV are enumerated in the introduction section of the chapter and it is impossible to localize and lateralize the involved semicircular canals based on the symptomatology alone. Two additional important points about the symptomatology of BPPV are:

- Vertigo in the HSC-BPPV occurs during the lateral movement of the patient's head in the supine position and is less frequent during extension or flexion of the head.[20]
- A prominent sense of continuous dizziness rather than true rotational vertigo still enhanced with the change of position but, overall, continuous is the hallmark of *apo*-PSC-BPPV.[4]

The experiments of Julius Ewald (1855–1921) in pigeons framed the three laws that bear his name, and these laws are fundamental for understanding the pathophysiology of the diagnostic positional tests namely Dix-Hallpike test (DHT), supine roll test (SRT), and straight head hanging test (SHHT), which generate the diagnostic oculomotor patterns for semicircular canals affected by the vestibular lithiasis.[21] Ewald (1892) cannulated each of the three semicircular canals and applied negative and positive pressures to observe the intensity and direction of the generated nystagmus. The two main outcomes of his experiments are:

- The generated nystagmus is always directed parallel to the plane of the stimulated canal (Ewald's 1st law).
- The generated nystagmus is stronger when the endolymph moves toward the ampulla (ampullopetal) in the case of the HSC (Ewald's 2nd law), and away from the ampulla (ampullofugal) in case of vertical semicircular canals (PSC and ASC) (Ewald's 3rd law). With this background knowledge of physiology of semicircular canals, the positional tests are discussed below.

Dix-Hallpike Test[22]

The positional nystagmus generated during DHT is always directed parallel to the plane of the stimulated canal as per the Ewald's 1st law. Lowering the 45-degrees rotated head in the yaw plane to the 20-degrees head hanging position during the DHT aligns the PSC with the sagittal plane and places its ampullary end to the superior most position. Consequently, there is an ampullofugal shift of the otoconial debris in the ampullary arm of the PSC, leading to an excitatory cupular deflection (Ewald's 3rd law) and this generates the oculomotor patterns characterized by an upbeating ipsitorsional positional nystagmus.

The patient is placed on the examination table in long-sitting, such that the distance between his bottoms and the head end of the table allows his head to hang during Dix-Hallpike positioning. The patient's head is held with both hands and is rotated 45-degrees to one side (for example left) in the yaw plane. Thereupon he is positioned supine such that his 45-degrees left rotated head extends 20-degrees on the support of the author's hands representing the left Dix-Hallpike position **(Fig. 1)**. Left Dix-Hallpike positioning is maintained for at least 60 seconds or until elicited nystagmus lasts. A similar sequence of positioning is done in the right head hanging position if no nystagmus is elicited on the initially tested side. The DHT results can be interpreted as:

- An upbeating ipsitorsional positional nystagmus suggests the most prevalent geotropic variant of the PSC-BPPV (*geo*-PSC-BPPV). The lateralization is to the side eliciting positional nystagmus in the 20-degrees head hanging position during the DHT (https://youtu.be/MBsbJeYRF7s).
- A downbeating torsional nystagmus suggests either ASC-BPPV or the *apo*-PSC-BPPV. The lateralization of the ASC-BPPV is suggested by the direction of the torsional component, which is too often little or inconspicuous. The DHT elicits positional downbeating nystagmus in the head hanging position to either side as well as in the deep or enhanced straight head hanging positions in the ASC-BPPV. The positional downbeating nystagmus of *apo*-PSC-BPPV is not typically crescendo-decrescendo, often lasts longer, and is contratorsional. However, initially, too often it is impossible to differentiate between an ASC-BPPV and *apo*-PSC-BPPV based on findings of the DHT alone (https://youtu.be/wlb-iYZThzU).

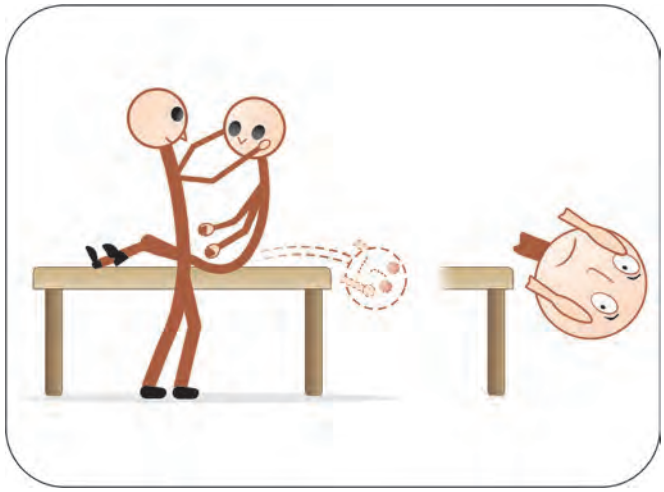


Fig. 1: ***Dix-Hallpike Test:*** The Dix-Hallpike test (DHT) involves moving the patient from a long sitting position on the examination table with the head rotated 45-degrees to a side (left in the figure) to 20-degree below horizontal head-hanging supine position. After a latency of few seconds it produces an upbeating ipsitorsional nystagmus in the PSC-BPPV, and downbeating ipsitorsional nystagmus in the ASC-BPPV. The torsional component is either little or inconspicuous in ASC-BPPV. If positional nystagmus is not elicited on one side even after 60 seconds, the patient is positioned to upright sitting, and an identical sequence is repeated with the head rotated 45-degrees to the opposite side

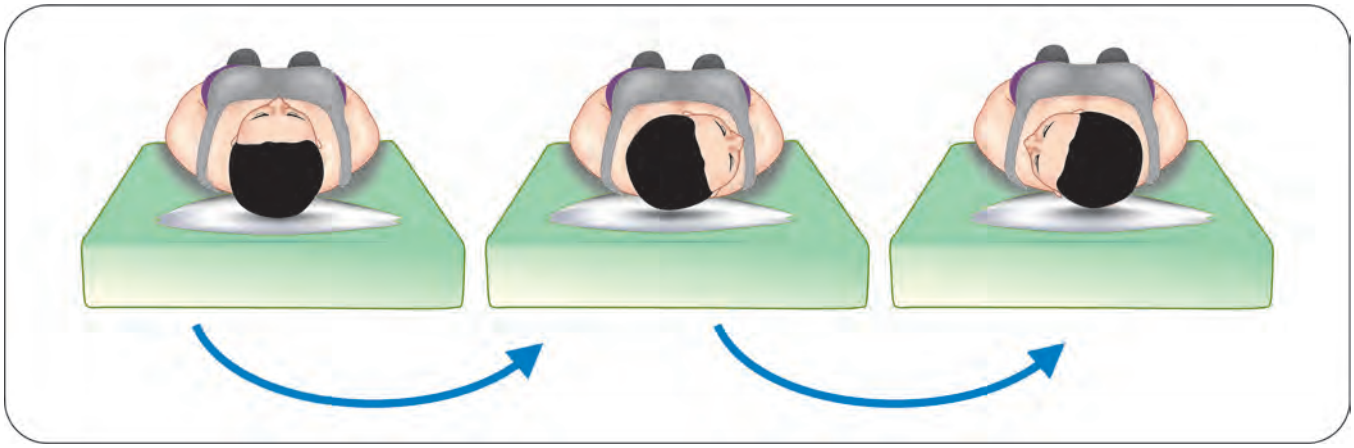
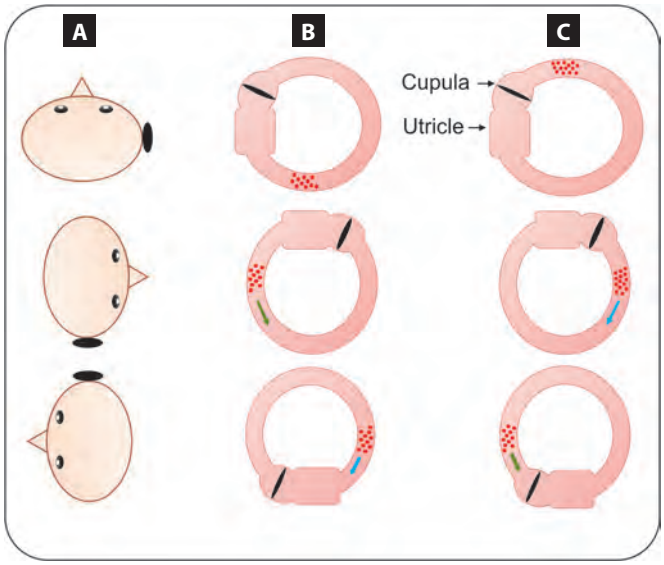


Fig. 2: ***Supine Roll Test:*** A pillow of about 4-inch thickness is placed at the head end of the examination table. The supine roll test is performed with the patient in long-sitting on the examination table. From long-sitting, the patient is shifted to a supine position so that the head is flexed to 30-degrees as the occiput lands on the pillow. The patient's head is rolled from neutral to one side while the patient is supine. After waiting for any nystagmus or vertigo to subside, the test is performed to the opposite side

Supine Roll Test (Head Yaw Test or Pagnini McClure Maneuver)[22]

A pillow of about 4-inch thickness is placed at the head end of the examination table. The SRT is performed with the patient in long-sitting on the examination table. From long-sitting, the patient is shifted to supine position so that the head is flexed 30-degrees as the occiput lands on the pillow. The patient's head is rolled from neutral to one side while the patient is supine. After waiting for any nystagmus or vertigo to subside, the test is performed to the opposite side **(Fig. 2)**. The positive test elicits horizontal positional nystagmus, which may be:

- *Geotropic:* Implying that the fast component of the nystagmus is directed toward the lowermost ear. The geotropic positional nystagmus is elicited on the lateral head roll to either side and is attributed to the long posterior non-ampullary arm horizontal semicircular canalolithiasis. The side to which the lateral head roll elicits stronger geotropic nystagmus is the affected side as per the Ewald's 2nd law (https://youtu.be/jwRgSZ71Ux8Or).
- *Apogeotropic:* Implying that the fast component of the nystagmus is directed away from the lowermost ear. The apogeotropic positional nystagmus is elicited on the lateral head roll to either side and is attributed to the



Figs. 3A to C: ***The location of otoconial debris in the supine neutral position and during lateral head rolls executed in the supine roll test.*** (A) Top to bottom—supine neutral position, lateral head roll to right and to left. (B) Otoconia in the posterior arm of right horizontal semicircular canal (geotropic variant) shifts ampullopetal (green arrow) on the lateral head roll to right and ampullofugal (blue arrow) on the lateral head roll to left. (C) Otoconia in the anterior arm of right horizontal semicircular canal (apogeotropic variant) shifts ampullofugal (blue arrow) on the lateral head roll to right and ampullopetal (green arrow) on the lateral head roll to left

short anterior ampullary arm horizontal semicircular canalolithiasis or cupulolithiasis. The side to which the lateral head roll elicits weaker apogeotropic nystagmus is the affected side as per the Ewald's 2nd law. (https://youtu.be/t_Ie7LGcCXQ).

In the geotropic variant of the HSC-BPPV (*geo*-HSC-BPPV), in which otoconial debris is free-floating in the long posterior non-ampullary arm of the HSC, an ipsilesional lateral head roll in the yaw-axis, during the SRT, produces an excitatory hydrodynamic drag of the endolymph toward the ampulla. This very reason in the variant, during SRT, elicits stronger geotropic nystagmus to the side of lesion than to the opposite side **(Figs. 3A and B)** (https://youtu.be/-gp7Dol6_jk). In the apogeotropic variant of HSC-BPPV (*apo*-HSC-BPPV), where otoconial debris is either free-floating in the short anterior ampullary arm of the HSC or is adherent to the cupula, thus making it heavier, the excitatory hydrodynamic drag of the endolymph toward the ampulla occurs when there is contralesional lateral head roll in the yaw axis during SRT. Accordingly, in the *apo*-HSC-BPPV during the SRT, stronger apogeotropic nystagmus is elicited when the head is yawed to the contralesional side **(Figs. 3A and C)** (https://youtu.be/v6vmGAJaRDs).

The duration of the positional nystagmus is up to 1 minute in the canalolithiasis and more than 1 minute in the cupulolithiasis. The HSC-BPPV caused by short anterior ampullary arm canalolithiasis presents with apogeotropic positional nystagmus that may last longer than 1 minute. However, if the SRT elicits persistent apogeotropic positional nystagmus lasting more than 1 minute and there are no changes in the direction of nystagmus even after repetitive head roll tests, it is explicable by the horizontal canal cupulolithiasis either on canal-side (Cup-C) or on the utricular-side (Cup-U)[19] (https://youtu.be/glT9HtAwaFc).

Straight Head Hanging Test[23]

The straight head hanging test (SHHT) is carried out with the patient in long-sitting on the examination table such that the distance of the patient's bottoms from the head end of the table allows the head to hang during supine positioning. The patient's head is firmly held and is positioned to the supine neutral position with the head 30-degrees or maximally extended (beyond the short edge of the examination table). The patient is held in the enhanced straight head hanging position till positional nystagmus is elicited and lasts or for at least 60 seconds if no positional nystagmus is elicited. The patient is instructed to keep their eyes open even when experiencing vertigo in the head hanging position to observe the pattern of induced positional nystagmus. A SHHT is positive if a downbeating nystagmus is elicited with or without a torsional component (https://youtu.be/Ubwsqx9J75c).

Table 2 summarizes the currently known variants of BPPV, the anatomico-physiological correlation between otoconial location and oculomotor patterns generated on the diagnostic positional tests in terms of the direction, latency, and duration of the elicited positional nystagmus. Column 7 of **Table 2** shows the YouTube links to access the videos of the oculomotor patterns of the generated nystagmi during the positional tests in different variants of BPPV. Because the management of BPPV exclusively depends on the repositioning maneuvers and/or physical therapy, it is imperative to localize as well as lateralize the involved semicircular canal by a meticulous execution of

TABLE 2 Synopsis of otoconial location, diagnostic positional test, elicited nystagmus characteristics, and YouTube links in different BPPV subtypes

BPPV variant	*Otoconial location in upright position*	*Positional test*	*Nystagmus direction*	*Nystagmus latency*	*Nystagmus duration*	*You Tube link*
geo-PSC-BPPV	Juxta-cupular in the ampullary arm of PSC	DHT	Upbeating & ipsitorsional	Brief latency (rarely up to 40 s)	<1 min	https://youtu.be/MBsbJeYRF7s
apo-PSC-BPPV	Non-ampullary arm of PSC near common crus	DHT & SHHT	Downbeating & contratorsional	Brief or no latency	>2 min	https://youtu.be/Ubwsqx9J75c
PSC-BPPV cupulolithiasis	Adherent to cupula of PSC	Half-DHT*	Upbeating & ipsitorsional	Brief or no latency	>1 min	-
ASC-BPPV	Juxta-cupular in ampullary arm of ASC	DHT & SHHT	Downbeating & ipsitorsional; torsion often too little or absent	Brief or no latency (rarely up to 30 s)	<1 min	https://youtu.be/wlb-iYZThzU
Long posterior-arm HSC-canalolithiasis	Long non-ampullary posterior-arm of HSC	SRT	Horizontal geotropic	Brief or no latency	<1 min (rarely up to 2 min)	https://youtu.be/-gp7Dol6_jk
Short anterior arm HSC-canalolithiasis	Short ampullary anterior arm of HSC	SRT	Horizontal apogeotropic	Brief or no latency	<1 min (rarely up to 2 min)	https://youtu.be/v6vmGAJaRDs
HSC cupulolithiasis	Adherent to cupula of HSC (Cup-C or Cup-U)	SRT	Horizontal apogeotropic	Brief or no latency	>1 min	https://youtu.be/glT9HtAwaFc

*The patient's head is turned 45° toward the side to be tested: the patient is then inclined 60° backward to one side, instead of 110° so that the cupula of PSC is earth horizontal. Rolling the head 180° to the other side (release position) should reveal a less intense nystagmus beating in the opposite direction, due to ampullopetal deflection of the cupula.

PSC-BPPV, Posterior Semicircular Canal Benign Paroxysmal Positional Vertigo; HSC-BPPV, Horizontal Semicircular Canal Benign Paroxysmal Positional Vertigo; ASC-BPPV, Anterior Semicircular Canal Benign Paroxysmal Positional Vertigo; geo, Geotropic; apo, Apogeotropic; Cup-C, Cupulolithiasis canal side; Cup-U, Cupulolithiasis utricular side; DHT, Dix-Hallpike Test; SHHT, Straight Head Hanging Test; SRT, Supine Roll Test

the provocative positional tests and observing the patterns of the elicited positional nystagmus thereon.

Management

The treatment of BPPV with drugs is neither indicated nor successful. In selected patients who develop severe nausea and/or vomiting during the repositioning maneuvers and/or physical therapy, promethazine may be used. Once accurate lateralization of the side and localization of the involved canal is known, an appropriate repositioning maneuver and/or physical therapy is carried out. In general, canalolithiasis is more amenable to treatment with repositioning maneuvers compared to cupulolithiasis. It is important to review the patient at short intervals at least twice, at 1 hour and 24 hours after the repositioning maneuver and/or physical therapy. The improvement is evaluated in terms of extirpation of the positional nystagmus and associated vertigo. The treatment of different BPPV variants with repositioning maneuvers and/or physical therapy is summarized in the **Table 3**. **Figures 4 to 8** illustrate the different maneuvers used in the treatment of the common variants of BPPV. Column four of the **Table 3** shows YouTube links to access the videos of the therapeutic repositioning maneuvers and/or physical therapy. After the repositioning maneuver, otoconial debris occasionally refluxes into a canal different from the one originally affected. This phenomenon is known as canal-switch and occurs in 6–8% of patients.[34-36] The appearance of a different oculomotor pattern on a verifying positional test than the one initially observed, after the patient has been subjected to a seemingly successful repositioning maneuver, is a harbinger of canal-switch. Patients undergoing canal-switch require treatment according to the protocol of the canal involved with the switch phenomenon. The appearance of persistent spontaneous nystagmus following a repositioning maneuver in HSC-BPPV may result from jamming of the otoconia within a canal or between the cupula and the adjacent ampulla wall. The canal jam results in partial or complete obstruction within the canal, resulting in spontaneous nystagmus that persists irrespective of a change in head position.[37] The physicians involved in the physical treatment of patients with BPPV should be aware of these two potential complications of physical therapy, namely the canal-switch and canal jam.

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The educational videos in the YouTube links mentioned in column 7 of the **Table 2** and column 4 of the **Table 3** are protected by the copyrights of the author. The author has

TABLE 3 Synopsis of BPPV variants, otoconial location, therapeutic repositioning maneuvers and/or physical therapy, and YouTube links

BPPV variant	*Otoconial location in upright position*	*Therapeutic repositioning maneuver and/or physical therapy*	*YouTube link*
geo-PSC-BPPV	Juxta-cupular in the ampullary arm of PSC	Epley Maneuver[22] **(Fig. 4)**	https://youtu.be/JSwRvT453M8
apo-PSC-BPPV	Non-ampullary arm of PSC near common crus	Demi Semont Maneuver[24]	https://youtu.be/cPOmsx68nfI
PSC-BPPV cupulolithiasis	Adherent to cupula of PSC	Epley Maneuver[22] **(Fig. 4)** (more sessions required compared to *geo*-PSC-BPPV[25])	https://youtu.be/JSwRvT453M8
ASC-BPPV	Juxta-cupular in ampullary arm of ASC	Yacovino maneuver[26] **(Fig. 8)**	https://youtu.be/frQ98anQTtk
Long posterior-arm HSC-canalolithiasis	Long non-ampullary posterior-arm of HSC	Gufoni Maneuver[27] **(Fig. 6)**, Lempert's 360-degrees Barbecue Roll Maneuver[28,29]**(Fig. 5)**, Forced Prolonged Positioning (FPP[30])	https://youtu.be/u_WNOpsxG30 (Gufoni Maneuver) https://youtu.be/ZEG-rKEYnZw (Lempert's 360-degrees Barbecue Roll Maneuver)
Short anterior arm HSC-canalolithiasis	Short ampullary anterior-arm of HSC	Appiani Maneuver[31] **(Fig. 7)**	https://youtu.be/EUW4GVhlPdI
HSC cupulolithiasis	Adherent to cupula of HSC (Cup-C or Cup-U)	Head-Shaking maneuver (HSM)[32], Cupulolith Repositioning Maneuver[33]	https://youtu.be/pOK0OFAqtuI(HSM)

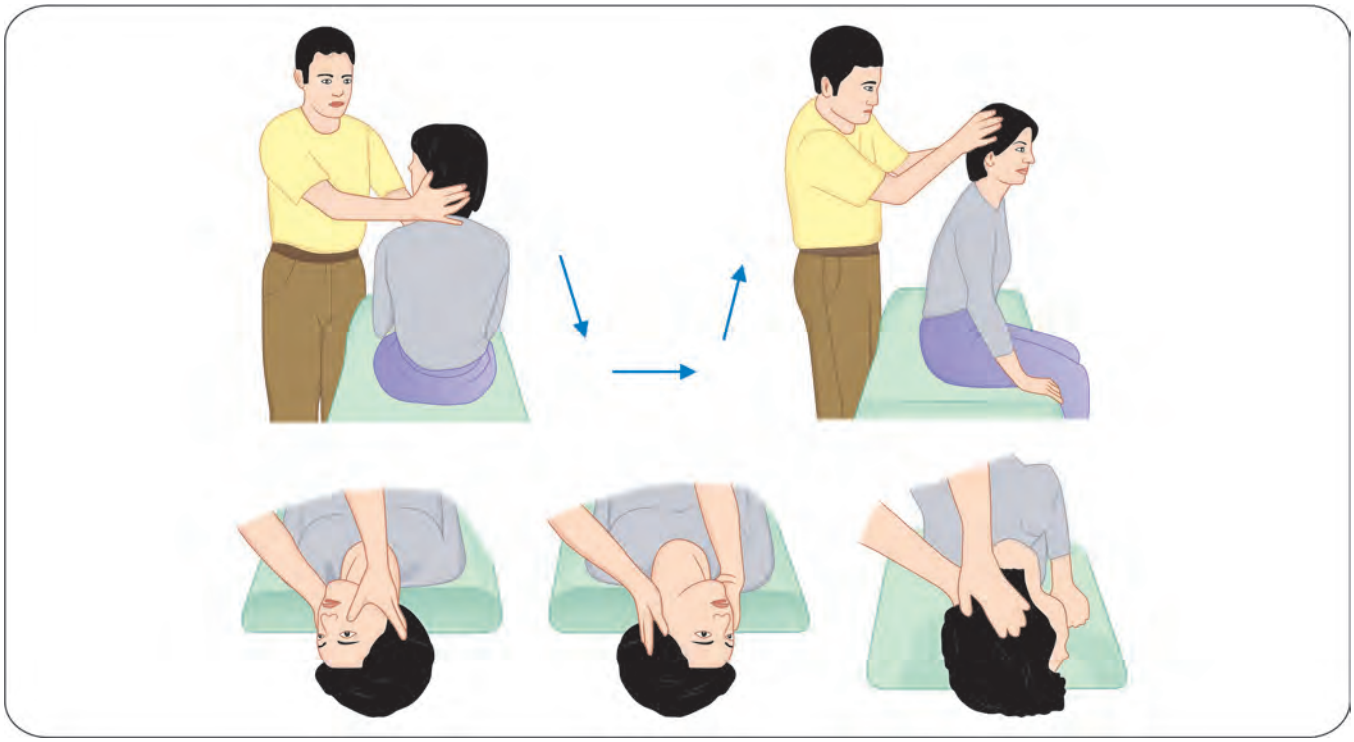


Fig. 4: ***Epley maneuver for left posterior semicircular canal BPPV:*** The patient is positioned in long-sitting on the examination table and head is rotated 45-degrees to the side (left in this case) to which the Dix-Hallpike test elicited the upbeating ipsitorsional positional nystagmus. Thereupon the patient is positioned supine such that the head hangs 20-degrees below the short edge of the examination table and remains in this position for 1 minute. Then the head is rotated 90-degrees to the patient's right and is maintained in this position for 1 minute. Then the patient is instructed to assume the right lateral recumbent position and to further rotate head rightward so that his nose orients at the right angle to the surface for another minute. Finally, the patient is positioned to short-sitting keeping the head position unchanged, until he is fully seated with his legs hanging on the examination table
(*Source:* Reproduced with permission from Prof. Dr. Thomas Lempert, Chief Physician of the Neurology Department at the Schlosspark Clinic in Berlin)

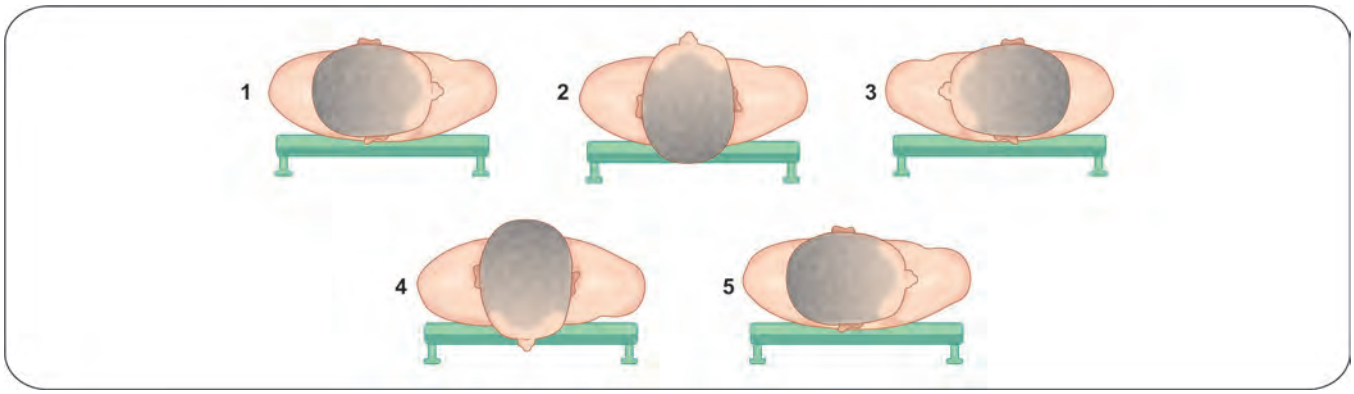
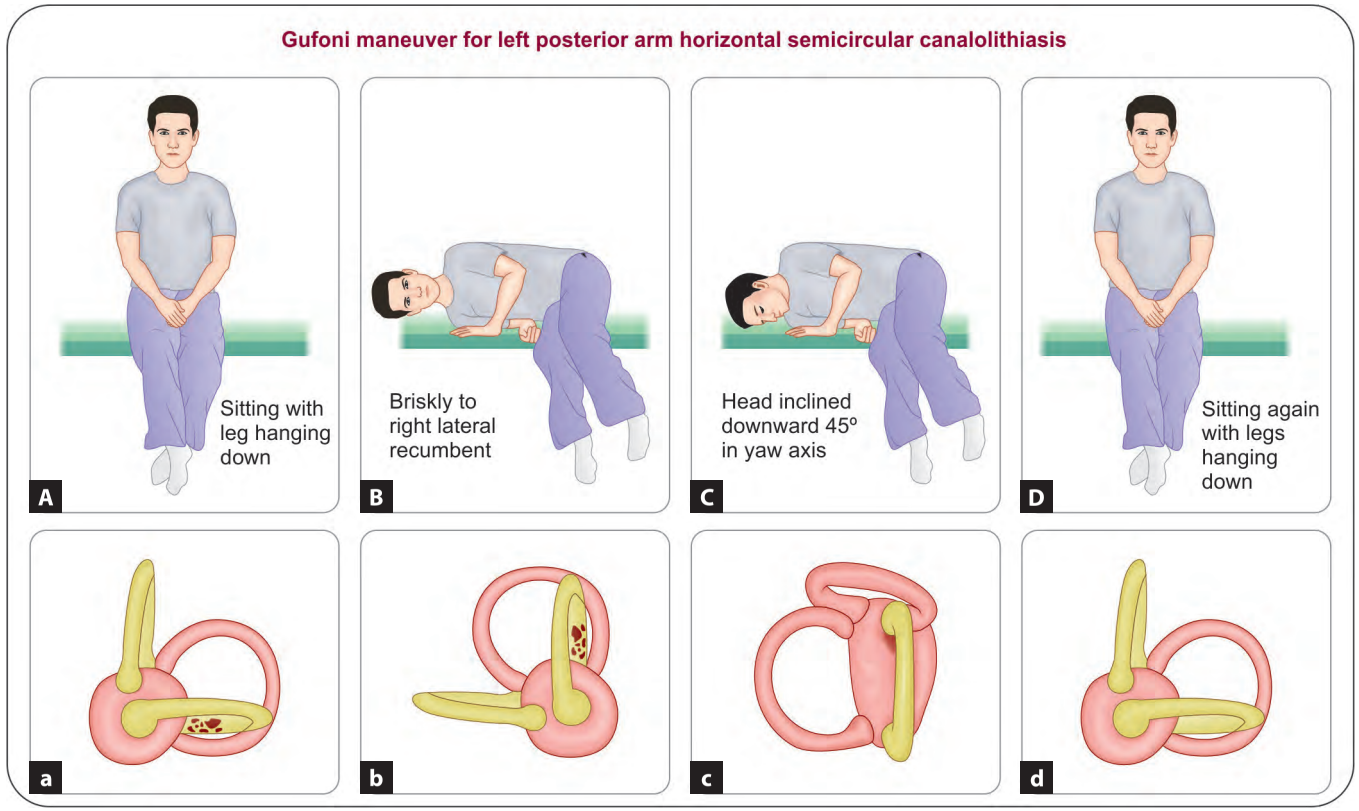
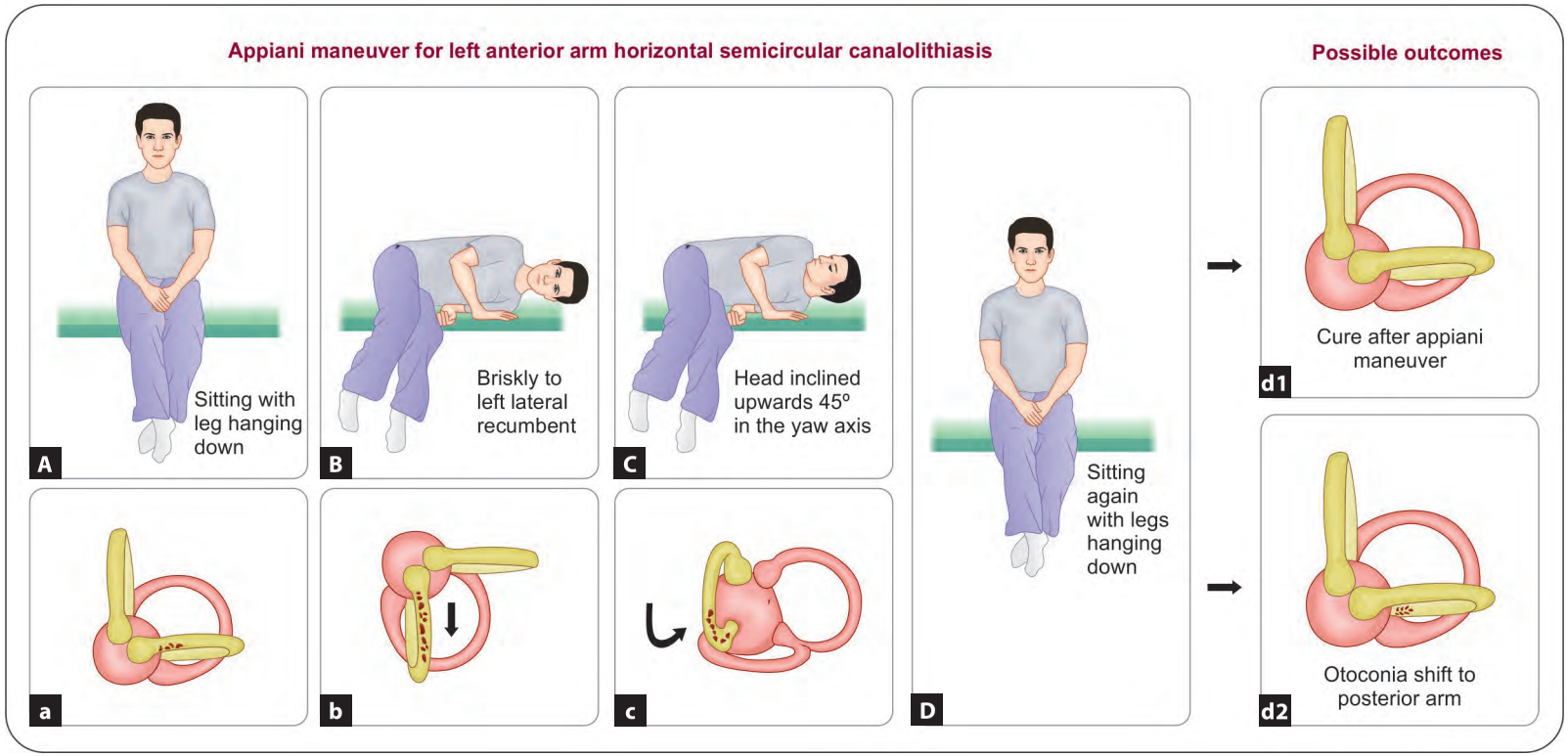


Fig. 5: ***Lempert's 360-degrees barbecue roll maneuver for right long posterior arm horizontal semicircular canalolithiasis:*** **Step 1**: The patient lies on his back on the examination table with his right ear down or the starting position can be right lateral recumbent. **Step 2**: The head is then slowly rolled away from right side until the face is pointing up and remains in this position for 30 seconds or till the vertigo ceases. **Step 3**: The head is then rolled in the same direction until the right ear is up or the patient can be positioned left lateral recumbent and remains in this position for 30 seconds or till vertigo ceases. **Step 4**: The head and body are then rolled in the same direction until they are face down and remains in this position for 30 seconds or till vertigo ceases. **Step 5**: The head and body are then rolled in the same direction until they reach the original position with right ear down and remain in this position for 30 seconds or till vertigo ceases. After 30 seconds the patient then slowly positioned to upright short sitting on the examination table



Figs. 6A to D: ***Gufoni maneuver for the left posterior arm horizontal semicircular canalolithiasis.*** (A) The patient is placed in short sitting on the examination table with lower limbs hanging down. (B) Briskly positioned to the contralesional right lateral recumbent on the examination table and the position maintained for 1 minute. (C) The head is rotated 45-degrees downward in the yaw-axis, and this position is maintained for 2 minutes. (D) Upright short sitting positioning is done. The lower panels a, b, c, and d show the transit of otoconial debris from the long posterior arm of the left horizontal semicircular canal to the utricle during the maneuver



Figs. 7A to D: ***Appiani maneuver for the left short anterior arm horizontal semicircular canalolithiasis***. (A) The patient is placed in short sitting on the examination table with lower limbs hanging down. (B) Briskly positioned to the ipsilesional left lateral recumbent on the examination table and the position maintained for 1-minute. (C) The head is rotated 45-degrees upward in the yaw-axis and this position is maintained for 2 minutes. (D) Upright short sitting positioning is done. The lower panels a, b, and c, show the transit of otoconial debris from the short anterior arm of the left horizontal semicircular canal to the utricle during the maneuver. The possible outcomes of the Appiani maneuver are either the otoconial debris is repositioned to the utricle thus clearing the left horizontal semicircular canal (d-1) or shift of otoconial debris to the posterior arm of the left horizontal semicircular canal thus transforming to left long posterior arm horizontal semicircular canalolithiasis (d-2)

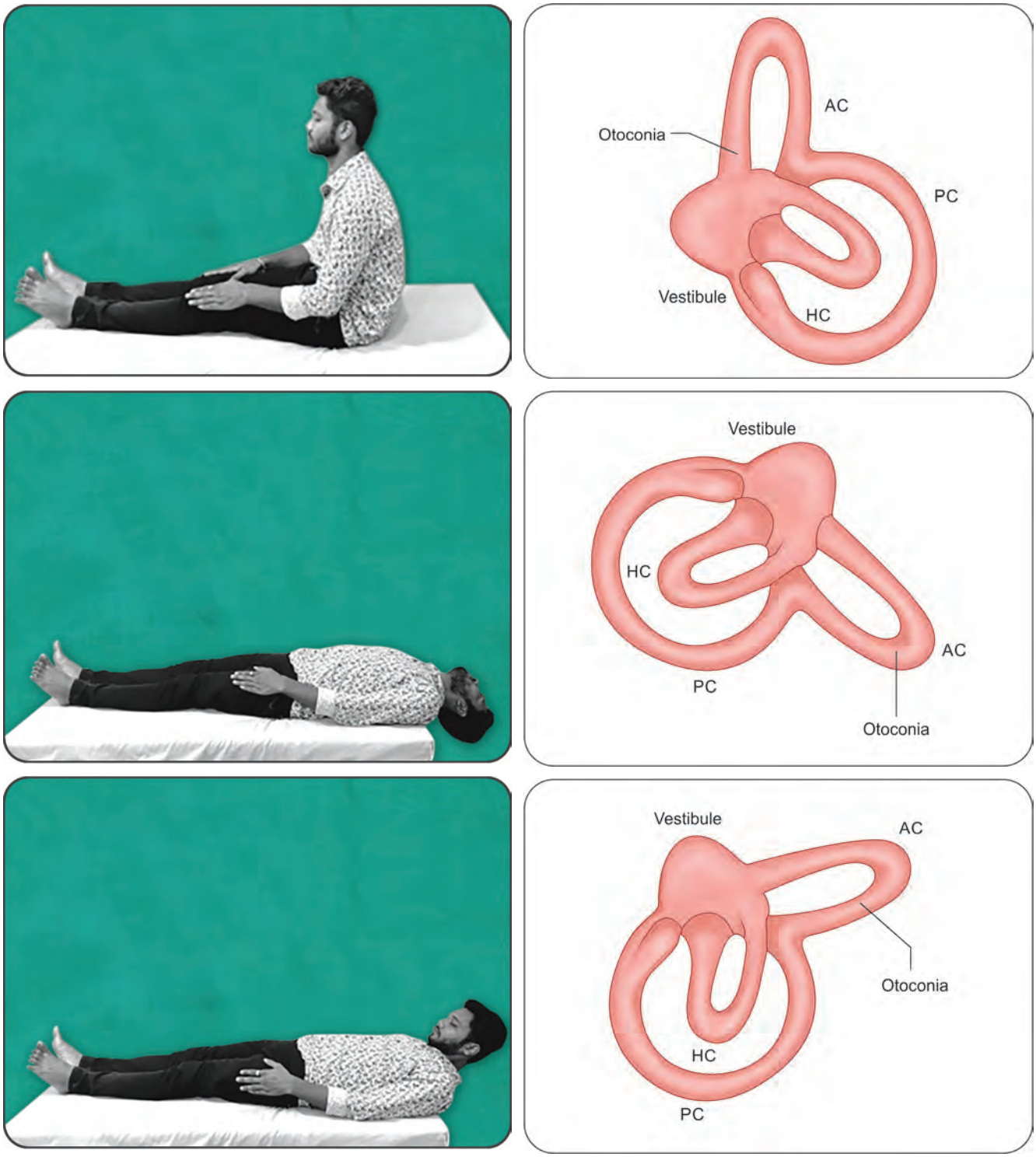

AC
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Fig. 8

Contd...

Contd...

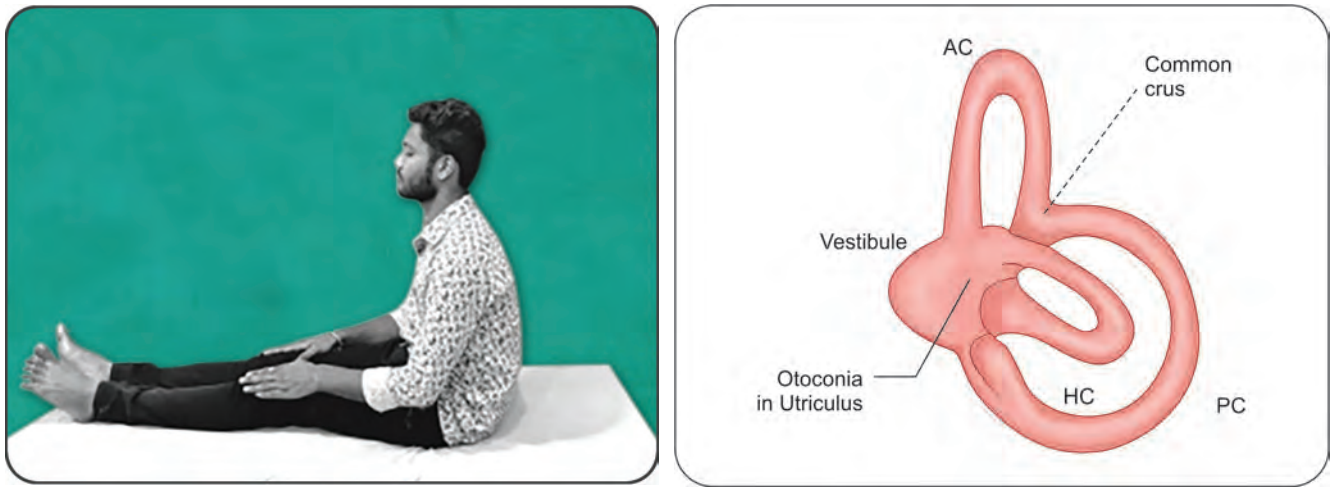

Fig. 8: ***Yakovino Maneuver.*** **Step 1**: The patient positions in the long-sitting on the examination table. The distance of the patient's bottoms from the head end of the table is such that it allows the head to hang on positioning supine. **Step 2**: The head is held in the neutral position, and the patient is positioned supine so that the head extends about 30-degrees or more below the horizontal. This position is maintained for 30 seconds or till the downbeating nystagmus lasts. **Step 3**: The head is now anteflexed 30-degrees above horizontal so that it attains a "chin to chest position" with vertex approximating the vertical axis. This position is maintained for 30 seconds. **Step 4**: The head and entire body are brought to sitting position with head in the straight position, and this is maintained for 30 seconds

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Acknowledgments

The author is grateful to Professor Thomas Lempert, Professor of Neurology, Chief Physician of the Neurology Department at the Schlosspark Clinic, Berlin, Germany, for his kindness in providing his illustration **(Fig. 4)** for this chapter. To Mr. Renith Kurian, who video recorded the diagnostic and therapeutic maneuvers (shown in the YouTube links) and precisely captured the nystagmus during the entire diagnostic and treatment period and to Mr. Ashraf for drawing the **Figures 6 and 7** on CorelDraw graphics suite 2019.

Conclusion

Successful treatment of BPPV with repositioning maneuvers and physical therapy has been one of the greatest accomplishments in the field of Otoneurology. This has been possible due to several factors like *in vivo* demonstration of otoconia in the SCC, application of physical laws to precisely lateralize as well as localize the otoconial debris within the SCC, and conceptualizing the movement of otoconia in the SCC during head movements in the physical models of the labyrinth to develop specific canal clearing maneuvers. A trained vestibular physician's role in the medical fraternity is to obviate the unnecessary and often expensive neuroimaging studies, which patients of BPPV often undergo due to ignorance of physicians at large to identify and treat this truly benign peripheral vestibular disorder by repositioning maneuvers and physical therapy.

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Section 7

Section Editor: **A Bhagwati**

Critical Care Medicine

CHAPTER

97 Tachyarrhythmias in ICU

Nikhileshwar Prasad Verma

Abstract

Tachyarrhythmia in ICU is very common. Their recognition and management are of paramount importance.

Introduction

It is not uncommon to see patients admitted in ICU to develop various tachyarrhythmias (HR >100 bpm) as they are on multiple drugs and in a state of stress. Tachyarrhthmias are more common than bradyarrhythmias and are well tolerated by some patients. But some may become unstable and manifestations in these patients could be:

- Dyspnea
- Hypotension
- Ischemic chest pain
- Altered sensorium

Tachyarrhythmias have profound effect on morbidity and mortality of the patient. Tachycardias result from enhanced automaticity, triggered activity or reentry and could be supraventricular or ventricular. There are various types of tachycardias, but the most common forms with whom an intensivist is confronted with a:

- Sinus tachycardia
- Supraventricular tachycardia (AT, AVNRT, AVRT)
- Atrial fibrillation
- Atrial flutter
- Multifocal atrial tachycardia (MAT)
- Ventricular tachycardia (monomorphic and polymorphic)

Assessment of Patient

An intensivist should first evaluate whether the patient is stable or not. Unstable patients must be urgently cardioverted. One should look for precipitating factors like electrolyte imbalance, hypovolemia, abnormal temperature, sepsis, abnormalities in gases, and drugs. When QRS complex is less than 0.12 second, it is termed as narrow complex tachycardia (NCT) and when QRS is more than 0.12 second, it is termed as wide complex tachycardia (WCT). The rhythm may be regular or irregular. A 12-lead ECG is mandatory to evaluate the arrhythmia. Response to vagal maneuvers as carotid sinus massage (CSM), valsalva maneuver and response to adenosine help in differentiating supraventricular tachycardia from ventricular tachycardia. Adenosine (6 mg) is given rapidly and 12 mg may be repeated after 2 minutes as second dose. Adenosine may cause severe bronchospasm and sometimes atrial fibrillation (AF). After giving adenosine it should rapidly be flushed with normal saline. Bedsides, echo will tell us about the status of heart.

NCT with Regular Rhythm

Sinus Tachycardia

It is the most common tachycardia seen in the ICU and the HR is between 100–180 bpm. It rarely requires

treatment. In ICU, most of the time it is an appropriate response to underlying causes like fever, hyopovolemia, pain, and hypotension. There could be iatrogenic causes too. Over enthusiastic treatment may sometimes backfire. Ischemia induced sinus tachycardia may be treated with beta blockers. It is difficult to differentiate from atrial tachycardia. The morphology of non sinus p wave of AT is the clue, which is different from sinus p wave in differentiating it from AT. The maximum sinus HR for a person is 220 – Age.

Atrial Tachycardia

Three continuous non-sinus APBs originating from the same focus make AT. If arrhythmia lasts for more than 30 second, it is called sustained. Mostly in ICU AT is non-sustained. The atrial rates range 100–260 bpm. Unstable patients are treated with synchronized DC shock. In stable patients AV nodal blocking agents are used to control the ventricular rate.

Atrioventricular Nodal Reentrant Tachycardia (AVNRT)

More than 60% of SVT is due to AVNRT. Here AV node has a dual conducting pathway. Since atria and ventricles are stimulated simultaneously p wave is usually submerged in QRS or sometimes appear just after QRS. It may also be seen as pseudo R' in V1. The HR is usually between 140–220 bpm. Patients complain of palpitation and lightheadedness. Majority of the patients tolerate it well and arrhythmia can be terminated by vagal maneuvers or AV nodal blocking agents. Long-term preventive therapy is catheter ablation or use of AV nodal blocking agents.

Atrioventricular Tachycardia (AVRT)

There is an accessory pathway between atria and ventricles. If the impulse travels through AV node from atria to ventricles and go to atria from ventricles through accessory pathway (orthodromic conduction) the QRS complex is narrow and the tachycardia would be NCT. But if antegrade conduction is through accessory pathway and retrograde through AV node (antidromic conduction) tachycardia would be WCT. The activation of ventricle and atria take place one after another so RP interval is long and p wave is seen on ST-T wave. Orthodromic AVRT responds to vagal maneuvers and AV nodal blocking agents. But these drugs are harmful in antidromic AVRT. In such cases amiodarone is preferred drug. It is rare for a patient to become unstable with SVT but if this happens so DC shock with 25–50 J is sufficient.

Atrial Flutter

Saw tooth flutter waves are best seen in II, III, AVF at the rate of 300 bpm (250–350 bpm) with 2:1 block in the setting of structural heart disease in most of the patients. Sometimes 4:1 block is also seen. Rarely atrial flutter with 1:1 AV conduction may occur in high catecholamine states as sepsis, shock, and with the use of flecainide in the presence of fast conducting accessory pathway and becomes an emergency requiring urgent cardioversion. 50J is sufficient with the success rate of above 90%. AV nodal blocking agents and digoxin (especially in heart failure) can control ventricular rate. Flecainide is good for its prevention but should be used in combination of AV nodal blocking agent. Anticoagulant is started if atrial flutter is of more than 48 hours. Atrial flutter should always be thought if ventricular rate is 150 bpm and regular.

NCT with Irregular Rhythm

Irregular NCT is seen in AF, MAT, and sinus tachycardia with frequent atrial premature beats.

Atrial Fibrillation (Fig. 1)

The chaotic atrial activities with the rates ranging 400–600 bpm are seen as coarse or fine fibrillatory waves

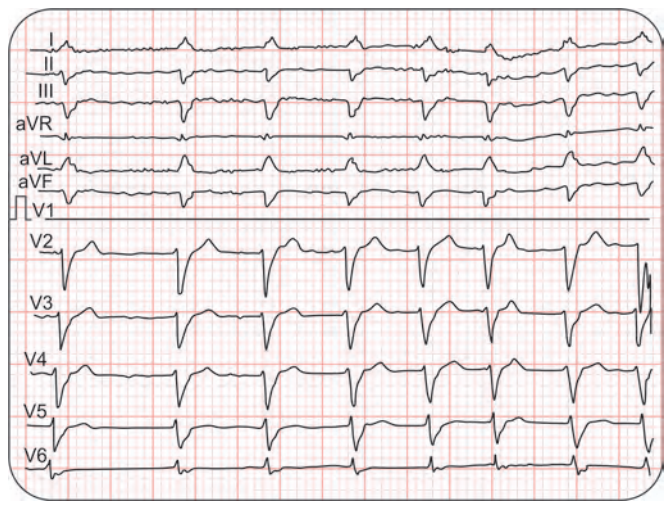

Fig. 1: Atrial fibrillation

without discernible p waves on surface ECG. It is very common in ICU. Advancing age, valvular heart diseases, thyrotoxicosis, large left atrium, sleep apnea, and chronic kidney disease are some of the important predisposing factors for AF. It is pertinent to identify and treat the cause. Management has three aspects:

- Rhythm control,
- Rate control, and
- Anticoagulation.

Urgent cardioversion is done if patient is hypotensive, there is ongoing ischemia, acute pulmonary edema, or underlying preexcitation with rapid ventricular rate. Synchronized shock of 200J is appropriate. Repeated shocks may be needed with increased energy up to 400J as success rate of cardioversion is less than 30% in ICU. If DC shock fails 300 mg amiodarone iv in 1 hour may be given and repeated as needed.

If onset of AF is within 48 hours, cardioversion is a common practice even if patient is not on anticoagulant, at risk of stroke and there is no mitral stenosis or large left atrium.

If duration of AF is not known or more than 48 hours, patient is anticoagulated for 3 weeks before cardioversion and for 4 weeks after cardioversion. The other approach is to rule out thrombus by transesophageal echocardiography start anticoagulation cardiovert the patient and continue anticoagulation for 4 weeks. In stable patient pharmacological cardioversion can be done by ibutilide, flecainide, and amiodarone.

Rate control can be achieved by AV nodal blocking agents IV diltiazem at a rate 5–15 mg/hr maintains the ventricular rate below 100 bpm in 90% cases during 24 hours infusion. Digoxin is seldom used as it takes longer time to slow the rate.

If AF persists for more than 48 hours iv heparin should be started but one should keep in mind that chances of bleeding increases with anticoagulants in sepsis without any benefit.

Wolf-Parkinson-White (WPW) Syndrome

WPW syndrome is triad of short PR interval, slurring of QRS (delta wave) and broadened QRS. Orthodromic conduction will produce NCT while antidromic conduction produces WCT. AF is very common in WPW and is life threatening as it causes rapid ventricular rate usually more than 200 bpm. QRS has a changing morphology in width and height unlike AF with fixed BBB where ventricular rate is not that fast and QRS morphology is always the same. It is the accessory path that propagates the impulses from atria to ventricles. Use of AV nodal blocking agents will be dangerous in this situation. Ibutilide, flecainide, and amiodarone are safe drugs in this condition. For unstable patient DC shock of 150–200 J is required.

Multifocal Atrial Tachycardia (MAT)

Three or more non-sinus consecutive p waves of different contours beating at a rate 100 or more per minute constitute multifocal atrial tachycardia. The P-P & P-R intervals are variable and ventricular rate is irregular. At times it is difficult to differentiate it from AF. In more than 50% cases of MAT the underlying cause is chronic obstructive lung disease. Coronary artery disease and valvular heart disease are frequently present along with chronic obstructive lung disease. Other precipitating factors may be low potassium and magnesium. Treatment should be directed toward underlying cause. DC shock is ineffective due to multiple atrial foci. AV nodal blocking agents are used to control the ventricular rate. Empirically magnesium is used with high success rate. $MgSO_4$ + 50 ccNS (2 gm) iv in 15 minutes is given followed by 6 gm $MgSO_4$ + 500 ccNS iv in 6 hours.

Wide Complex Tachycardia

When QRS duration is more than 0.12 second it is called wide complex. About 85% of wide complex tachycardia (WCT) are due to VT. About 10% are due to supraventricular tachycardia with aberrancy (SVT-A). The aberrancy could be fixed bundle branch block, functional or rate dependent block, or accessory pathway. The other causes of WCT could be pacemaker induced tachycardia where rate will never go beyond the upper limit fixed for the pacemaker, artifact where rate is very very fast but patient is hemodynamically stable and QRS complex march with regularity. Hyperkalemia where QRS is very very wide but rate is not so fast usually below 120 bpm and drugs like tricyclic antidepressants, CLASS IA and IC antiarrhythmic drugs may cause WCT.

Ventricular Tachycardia (Fig. 2)

When there are three or more consecutive ventricular premature complexes present at a rate more than 100/min it is called ventricular tachycardia (VT) and if it persists for 30 or more seconds it is termed sustained.

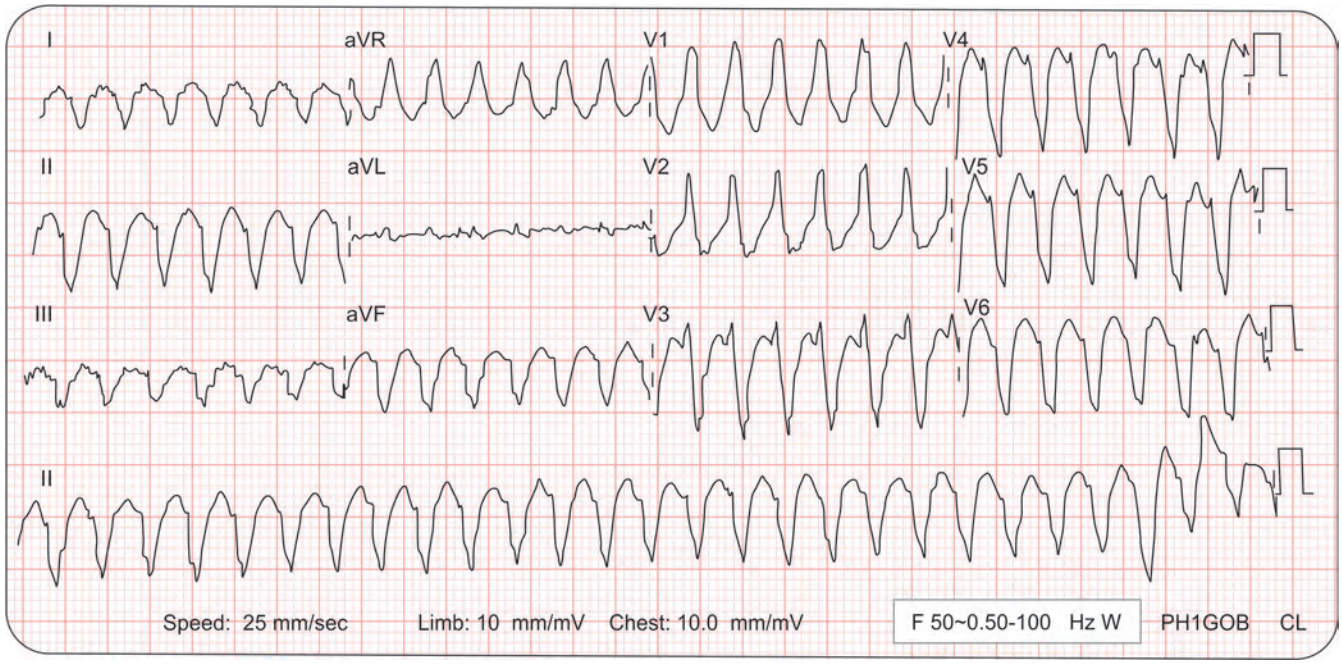

Fig. 2: Ventricular tachycardia

VT could be monomorphic where morphology of all ventricular complexes are same and polymorphic where there is continuous change in morphology of ventricular complexes.

There are certain features though not always but if present suggest VT while differentiating it from SVT-A. They are:

- H/o heart disease or previous MI.
- QRS width >0.16 second.
- AV dissociation (ventricular rate more than atrial).
- Presence of capture and fusion beats.
- RBBB with left axis and LBBB with right axis, extreme north west axis.
- Presence of concordance.
- Presence of Brugarda's sign (onset of QRS to nadir of S is >100 msec) and Josephson's sign (notch in S wave).
- All precordial leads showing QS pattern.
- Presence of RBBB like morphology (dominant R wave in V1-2 & R/S<1 in V6).
- Presence of LBBB like morphology (initial R >0.04 second RS interval>0.07second in V1-2 & any Q in V6).

Monomorphic VT

This may occur in structurally normal or diseased heart. If it is non-sustained and heart is not diseased no treatment is needed. AV nodal blocking agents are used to prevent its recurrence. But patients who have structural heart disease (coronary heart disease, dilated cardiomyopathy, valvular heart disease) need further evaluation. Hemodynamically unstable patient with monomorphic sustained VT DC shock of100–200 J is given and increment may be done up to 360 J, followed by lidocaine 1–4 mg/min iv infusion. In stable patient either shock or drugs can be given. In patients with preserved LV function procainamide, amiodarone, lidocaine, and sotalol may be given but preferred drug is amiodarone. In patients with compromised LV amiodarone or lidocaine may be used.0.5–1 mg/kg lidocaine is given iv bolus followed by iv infusion at 1–4 mg/min lidocaine is more effective if VT is due to ischemia. One should never forget to correct hypokalemia and hypomagnesemia as they are precipitating factors. When VT is unstable, recurrent, and nonresponsive to cardioversion iv amiodarone may be given.

Polymorphic VT

Polymorphic VT may occur with normal or prolonged QT interval. PMVT with normal QT is mostly due to ischemia and almost always causes significant hemodynamic instability. Therefore, patient should be shocked.

Medication that predisposes to ischemia should be withdrawn. Electrolytes should be corrected. Beta-blockers may be used to prevent recurrence. PMVT with normal QT is treated in the same way as monomorphic VT.

The prolongation of QT (QTc >460 msec) may be:

- Congenital or
- Acquired due to drugs (antibiotics, antihistamines, antiarrhythmic drugs, antidepressants, etc.), electrolyte abnormalities (hypokalemia, hypocalcemia), etc.

Torsades De Pointes

It is a form of polymorphic VT with QT prolongation seen in 12 lead baselines ECG. There is beat to beat variation and appears to be twisting around the isoelectric line of ECG. This is treated with 1–2 gm of $MgSO_4$ iv over 15–20 minute iv atropine and isoproterenol or overdrive pacing are also used for acquired form as they increase the heart rate and thus shorten the QT interval. Correction of electrolytes and removal of offending factor is a key to treatment. Congenital QTc prolongation is adrenergic mediated; hence beta-blockers are used.

Pulseless VT/Ventricular Fibrillation

Most of defibrillators in use these days are biphasic. Along with CPR and vasopressor (epinephrine) asynchronous shock of 120–200 J is given. Energy of shock is increased in stepwise manner.

Antiarrhythmic Drugs Commonly Used in ICU

- Adenosine 6 mg iv fast followed by rapid saline flush if no response repeat 12 mg iv fast.
- Esmolo 500 mcg/kg iv bolus then infusion at 50 mcg/kg/min. If needed increment of dose 25 mcg/kg/mim every 5 minute maximum up to 200 mcg/kg/min.
- Diltiazem 0.25 mg/kg iv in 2 minutes bolus if needed second bolus dose after 15 minutes at 0.35 mg/kg and maintain the infusion at 5–15 mg/min.
- Metoprolol 2.5–5 mg iv in 2 minutes. If needed may be repeated every 5–10 minutes up to three doses.
- Amiodarone 150 mg iv bolus over 10 minutes. Repeat if needed, then 1 mg/min for 6 hours followed by 0.5 mg/min for 18 hours. Total dose in 24 hours should not exceed 2.2 gm.
- Lidocaine 0.5–1 mg/kg bolus instant followed by 1–4 mg/min.
- $MgSO_4$ 1–2 gm iv in 20 minutes. A continuous infusion at the rate of 2–4 mg/min may also be administered after bolus, if needed.

DC Shock and Pacing

A critically ill patient has many precipitants of tachyarrhythmia such as infection, high catecholamine state, involvement of multiorgan so response to shock is a challenge. Moreover, critically ill patient does not tolerate shock well. Taking care of precipitants is necessary to get a successful response of shock. Serial DC shocks are not appropriate for self limiting recurrent tachyarrhythmias.

Overdrive pacing is done by pacing the heart at higher rate than its native rate. It is done to treat SVT, atrial flutter, VT, who have either failed to response or recurrent. Rhythm of sinus tachycardia, AF, and VF cannot be controlled by this.

Conclusion

Although some patients are admitted in ICU because of tachyarrhythmias majority develop them in ICU because of multiple illness and treatment. The adverse effect of tachyarrhythmia is well established and treating them in ICU is difficult also. So a very judicious approach is needed to address this problem.

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CHAPTER

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POCUS in Medical ICU

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Abstract

Point-of-care ultrasound (POCUS) is a useful imaging modality in the era of modern evidence-based medicine. This article will summarize the historical development, basic physics, advantages of POCUS, and its applications in the medical intensive care unit (ICU). Based on improved accuracy and reduced time in narrowing diagnosis, it positively influences patient outcomes. Structured training programs with hands-on practice can equip the doctors acquire the necessary knowledge and skill in the field of POCUS.

Introduction

Point-of-care ultrasound (POCUS) literally refers to the point-of-care ultrasound, which is usually performed by non-radiologists in close proximity of the patient. The scope and goals are limited to specific clinical questions, which help in narrowing the diagnosis and guiding clinical therapy. It is an extremely useful imaging modality particularly for the critically ill patients. The advantages of POCUS of being quick, accurate, reproducible, radiation free, and available bedside for serial monitoring make it stand-out from other imaging modalities. In the western world, POCUS has become an integral part of the emergency medicine department and critical care. Moreover, Royal College of Emergency Medicine has made POCUS a mandatory part of the curriculum of emergency medicine training.[1] Though the use of ultrasound by emergency medicine physician and by an intensivist requires the same instrument and skill, still there are important differences in their application. POCUS is primarily used by an intensivist in the medical ICU for focusing on heart, lung, pleura, procedural guidance, and for vascular access. The intensivist does serial examinations to monitor the response to treatment, which aids in patient's management. On the other hand, the emergency medicine physician does a single extended evaluation of the whole body including heart, lungs, abdomen, testes, obstetrics, musculoskeletal, and eyes for making a provisional diagnosis.[2]

Advantage of POCUS over Routine Ultrasound

POCUS in ICU is performed by the intensivist bedside who has full knowledge of the patient's issues and there is rapid implementation of these results to patient's management. There is no time lag in decision-making, provided the intensivist has the appropriate skill at image acquisition and interpretation. On the other hand, routine ultrasound is done by a radiologist or a cardiologist who are not in constant touch with the patient and there is always a time lag due to logistic issues. Moreover, serial monitoring of the patient is difficult with routine ultrasound.[2]

History

The use of POCUS is not new and can be traced back to 1990s when the first paper supporting the use of POCUS

was published by The American College of Emergency Medicine.[3] It was followed by a series of publications highlighting POCUS to be one of the important tools in dealing critically ill patients. The use of ultrasound for central venous access was made compulsory by the National Institute for Clinical Excellence in 2002.[4] Today, there are many fellowship programs in POCUS giving training to the intensivists. In 2016, the Society for Acute Medicine published the first POCUS curriculum for the physicians in the United Kingdom.[5] Though there is no national certification course for POCUS in India, there is still a lot of potential in increasing the use of this modality. Further, the residents have an easy access of doing bedside POCUS with the advent of small portable ultrasound machines. We, therefore, need to overcome the inertia of using POCUS routinely for patient management.

Basic Physics

A clear mental picture of the three-dimensional anatomy and basic understanding of the physics of ultrasound are the prerequisites for optimal image acquisition and interpretation. The ultrasound transducers send ultrasound waves (1–15 MHz) through their piezoelectric crystals and receive reflected waves. A two-dimensional image is formed on the screen which can be optimized by using the correct transducer and adjusting its position. Higher frequency transducers produce high resolution images of superficial structures, while lower frequency transducers produce low resolution images of deeper structures. There are basically three types of transducers used in POCUS—linear, curvilinear, and phased array **(Table 1)**.

Denser media reflect most of the sonographic waves, generating a white image. On the other hand, rarer media transmit most of the waves and reflect back very few waves, generating an echogenic black image. Thus, fluid appears black, soft tissue (liver) appears gray, fibrous tissue appears white without a shadow, and bones or stones appear white with a shadow **(Figs. 1A and B)**. Air is very hyperechoic and thus prevents visualization of deeper structures.[7]

Components of POCUS

POCUS usually involves evaluation of the heart, lung, pleura, lower limb Doppler, screening abdomen and for venous access. Still, the most important aspect in medical ICU is the cardiorespiratory evaluation to identify the cause of dyspnea or hypoxia.

Heart

A quick goal directed echocardiography is the hallmark tool for evaluation of the cause of shock or acute onset dyspnea. A combination of basic two-dimensional echocardiography combined with color flow mapping and Doppler imaging of the heart and great vessels gives a basic idea of the structure and function of the heart. All the views including parasternal long and short axis views, apical views, and subcostal views must be imaged wherever possible, for addressing specific abnormalities. The intensivist can promptly look for an immediately life threatening cause of hemodynamic collapse like major valve failure, massive pulmonary embolism, cardiac tamponade, acute cor pulmonale, or regional wall motion abnormality, which needs prompt treatment. With the addition of speckle tracking, one is able to negate the subjective error in assessing regional wall motion abnormality. Serial monitoring of inferior vena cava and its collapsibility by the subcostal view helps in assessment of the fluid status of the patient.

Thoracic Ultrasonography (Lung and Pleura)

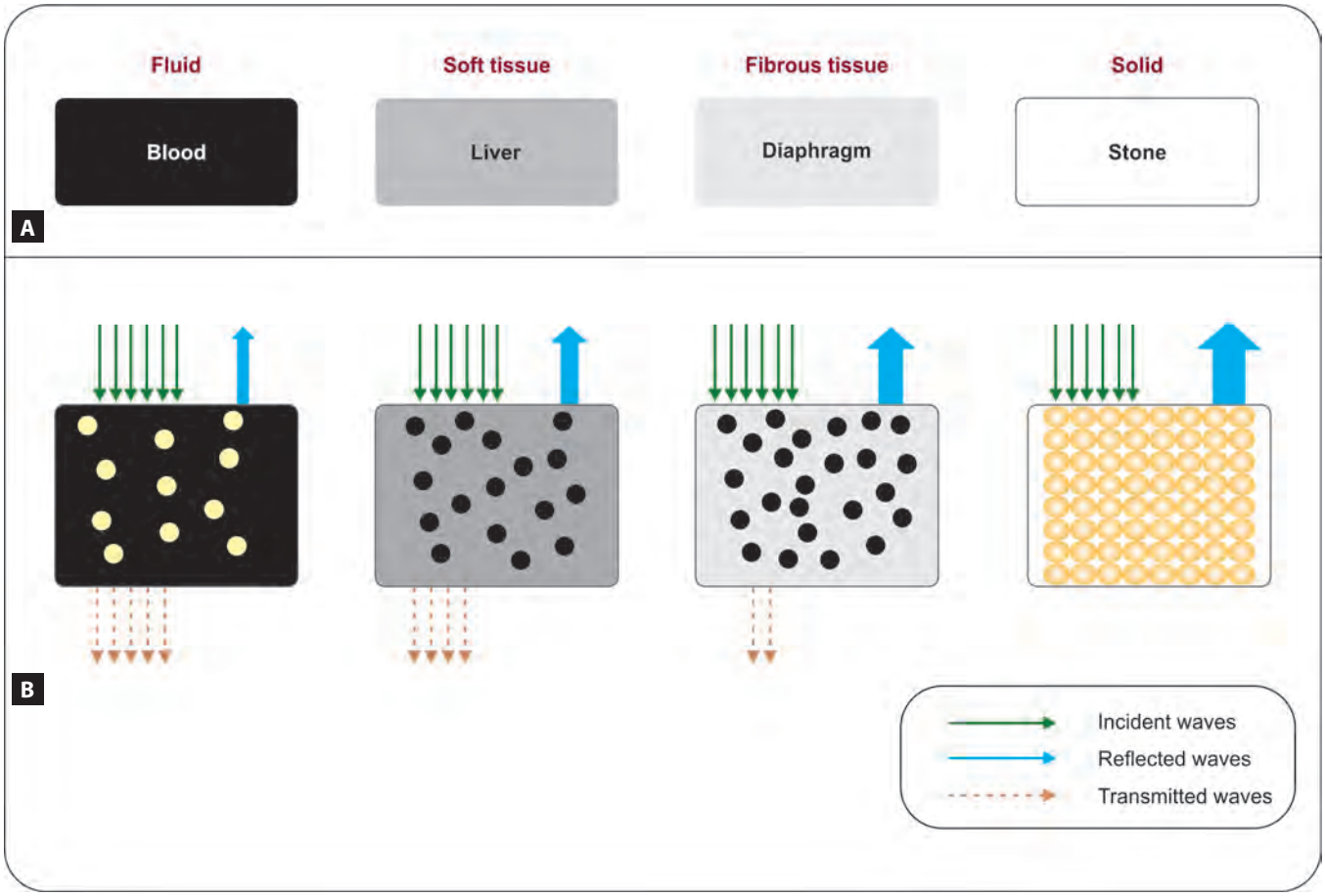
Evaluation of the cause of dyspnea can never be complete without having a look at the lungs and pleura. It is not uncommon to miss the diagnosis of a small posteriorly located consolidation in an obese patient on clinical examination.[8] Even chest X-ray in a critically ill ventilated patient does not give accurate information as there can be motion artifacts, rotation, coexisting fluid overload, and the views are usually anteroposterior.[9] However, ultrasound has a similar accuracy as compared to computed tomography and can appreciate pathologies like consolidation, pleural effusion, pneumothorax, diaphragmatic dysfunction, and one should spend time to look at both sides of the chest. Thoracic ultrasound has a sensitivity and specificity of more than 90% for diagnosing these pathologies.[10]

Some of the important findings in a thoracic POCUS are:

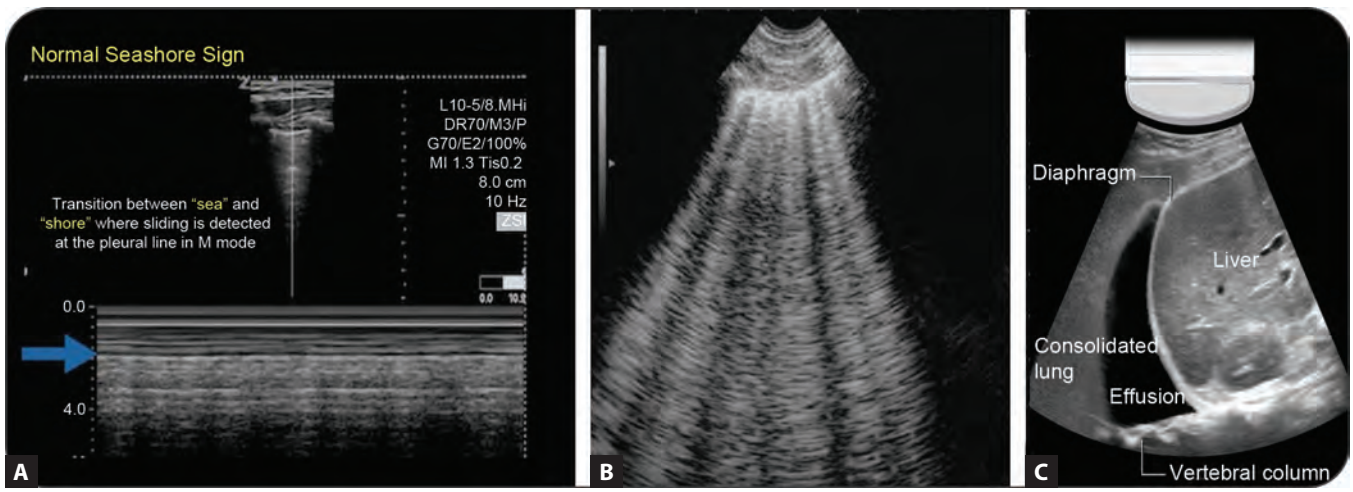
- *Seashore sign* **(Fig. 2A)** refers to the normal aeration pattern, which consists of lung sliding with A-lines.

TABLE 1 Types of transducers used in POCUS[6]

Transducer type	**Linear**	**Curvilinear (convex)**	**Phased array**
			
Frequency range (MHz)	5–10	2–5	1–5
Imaging depth (cm)	9	30	35
Applications	• Arteries/veins • Eyes • Skin/soft tissue • Pleura • Procedures – central venous catheterization, lumbar puncture	Abdominal viscera like • Liver • Gall bladder • Kidney • Urinary bladder	• Heart • Inferior vena cava • Great vessels • Pleura • Lungs



Figs. 1A and B: (A) Appearance of fluid, soft tissue, fibrous tissue, and solids on ultrasound screen. (B) Propagation of ultrasound waves through various media



Figs. 2A to C: (A) Seashore sign demonstrating lung sliding with A-lines in M-mode ultrasound. (B) Two-dimensional image of vertically oriented B-lines or lung rockets in a thoracic ultrasound. (C) Two-dimensional image showing a clear pleural effusion with lung consolidation (echogenicity similar to that of liver)

Lung sliding refers to the opposition of visceral and parietal pleura. Absence of lung sliding indicates presence of air or fluid between the visceral and parietal pleura. A-lines constitute the horizontal, hyperechoic reverberation artifacts created by repetitive reflection of ultrasound waves between the pleural line and transducer.

- *B-lines or lung rockets* **(Fig. 2B)** are the vertically oriented discrete hyperechoic lines, which extend to the sonographic window edge. They represent widened fluid-filled interlobular septa and indicate pulmonary edema, pneumonia, acute lung injury, or fibrosis, depending upon their distribution and characteristics.
- Consolidations appear with an echogenicity similar to that of liver, and thus called hepatization. Infective consolidations need to be differentiated from basal lung atelectasis **(Fig. 2C)**.
- *Pleural effusion* as small as 5 mL can be picked up.[11] Anechoic, clear fluid indicates transudate while hyperechoic, debris-filled fluid indicates exudate. Also, pleural effusion can be differentiated from pleural thickening.[12]

Abdomen

The importance of abdominal assessment cannot be undermined especially in cases of acute abdomen. Appreciation of intra-abdominal fluid, any septic foci, bladder distension, hydronephrosis can be done by the intensivist rapidly without waiting for the radiologist. Free fluid is most commonly detected in the perisplenic space and in the Morrison's pouch in the supine position.[13] Ultrasound can be used therapeutically in cases of drainage of abscesses.

Lower Limbs

Patients in ICU remain bed-ridden for prolonged periods and require regular screening of their lower limb veins. Early identification of deep vein thrombosis and subsequent prevention of pulmonary embolism is one of the important aspects in managing complications of such patients.

Ocular Ultrasound

The most important aspect of ocular ultrasound in medical ICU is to assess the intracranial pressure by the measurement of optic nerve sheath diameter. A cut-off value of 5 mm has 100% sensitivity of raised intracranial pressure which is comparable to a non-contrast CT.[14] Serial monitoring of optic nerve sheath diameter helps in optimizing therapy. Pathologies such as globe rupture, traumatic detachments, lens dislocation, and vitreous hemorrhage can also be easily picked up but these are uncommon issues encountered in medical ICU.

Ultrasound for Procedural Guidance

A variety of procedures can be performed in the ICU for routine management of patients for both diagnostic and therapeutic purposes. Ultrasound greatly increases the success rate and reduces the complication rate in cases of thoracocentesis, paracentesis, abscess drainage, regional anesthesia, lumbar puncture, and central venous catheter insertion.[15] Upper extremity deep vein thrombosis secondary to central venous catheters can also be readily picked up.

Miscellaneous

Several other uses of POCUS include looking for ectopic pregnancy, testicular torsion, epididymo-orchitis, tendon injury, etc., but these are uncommon issues encountered in the medical ICU.

Conclusion

The enthusiasm and interest in using POCUS is rising across the globe owing to its speed and accuracy in diagnosis, in an acutely unwell patient. It acts as an aide to the traditional clinical and radiological techniques in reducing the morbidity and mortality of the patients. However, there is still a huge gap in expanding the utility of this modality due to lack of training programs and trained supervisors. Therefore, this rapid and reliable diagnostic tool should be included in routine medical curriculum to make it an integral part of the patient care.

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CHAPTER

99 Disease-specific Ventilation—Strategies and Evidences

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Abstract

- Normal respiration is NEGATIVE **(Table 1)** Pressure, and Ventilator driven is POSITIVE Pressure Ventilation.
- Disease-specific ventilation strategies and evidences is done in respiratory failure as evidenced by clinical symptomatology and ABG.
- Whatever mode selected, the treating physician should maintain SYNCHRONY between the ventilator and the patient. Then the mode NIV or Invasive and finally to TROUBLE SHOOT. based on the specific diseases and the ventilator alarms.

Introduction

- The topic disease specific ventilation deals in brief about the basic steps in ventilation and then disease-specific strategies in patients presenting with respiratory failure
- This could be achieved by mechanical ventilation (MV)
- There is wide variety of MV available for use in modern pulmonary care[1]
- The principles in MV are:
  - Disease-specific ventilation strategies
  - Lung protection strategy by applying safe ventilation practices

Respiratory Failure: Four Types

- The respiratory system helps to maintain adequate oxygenation.[2]
- Respiratory failure results in either inadequate oxygenation or CO_2 removal [3]or both.
- It's one of the most common medical emergencies that warrant ICU admission.[4]

TABLE 1 Negative and positive pressure ventilation

Normal respiration/negative pressure ventilation[30]	*Ventilator generated/positive pressure ventilation*
Inspiration done by respiratory muscles by sucking of air into the lungs, increasing the negative intrapleural pressure (-6 to -8 cm H_2O)	According to disease status, ventilator generates pressure in the airways to drive air into the lungs, pushing the chest wall outward

Type 1/Hypoxemic Respiratory Failure (Table 2):[5]
- Most common type
- PaO_2 <60 mm Hg **(Table 3)**
- $PaCO_2$ <45 mm Hg
- Patient presents as tachypneic, hypoxic, and hypocapnic

Type 2/Hypercapneic Respiratory Failure:[5]
- Seen in airway diseases (COPD), neuromuscular diseases, and chest wall abnormalities
- Patient presents with low-respiratory rate, hypoxia, hypercapnia, and acidotic[6]

TABLE 2 Causes of RF (respiratory failure)[9]

Acute	*Chronic*
Type 1: Acute pulmonary edema Pneumonia ARDS Pneumothorax Pulmonary embolism	**Type 1:** ILD-sarcoidosis Idiopathic pulmonary fibrosis Pulmonary artery hypertension Chronic heart failure Cyanotic congenital heart disease
Type 2: Acute exacerbation of COPD GBS Myasthenia gravis Poisoning head injury/raised ICP	**Type 2:** COPD Obesity hypoventilation syndrome Neuromuscular disorders Kyphoscoliosis Ruptured esophagus
Type 3: Upper abdominal emergencies Obesity/ascites Prolonged GA Peri-operative Smoking	**Type 4:** Cardiogenic shock Septic shock Hypovolemic shock

TABLE 3 Respiratory parameters[9]

	Normal people	*Respiratory failure*
PaO_2 (Kpa)	10.5–13.5	<7
$PaCO_2$ (Kpa)	4.7–6	>7
RR (/min)	10–25	>30
Tidal volume (mL/kg)	5–8	<3
Vital capacity (mL/kg)	30–70	<15

Type 3/Perioperative Respiratory Failure:[7] Due to atelectasis following GA

Type 4/Shock Related Respiratory Failure: Due to hypoperfusion[7]

- **Presentation of RF**

  Acute Respiratory Failure:[8]
  - Develops before compensation

  Chronic Respiratory Failure:[8]
  - Compensated to buffer respiratory acidosis

Diagnosis

Always by clinical, supported by ABG, PFT, pulse oximetry, CXR, ECHO.

Clinical Features

- **Type 1:**
  - *Mild to moderate:* Hypoxia, tachypnea, tachycardia, diaphoresis
  - *Severe hypoxia:* Bradycardia, vasodilation, hypotension, infarction, arrhythmia, cardiac failure
- **Type 2:**
- **CNS disturbances:**[10] Depression, lethargy, headache, seizure
- **ABG:**[11] To confirm and differentiate the types of RF
- **Pulse oximetry:**[10] Assessing 02 status
- **CXR and ECHO:** To differentiate between cardiogenic and noncardiogenic pulmonary edema

Treatment

- To correct arterial hypoxemia and to maintain target SpO_2 >89–90%[11] and PO_2 >55–60 mm Hg
- It is done by:
  - Oxygen supplementation[12] usually **HFNO/NIV/Invasive ventilation**

  HFNO:[13]
  - Supplies as much as 40 L/min to maintain constant O_2 flow

  NIV:
  - Nowadays useful in acute respiratory failure as an initial tool especially in COPD exacerbation,[14] weaning after extubation[15] in COPD, in immunosuppressed[17] patients in ARF, cardiogenic pulmonary edema[16]
  - NIV[18] avoids the need for intubation, nosocomial infection
  - A successful NIV depends upon properly fit interface & optimal ventilator settings
  - Full face masks[19] for ARF, nasal mask for COPD
  - Noninvasive ventilation[20] within 1–4 hours of MV, the response is observed and assessed for failed NIV trial
  - In acute severe asthma,[21] if NIV fails, requires endotracheal intubation
  - Finally NIV is beneficial in COPD and cardiogenic pulmonary edema
- *Noninvasive positive pressure ventilation:* Used in COPD, ARDS, cardiogenic pulmonary edema
- *Noninvasive negative pressure ventilation:* Used in neuromuscular disease, central hypoventilation and chest wall abnormality

TABLE 4 Parameters and goals of invasive[25] MV in different respiratory diseases

Prototype	*Restricted lung-ARDS*	*Obstructed lung-asthma*	*Neuromuscular diseases*
Mode	V-ACMV	V-ACMV	V-ACMV
VT [per KG]	4–6 mL/kg	4–6 mL/kg	6–8 mL/kg
RR [per minute]	18–35	8–12	14–18
PEEP	High PEEP based on FiO_2	5–8 cm H_2O	Up to 5 cm H_2O
I:E ratio	1:1 or 1:2	1:3–1:6	1:2–1:3
Plateau pressure	<30 cmh 20	<30 cm H_2O	
PaO_2	55–60 mm Hg	55–60 mm Hg	60–80 mm Hg
PH	7.2–7.4	7.2–7.4	-

Other uses of NIV:

- NIV weaning or postextubation
- *Facilitation technique:* For early extubation
- *Rescue or curative technique:* For avoiding reintubation who fails extubation

Invasive Mechanical Ventilation

- **Done in failed 02 therapy and NIV trial[22] and for airway protection:**
  - **Always start with a volume ACM[9] (Table 4)** (assist control mode of ventilation), then if the patient improves, shift to Pressure Support Ventilation[23] **(PSV)**
- To avoid ventilator induced lung injury (VILI), a low-tidal volume and high PEEP is always set to reduce mortality in ARDS—ARDS NETWORK STUDY[24]

Mechanical Ventilation[26] (Basics and Modes)

Mainly indicated in:

- **Depressed respiratory drive:** Sedatives, stroke, head injury
- **Excessive respiratory workload:** ALI, ARDS, pulmonary embolism
- **Ventilatory pump failure:** Flail chest, tension pneumothorax

Four Phases of Breath[28]

- **Inspiration**
- **Change from inspiration to expiration**
- **Expiration**
- **Change from expiration to inspiration:**
  - **Triggering of a breath:**
    - It describes the phase variables that changes from expiration to inspiration
    - Trigger is what initiates a breath

Time triggered—inspiration begins when a certain time has lapsed

Pressure triggered—ventilator senses the inspiratory effort reflected by drop in airway pressure and initiates inspiration

Volume triggered—when the baseline flow variable drops below the fixed flow (5–20 L/min), the machine initiates inspiration:

- **Limiting a breath**:
  - It's the set flow in pressure beyond which the variable never goes in inspiration or expiration.
- **Cycling of a breath:**

Time cycled ventilation—common cycling mechanism. Inspiratory flow is terminated once the preselected time interval has lapsed after the start of inspiration and expiratory phase is started.

Pressure cycled ventilation—useful in SIMV/IRV modes. When a preselected air pressure has been reached, expiratory valve opens and ends the inspiration.

Volume cycled ventilation-with pressure limiting valve—When a preset volume is delivered, inspiration is terminated, delivers constant VT.

Flow cycled ventilation—Here a preset flow ends the inspiratory flow useful in PSV.

Patient Ventilator Interactions

A patient interacts[31] with the ventilator based on the ventilatory drive, when inspiration starts and ventilator

requirement, to satisfy metabolic demands whereas **the ventilator interacts with the patient** based on the inspiratory trigger, delivery of gas, and cycling **(Fig. 1)**.

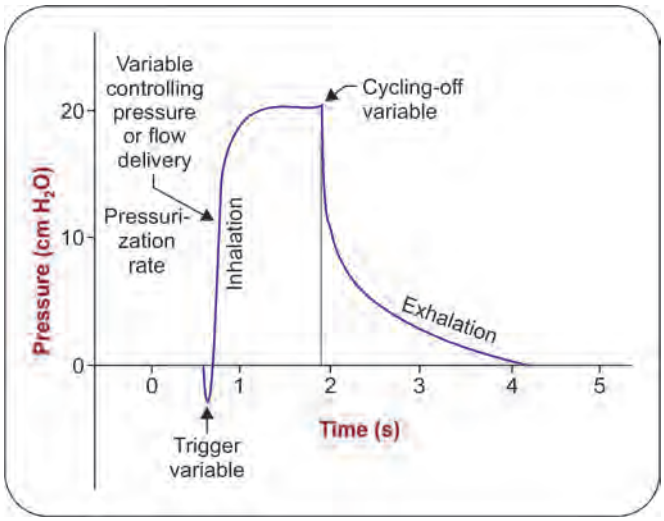

Fig. 1: Graphical representation of breath[29]

- **CMV:**
  - Patient cannot trigger the ventilator, but PCV always ensures Pplat <30–35 cm H_2O—used as a lung protective strategy in ARDS.[32]
- **ASSIST CONTROL MODE (ACM) (Fig. 2):**[33]
  - **Commonly used**. It delivers controlled breath as well as assists patient triggered breath **(Fig. 3)**; hence the patient continues to do inspiratory work even on ventilator.[34]
- **SIMV:**
  - Ideal mode for weaning providing partial ventilatory support.
- **PSV:**[23]
  - Allows breathing, providing full support making the patient fully comfortable used for weaning. **Ultimately, SIMV and PS—an ideal choice of ventilatory support facilitating quick weaning as well**.

No mode is superior one over the other. The initial settings:—FiO_2 0.5–1, tidal volume—8–12 mL/kg, RR—8–12/min, inspiratory flow rate of 40–60 L/min.

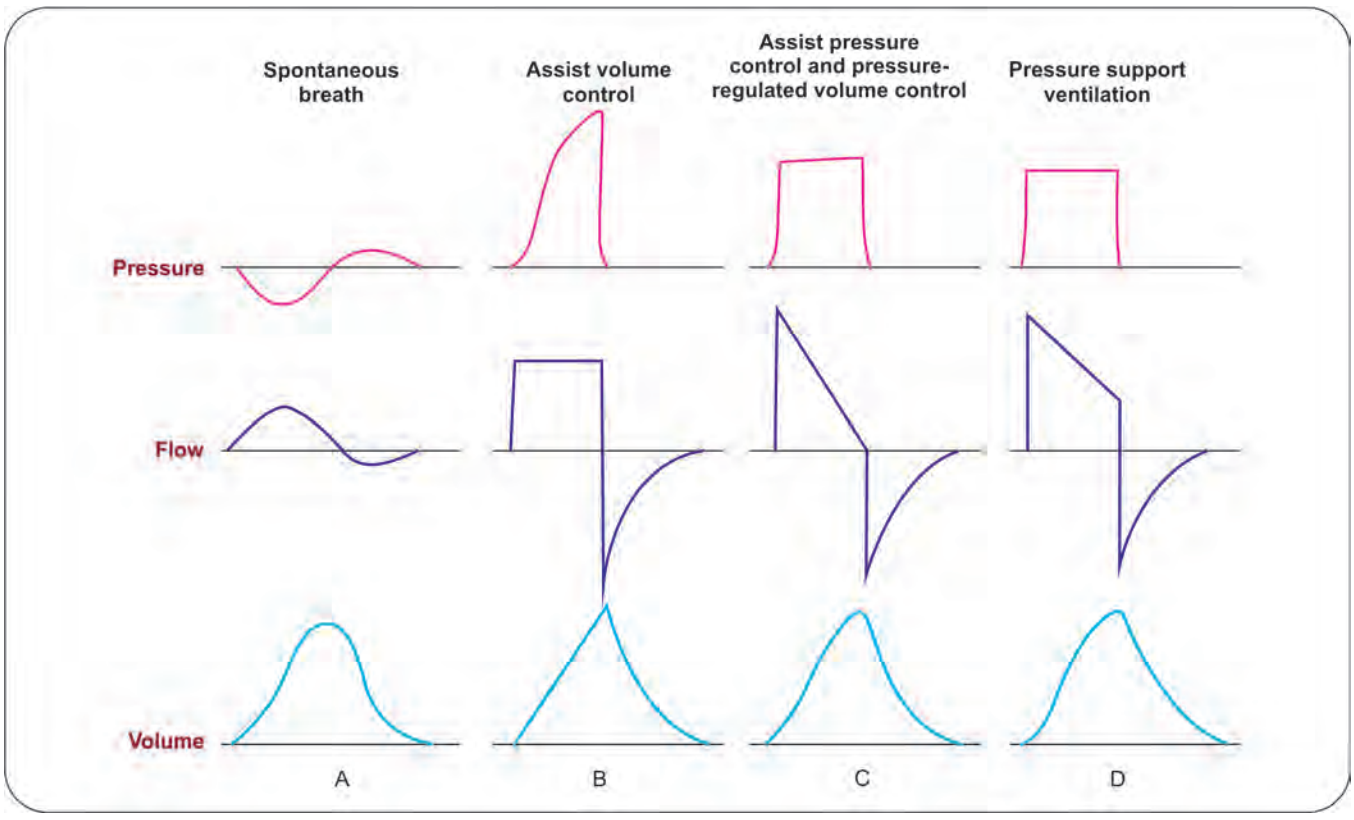

Fig. 2: Basics of mechanical ventilation[27]

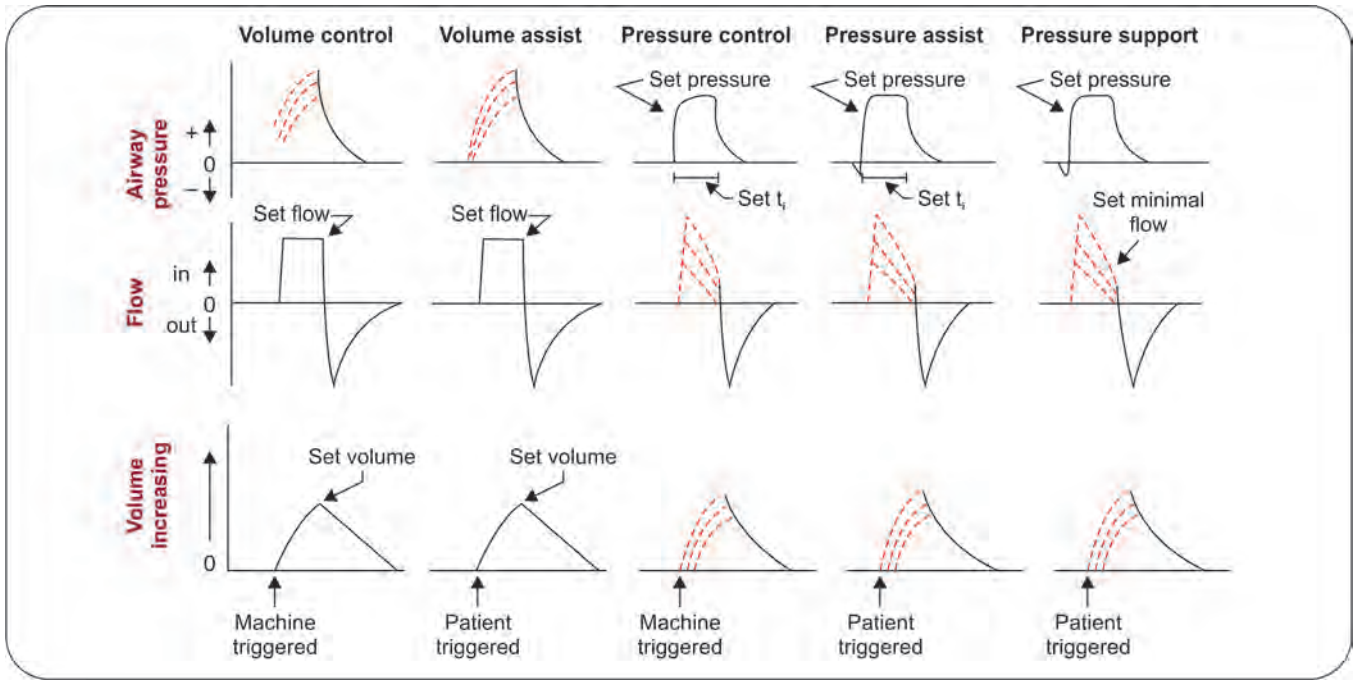

Fig. 3: Machine and patient triggering graph

Management of Patients with Severe Airflow Obstruction

- **Acute Severe Asthma**[35]
  AC mode or SIMV mode—settings:
  - Small VT: 5–7 mL/kg
  - RR: 12–15/min
  - Peak flow: 60 L/min
  - FiO_2: 0.5[35]
  - To prevent Barotrauma auto PEEP should be <10 cm H_2O
- **COPD**[36]
  SIMV or AC mode—settings:
  - VT: 5–7 mL/kg
  - RR: 24–28/min
  - FiO_2: 0.4
  - They have expiratory flow limitation, and hence auto PEEP,[36] which is balanced by setting extrinsic PEEP, which reduces patient's work of triggering

ARDS—Advances in Diagnosis and Treatment

- Berlin definition of ARDS[37]

  Based on the severity of hypoxemia:
  - **Mild:** 200–300 mm Hg with PEEP >5 cm H_2O
  - **Moderate:** 100–200 mm Hg with PEEP >5 cm H_2O
  - **Severe:** <100 mm Hg with PEEP >5 cm H_2O
- (Berlin definition has greater predictive validity for mortality)
- Timing of onset of symptoms: within 1 week of clinical insult.
- Chest X ray: bilateral opacities.
- Origin of edema: not fully explained by heart failure.

Early spontaneous breathing[38] **in mild and late ARDS**—by ACM, PSV, or APRV similar to PCM pressure control mode.

Advantages of spontaneous breathing (Fig. 4):
- to reduce ventilation induced diaphragmatic dysfunction (VIDD)[38]
- to improve tidal ventilation, O_2 exchange, delivery

THE STRATEGY OF VENTILATION IS:
- **Minimal distension strategy**—low VT <6 mL/kg[39]
- **Increased recruitment strategy**—open lung approach—high PEEP >10 cm H_2O[40]
- **Goal of plateau pressure** <30 cm H_2O to avoid shunt and improve oxygenation

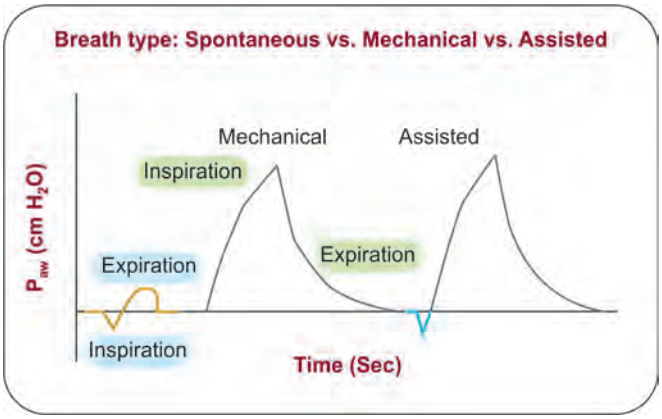

Fig. 4: Breath types graph

- This lung protective strategy ends with permissive hypercapnia[41] (treated with a higher respiratory rate of 24–28 breaths/min) and benefited by decreased mortality.[42]

Prone Positioning in ARDS

Earlier and prolonged prone positioning[42] for more than 16 hours in severe ARDS improved 28 day, 90 day mortality.

Other therapies:

- Inhaled Nitric Oxide—used in refractory ARDS
- Surfactant recombinant protein C
- Steroids[43]—methyl prednisolone 1–2 mg/kg in early severe ARDS
- ECMO[44]—useful in severe refractory ARDS

In any settings

Manipulations to Increase Oxygenation

Increase:

- FiO_2
- PEEP
- Ti

Settings to Improve Ventilation

Increase:

- RR <35/min
- VT up to 10 mL/kg
- PIP (peak inspiratory pressure)

Complications of mechanical ventilation:

- Always whatever mode is set, see to that LPS is adapted—low VT is set even in normal and diseased lungs to avoid VILI[25]

Trouble Shooting

Clinically

- **Breath stacking/dyssynchrony:**
  - Increase inspiratory flow rate
  - Sedation
- **Hypotension:**
  - Minimize PEEP/sedation
- **Altered sensorium:**
  - Especially in NIV adjust IPAP, EPAP, and increase backup RR

Based on ABG

- **Low PaO_2:**
  - Adjust flow rate or FiO_2
  - Increase:
    - EPAP/PEEP
    - Ti
- **High $PaCO_2$:**
  - Increase:
    - IPAP/PS
    - Backup RR
- **Low $PaCO_2$:**
  - Decrease:
  - IPAP
  - Backup RR

CARDS—COVID-19 with ARDS

- Management of COVID-19—Respiratory distress—Vasocenteric problem
- CARDS 2 types:
  - L-CARDS [low lung elastance—high compliance]
  - H-CARDS [high lung elastance—low compliance] [Typical ARDS lung]

Ventilatory Strategies for CARDS[45]

- **L-CARDS [mild cases]**
  Before intubation:
  NIV:
  - HFNO
  - CPAP
  - BIPAP
  - Awake prone positioning

After intubation:
  - Lower PEEP [<10 cm H_2O]
  - Liberal VT [7–9 mL/kg]
  - Prone positioning
- **H-CARDS**
  - Treated as typical ARDS lung, requiring invasive ventilation:
    - Higher PEEP [<15 cm H_2O]
    - Lower VT [5–7 mL/kg]
    - Prone positioning

Abbreviations

ACM, Assist Controlled Mode
ALI, Acute Lung Injury
ARDS, Acute Respiratory Distress Syndrome
CARDS, COVID-19 with ARDS Patients
HFNO, High Flow Nasal Cannula Oxygenation
IRV, Inverse Ratio Ventilation
MV, Mechanical Ventilation
NIV, Noninvasive Ventilation
PEEP, Positive End Expiratory Pressure
PIP, Peak Inspiratory Pressure
RF, Respiratory Failure
SIMV, Synchronized Intermittent Mandatory Ventilation
VCM, Volume Control Mode
VT, Tidal Volume

Conclusion

Ultimately one should know the basics of MV and then to decide NIV/INVASIVE VENTILATION according to specific diseases like COPD, ALI/ARDS, CCF, etc. and also see to that you always follow LPS (lung protective strategy) in ventilation.

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CHAPTER

100 Prone Ventilation for Adults with ARDS

A Bhagwati

Abstract

Prone ventilation for adult respiratory distress syndrome (ARDS) patients is a resurrected concept, initially proposed in 1970s and widely used in 1990s for treatment of ARDS. However, it was not popular due to some studies and meta analysis. But the practice was reintroduced in 2015 Sepsis guidelines and currently is very popular particularly in patients with lung involvement due to COVID-19. The principle is to recruit the posterior lungs which are affected to improve oxygenation and FiO_2/PaO_2 ratio. This article briefly introduces the concept of prone position ventilation and also highlights the problems that are associated with it.

Introduction

Adult respiratory distress syndrome (ARDS) is a condition in which the lungs suffer severe widespread injury, interfering with their ability for gas exchange. Increasing pulmonary edema and alveolar collapse create a physiologic dead space, where no gas exchange can take place in the pulmonary capillaries, causing ventilation-perfusion mismatch. ARDS is a life-threatening respiratory condition characterized by hypoxemia, and stiff lungs ventilation. ARDS represents a stereotypic response to many different inciting insults and evolves through a number of different phases: Exudative phase, Fibrotic phase, and Proliferative phase. ARDS is a syndrome with multiple risk factors that trigger the acute onset of respiratory insufficiency and respiratory failure.

Causes of ARDS

Direct Lung Injury

- Aspiration of gastric contents or other causes of chemical pneumonitis
- Lung contusion, penetrating injury of the thorax affecting the lung tissues, fat emboli
- Near drowning
- Inhalation injury, pulmonary vasculitis
- Pulmonary edema due to repercussion due to transplant of lungs.

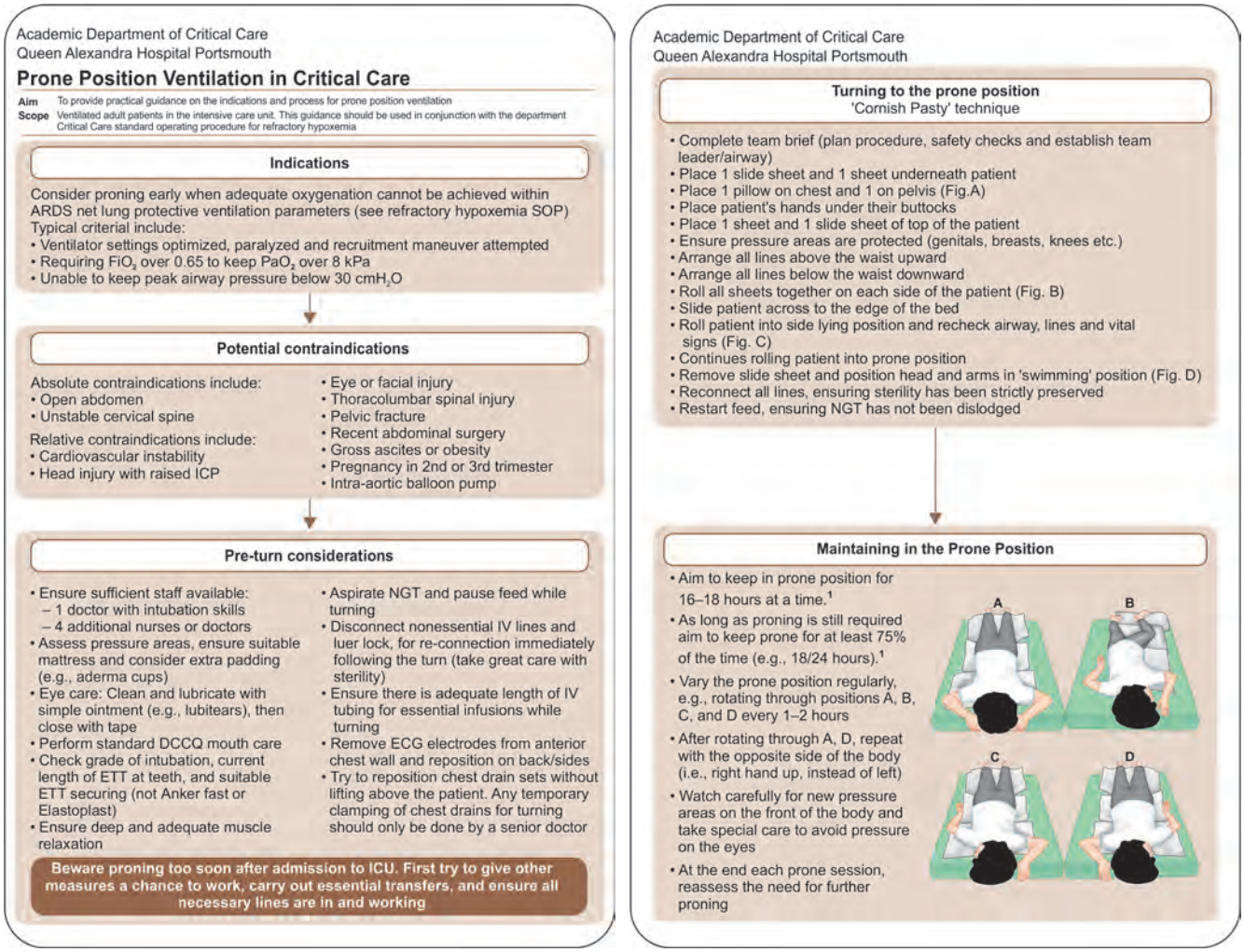
Indirect Lung Injury

- Sepsis
- Pancreatitis
- Shock with hypoperfusion
- Multiple blood transfusions (TRALI)
- Major trauma
- Burns, drug overdose
- Non-cardiogenic pulmonary edema.

Management of ARDS (Prone Ventilation)

In the intensive care unit (ICU), different types of patients requiring mechanical ventilation (MV) are admitted. It is challenging for a clinician when patient develops ARDS. Several strategies are employed, the currently

Flowchart 1: Strategies in prone ventilation



practiced and quite popular is prone positioning of a patient with ARDS on MV. Several studies and practical experience in recent times have shown improvement of oxygenation when a patient is placed in prone position. Prone ventilation was practiced in the 1995–1997 by me in Mumbai at Bhatia Hospital along with another center in Mumbai with excellent results. Unfortunately studies and meta-analysis did not evoke scientific justification for use of this protocol in MV, and fell out of use with other modalities.

However, in 2015, Surviving Sepsis guidelines revived the interest and recommended use of prone ventilation in ARDS as a part of recruitment maneuvers and thereafter it is now an accepted modality in management of ARDS patients, including finding its way in management of COVID pneumonia and COVID-induced ARDS.

Pathophysiology

In supine position, the positive pressure from the ventilator raises the anterior chest wall, but hardly has any effect on the posterior chest wall. When patient is placed in prone position, the posterior chest wall, which is less compliant, is elevated leading to more diaphragmatic excursion, which leads to increased recruitment of the posterior lung. This causes improved overall aeration of the alveoli of the posterior lungs thereby improving the lung compliance. This causes improvement of ventilation-perfusion ratio, which is compromised in ARDS patients.

Prone Position Protocol

Best Practice in Implementing Prone Position for Patients with ARDS

- Take written consent for prone ventilation, explaining to relatives in details advantages and risks involved.
- Assess the hemodynamic status and oxygenation to determine the eligibility of the patient.
- Administer sedation and muscle paralytic drugs, with sedation holiday.
- Provide care of eyes and tape eyelids, if indicated.
- Maintain adequate oral hygiene. Secure the patients tongue with oral airway to prevent tongue bite. Oral suction as and when required.
- Secure endotracheal tube and monitor to ensure that extubation or ventilatory disconnection does not occur.
- Maintain proper skin care and place hydrocolloid dressings on bony prominence, chin, and forehead.
- Position the patient's face away from the ventilator to prevent tube kinking. Reposition the patient's head hourly to prevent skin breakdown.
- Place ECG electrodes on the patient's posterior chest.
- Empty the drainage bags.
- Appoint dedicated inter-professional team to take care (airways/ventilator tubing/line) of patient in prone position.
- Monitor effectively the hemodynamic status, blood gases within 1 hour of pruning the patient and then 4 hourly intervals.

Contraindications

- Burns, open wounds on face or ventral body surface
- Spinal instability
- Facial and pelvic fractures
- Life-threatening circulatory shock
- Increased intracranial pressure
- Pregnancy
- Abdominal trauma or surgery
- Acute bleeding
- Shock

Complications

- Facial and periorbital edema
- Pressure sores
- Accidental loss or displacement of ET, thoracic or abdominal drains, and central venous catheters
- Airway obstruction
- Hypotension
- Arrhythmias
- Vomiting

Summary of Strategies in Prone Ventilation

See **Flowchart 1**.

Conclusion

Prone positioning was first proposed in the 1970s as a method to improve gas exchange in ARDS. However, translation of this application in clinical practice is challenging as discussed. Prone position ventilation has been effective in management of moderate to severe ARDS patients, begun early in the course of the disease within 36 hours of the onset, for a period ranging 12–18 hours per session. However, prone positioning is not without harm and problems as discussed earlier.

Suggested Readings

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CHAPTER

101 Respiratory Emergencies: Golden Hour Rules in the First Hour

T Geetha, Ramesh Duraisamy

Abstract

Respiratory Emergencies are most common and sometimes life threatening. The Spectrum may range from Mild Respiratory Distress to Respiratory Arrest. The "Golden Hour" management is crucial to save the life. We divide the topic in to Immediate, Emergent, and Urgent management with time frame. "Every Breath is like a little rebirth" as quoted by Cristen Rodgers. So, the Emergency Team should act promptly using clues from the Brief History, Quick Physical Examination with Essential Investigations.

Introduction

"A-B-C" is the unofficial mantra of any emergency care, which describes airway, breathing, and circulation. The first two letters in this mantra relate to the patient's respiratory status. Compromise of the airway and respiration is the leading cause of death in many conditions in emergency setting. Respiratory emergencies are potentially life-threatening conditions that require immediate attention to avoid delay in treatment.

Spectrum of Respiratory Emergencies

In emergency department (ED), the patients with respiratory emergencies present with a spectrum,[1] that can range from mild respiratory distress to respiratory failure and finally respiratory arrest, which leads to death **(Fig. 1)**. Respiratory emergencies are generally identified by "Acute dyspnea" as a presentation. Dyspnea can result from respiratory, cardiac, neurological, traumatic causes, etc. **(Table 1)**.

Management of Respiratory Emergencies

For effective management of respiratory emergencies, we must have the following basic principles:[4]

- Rapid assessment of respiratory distress to arrive at the correct working diagnosis.
- With the working diagnosis, aggressive targeted treatment without delay.
- Continuous and frequent reassessment to ensure response to the appropriate treatment.

With the above principles, we can divide the Golden Hour management of respiratory emergencies into the following three parts:[5]

- Immediate management—to be done in 0–5 minutes **(Table 2)**
- Emergency management—to be done in 5–15 minutes **(Table 3)**
- Urgent management—to be done in 15–60 minutes **(Table 4)**

Indications of Noninvasive Positive Pressure Ventilation[6]

The following clinical and laboratory clues give an idea for indication of noninvasive positive pressure ventilation (NIPPV) in respiratory emergencies:

- Respiratory distress (dyspnea, tachypnea, and the use of accessory muscles of respiration)
- Acidemia (pH <7.35)

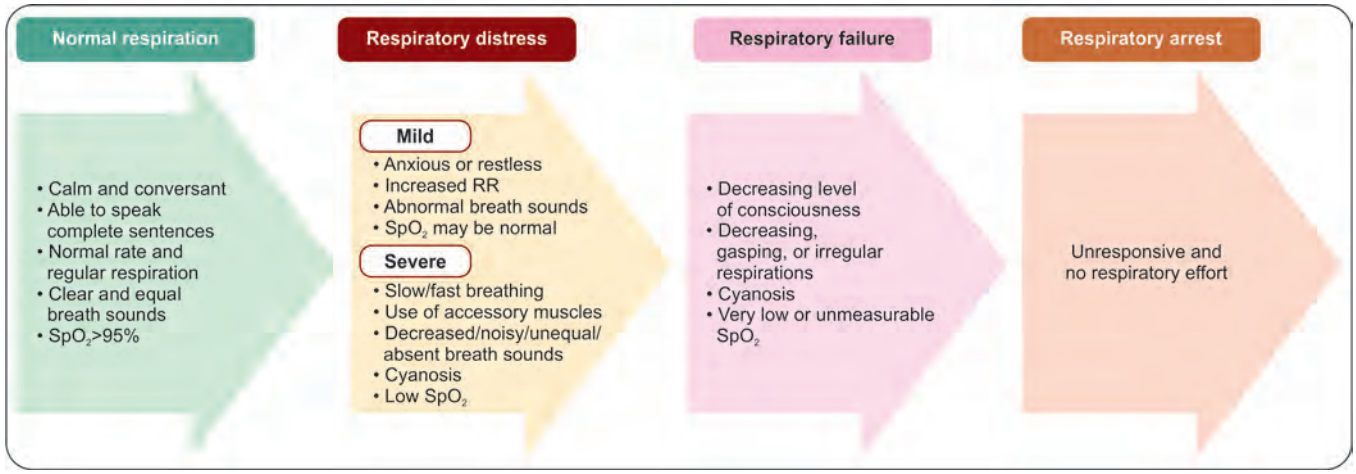

Fig. 1: Spectrum of respiratory emergencies

TABLE 1 Common causes of respiratory emergencies[2]

Respiratory:

Upper airway obstruction[3]

- Croup
- Supraglottitis
- Epiglottitis
- Neck abscess
- Ludwig's angina
- Angioedema
- Subglottic stenosis
- Tumor
- Foreign body

Other:

- A/E Asthma & COPD
- Obstructive Sleep Apnoea
- Tracheomalacia
- Tension Pneumothorax
- Trauma causing Hemothorax
- Acute Pneumonitis (Bacterial/Viral)
- Hypersensitivity pneumonitis
- Drug induced
- Pulmonary embolism

Cardiac:

- Pulmonary edema
- Arrhythmias
- Cardiac tamponade

Neurological:

- Guillain-Barré syndrome
- Myasthenia gravis
- Snake bite envenomation

Metabolic:

- Diabetic Keto Acidosis

Psychogenic:

- Anxiety
  - Panic attacks

Others:

- Anaphylaxis causing Angioedema
- SVC obstruction
- OPC poisoning

- Hypercapnia ($PaCO_2$ >45 mm Hg)
- Hypoxemia (PaO_2/FiO_2 <200)

Most frequently used types of NIPPV are CPAP and BiPAP:

- CPAP—in acute pulmonary edema, CCF, pneumonia, acute respiratory distress syndrome (ARDS), and chest wall trauma.
- BiPAP—in COPD with type 2 respiratory failure, neuromuscular disease, and sleep apnea.

Indications for Converting Noninvasive Ventilation to Invasive Ventilation[7]

- Inability to tolerate NIV
- Excessive secretions

TABLE 2 Immediate management (0–5 min)[5]

History	*Examination*	*Investigation*	*Intervention*
AMPLE H/o: (Allergies, Medications, Past H/o, Pregnancy, Last meal, Events before the presentation) **Also ask for:** • Lip/tongue/throat /Neck swelling • Stridor/Grunting • Voice change • Trauma • Chest pain • Emesis	• Ability to speak, aspiration, oropharyngeal edema, trauma • Breath sounds, Hypoxia, posturing/work of breathing/ tracheal shift • Check for shock (BP, extremities, weak pulse, sweating, tachycardia) • Disorientation/ Delirium, signs of trauma ***Look for red flag signs* (Box 1)**	• SpO_2 • Capillary glucose	**General Measures:** • Pt Positioning • IV-line placement • Airway repositioning—Jaw thirst, chin lift • Suction • O_2/bag ventilation • Urinary catheterization **Specific Measurements:** • Choking maneuvers • Airway in case of altered mental status • NIPPV—for conscious pt with Pulmonary edema, OSA, COPD. • Needle decompression for pneumothorax • Nebulized Salbutamol—for severe asthma • Adrenaline—for anaphylaxis • Call for help

TABLE 3 Emergency management (5–15 min)[5]

History	*Examination*	*Investigation*	*Intervention*
• Onset/progression • Similar episodes/Asthma/ COPD • Fever/cough • Chest pain • Unilateral leg swelling • Renal/Cardiac disease • Allergy H/O	• **Vital signs** • **Focused Respiratory Exam** ***Look:*** • Pt posture • Diaphoresis, cyanosis, pallor, ability to complete a sentence, single breath count, neck veins ***Listen:*** • Breath sounds/Wheeze/crepts • Heart sounds/murmur/rub ***Feel:*** • Pulses, pedal oedema, peripheries • Trauma • Red flag signs	• ECG • Urine Acetone • USG—for effusions, pneumothorax • ABG/VBG	**General Measures +** **Specific Measures:** • Intubation/NIPPV • Chest tube—for Pneumo/ hemothorax • Pericardiocentesis—for tamponade • Salbutamol/adrenaline—As per indication • Fluid challenge for hypotension • Antibiotics for infection • Atropine for OPC poisoning • ASV—for snake bite • Diuretics for pulmonary edema/CCF • NTG—for accelerated Hypertension/Pulmonary edema • Call for help

- Ill fitting mask/leak due to facial abnormalities
- Progressive fatigue or impending respiratory arrest
- Hypoxia despite adequate positive airway pressure and high FiO_2
- Progressive and persistent hypercapnia (>1 hour)
- High airway pressure requirement (>20 cm H_2O)

Drugs Commonly Used in Respiratory Emergencies

- Nebulized Salbutamol—Severe asthma
- Adrenaline—Anaphylaxis/Asthma (Nebulization)
- Steroids—Asthma/COPD/COVID-19 pneumonia

TABLE 4 Urgent management (15–60 min)[5]

History	*Examination*	*Investigation*	*Intervention*
• Detailed H/o including past H/o, Family H/o • CCF: orthopnea, PND, leg swelling • H/o asthma/COPD—medication H/o, past ICU admissions for the same • Cardiac ailments/ HT/Diabetes/ Dyslipidemia, etc. • Chest pain: Anginal/pleuritic • DVT: Leg pain and swelling, H/o immobilization • HIV/TB status • Smoking H/ o	• Vital Signs • Complete Systemic examination • Repeat clinical examination if there are abnormal findings in lab investigations	• CBC • RFT, Electrolytes • Ketones • RBC • ECG • Chest X-ray • HIV • Echo • Cardiac enzymes • CT Chest • D Dimer • ABG/VBG	**General Measures +** **Specific interventions:** Depending upon on the diagnosis arrived: • Needle thoracentesis in cases of pleural effusion • Steroids/NTG/Salbutamol/ Bronchodilators/Inotropes depending on the condition • NIV/Intubation: for Neuromuscular/ envenomation • Call for help

BOX 1 'Red flag signs" of acute dyspnea[2]

- Altered mental status
- Shallow breathing
- Tachypnea (RR >40/min)
- Hypotension
- Hypoxia
- Cyanosis
- Stridor
- Tracheal deviation
- Absent breath sounds (Unilateral/Bilateral)
- Unstable arrhythmia

- Antibiotics—Infective exacerbations of COPD/asthma, Sepsis, Aspirations (Foreign body/Secretions), GBS, Trauma
- Diuretics—Pulmonary edema, CCF
- Nitroglycerin—Pulmonary edema
- Atropine—Organophosphorus poisoning
- Anti-snake venom—Cobra/Krait bite

Venous Blood Gases in ED

Arterial blood gas analysis is what is generally expected to be done in emergency setting. But venous blood gas (VBG) analysis is equally valuable, and has now become routine in the initial work up of cases presenting to the ED. There are many advantages of VBG analysis: arterial puncture which causes bleeding and pain can be avoided. VBG analysis can be done with the blood drawn for other lab analysis. VBG is easy to process by modern analyzers. A venous blood gives accurate measurement of glucose, K^+, lactate, HCO_3^-, hemoglobin, and COHb. In addition, a normal venous pCO_2 will exclude hypercarbia. Venous lactate level gives early diagnosis of sepsis. Treatment response can be established by serial VBG in terms of lactate and K^+.[8]

Ultrasonogram in Respiratory Emergencies[5]

- The Bedside Lung Ultrasonography in Emergency (BLUE) protocol plays a major role in ED to diagnose various causes of respiratory failure.
- Focused Assessment with Sonography in Trauma (FAST) to diagnose pneumothorax and hemothorax.
- Bilateral increased B-line density in pulmonary edema.
- Unilateral B-lines in pneumonia with edema, or foreign body with lung collapse.
- Cardiac USG: to r/o cardiac failure, pericardial effusion and tamponade.
- Right heart strain indicates pulmonary embolism.
- A normal lung USG may be seen in bronchospasm, pulmonary embolism, anemia, or acidosis.

Conclusion

Respiratory emergencies are very common in the ED and it is imperative that all the team members be prepared to stabilize patient's oxygenation and ventilation. Using clues from the history and quick physical examination, an emergency physician can guide the work up and intervene in the golden hour. Early use of bedside testing, including USG may limit unnecessary tests and save time in determining the best treatment course.

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CHAPTER

102 Basics of Mechanical Ventilation—Must Know for All Physicians

Rudrajit Paul

Abstract

Mechanical Ventilation (MV) has come to the limelight over the last 1 year due to the Covid-19 pandemic. Ventilation has saved numerous lives all over the world. Clinicians have been forced to familiarize themselves with this technology. In India, the government has supplied ventilators to many health facilities as an emergency. After the pandemic subsides, these machines will remain and there will be a huge demand for their use in different diseases. Thus, this is a good time for internists to learn about the basics of mechanical ventilation. This article describes the basic functions of the ventilator. This is not meant to be an exhaustive text on the topic. Rather, this article is meant to be a ready reckoner for the busy clinician. Essential topics like FiO_2, I:E ratio, PEEP, and plateau pressure have been discussed. Some tips for tracheal intubation have also been touched upon. Towards the end, the overall ventilator strategies for common diseases like COPD, DPLD, and, of course, COVID-19 have been discussed. The importance of arterial blood gas report in a ventilated patient has also been discussed. The various output parameters in a modern ventilator have been mentioned. So, overall, this article is meant to help the clinician during a busy shift.

Introduction

The recent Covid-19 pandemic has proved the importance of mechanical ventilation (MV) for saving lives, and every physician in the future should have some basic knowledge of this technology. This article is meant not for intensivists but mainly for physicians working regularly with critical patients. The following pages are meant to help the young medicine resident who is alone in a Critical Care Unit (CCU) with a collapsing patient. The article is written in such a way that the pages can be scanned and kept in smartphone for ready reference.

What is Mechanical Ventilation?

MV is the process of delivering inspiratory breath with predetermined parameters like target volume, target time, and target oxygen concentration.[1] This has two types: invasive and noninvasive. Among noninvasive devices, the BiPAP device is very popular and can be tried initially in many cases. Recently, the hi-flow nasal cannula has also become very popular and can reduce the need of invasive ventilation.[2] However, to honor the word limit of this publication, the following discussion will be mostly on invasive ventilation.

Historical fact: The first negative pressure "tank" ventilator was described by Dr John Dalziel in 1838. The later polio epidemic led to rapid development in this technology.

Indications

When should one consider mechanical ventilation? The *following list* will give a rough guide to the most common indications.[1,3] But it must be remembered that the initiation of MV ultimately depends on the clinical judgment of the physician. If the physician thinks that the patient cannot maintain his/her oxygen levels or

cardiopulmonary stability, then MV may be started as benefit of doubt. It must be remembered that *MV shows the greatest advantage if used early*. So, it is better to err on the side of overzealous ventilation than to wait longer when the underlying pathology has already gone into a tailspin.

- **Acute or chronic respiratory failure**
  - Central respiratory depression
    - Poisoning
    - Stroke
    - Post-neurosurgery
  - Peripheral respiratory compromise
    - Guillain-Barré (GB) syndrome
    - Myasthenia
    - Severe myositis
    - High cervical myelopathy
  - Lung pathology
    - Parenchymal pathology
  - Severe pneumonia
  - Acute respiratory distress syndrome (ARDS)
  - Severe pulmonary edema
    - Airway pathology
  - Acute chronic obstructive pulmonary disease (COPD)/Asthma
  - Airway edema in toxic gas inhalation
    - Vascular pathology
  - Pulmonary embolism
- **Severe shock**
- **Prophylactic ventilation**
  - Patient with recurrent vomiting when pharyngeal reflexes are deemed inadequate
  - After poisoning, especially if patient is anticipated to deteriorate
  - Severe cerebral edema, if hyperventilation is planned in the future
  - Severe sepsis with hyperventilation, when respiratory muscle fatigue is anticipated
  - Recurrent refractory seizures, when aspiration is a possibility or where the use of anesthetic drug is planned

This list is not exhaustive and other pertinent indications may be there. A study in the USA found that COPD, heart failure, and pneumonia were the main indications for the use of MV.[4] Another international study found that in the intensive care, acute respiratory failure was the commonest indication of MV, followed by acute chronic COPD and coma.[5] Acute respiratory failure can occur in a variety of indications from opiate poisoning to head injury.

Some Notes on Intubation

Endotracheal intubation is one skill which every physician must acquire. This is a lifesaving procedure even if ventilator is not available. For example, in a patient with poisoning and laryngeal edema, immediate intubation can prevent airway closure. The steps of intubation will not be discussed here. They may be found in great details in anesthesia texts. But only certain *relevant points* will be mentioned:[3]

- There must be a breathing circuit (Bain's circuit) in the CCU. This will help in preoxygenation of the patient before intubation. Also, if during intubation, there is sudden hypoxia, the procedure may be temporarily abandoned and breathing circuit used to improve oxygenation.
- The physician must ensure that the laryngoscope is in working condition. In personal experience of the author, the battery of the laryngoscope is not checked properly in many Indian hospitals and often, at the times of crisis, the laryngoscope light source is found defunct.
- *An IV cannula must be in situ before the procedure*. There may be sudden hypotension or hypertension during the procedure and then, IV drugs may be needed as emergency.
- Suction apparatus must be ready at the bedside.
- Do not insert the tube until you can see the vocal cords well.
- A bougie must be present in the intubation tray. This often makes the procedure easier.
- Size of tube: adult male: 7.5–8.5; adult female: 6.5–7.5.
- If the procedure gets prolonged, either call expert help or abandon the procedure temporarily; sedate the patient, oxygenate him/her; then try again.
- Do not overinflate the cuff.
- It is a good practice to perform portable X-ray after the procedure.
- If prone ventilation is planned (e.g., Covid-19), a flexometallic tube may be used.
- Please remember that laryngeal manipulation can cause sudden sympathetic surge and hypertensive emergency. Thus, if difficult intubation is anticipated,

IV fentanyl/beta-blocker may be used beforehand to prevent this surge.

Initial Settings

Often a physician is able to diagnose respiratory failure early and connect the patient to the ventilator. But then, the problem arises: how to control the settings? The touchscreen of a modern ventilator has numerous options, many of which seems daunting to a non-trained observer **(Figs. 1 and 2)**. However, the following basic steps are easy to follow and can be adequate in most cases:

- *Mode:* After intubation, it is best to put the patient in assist-control (A/C) mode, at least for some time. This is the safest mode, especially if the patient is unstable.
- *FiO_2:* This indicates the fraction of inspired oxygen. It can vary from 21 to 100. Just after intubation, especially if the intubation has been prolonged or difficult, it is best to keep the FiO_2 at 100 for a few minutes. Then, once the SpO_2 stabilizes, the FiO_2 should be quickly reduced. It must be remembered that one *should not* aim for a SpO_2 of 100%. This is unnecessary and harmful. Any SpO_2 more than 94% is considered adequate. If the SpO_2 is consistently above this level, the FiO_2 should be reduced.
- *Tidal volume:* Usually, the tidal volume is kept at 8–10 mL/kg. The body weight used for this calculation is the *Ideal Body Weight (IBW)*. But in ARDS or restrictive lung disease, the tidal volume is kept low at 5–6 mL/kg.
- *I/E ratio:* Normally, this ratio is 1:2. In COPD, this may be changed to 1:2.5 or 1:3. Conversely in ARDS or diffuse parenchymal lung disease (DPLD), this ratio may be 1:1.7 or even 1:1. The principle is that in obstructive airway disease, there is air trapping. So, the expiratory time should be increased to allow more lungs emptying and prevent auto-positive end expiratory pressure (PEEP). Some ventilators have an option, inspiratory flow rate, which is an indirect control of the inspiration:expiration time (I:E) ratio. Normal flow rate is kept around 60 L/min. If the inspiratory flow rate is higher, the time of inspiration is

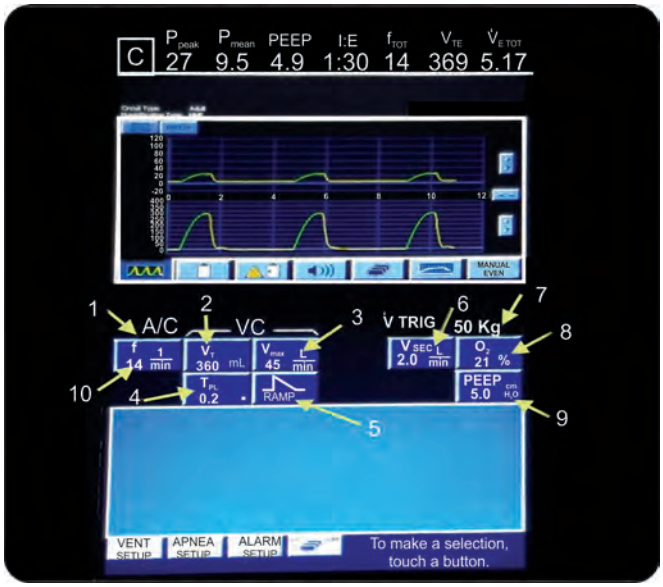

Fig. 1: Touchscreen of a typical ventilator [1—the mode (A/C: Assist Control); 2—tidal volume; 3—maximum inspiratory flow rate; 4—pause time (a short period between inspiration and expiration when there is no air flow. This pause time allows more gas exchange); 5—the shape of flow-time curve. This is usually kept decelerating to prevent barotrauma; 6—trigger for inspiratory flow; 7—IBW, based on which tidal volume is calculated; 8—FiO_2; 9—PEEP; 10—respiratory rate]. Each of these 10 parameters can be changed independently

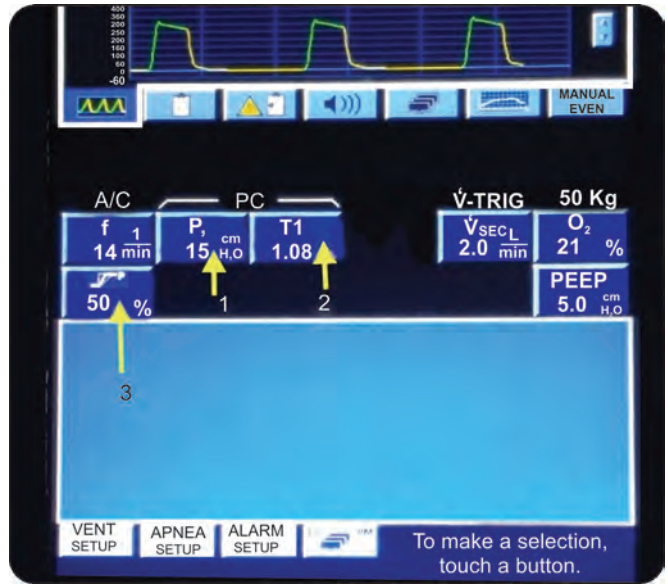

Fig. 2: Control panel of ventilator in PCV mode [1—inspiratory pressure; 2—inspiratory time (this determines the I:E ratio); 3—rise time (this means the fraction of time during inspiration after which the set inspiratory pressure is reached. Here it is set at 50%. This means after half of inspiration, the peak pressure of 15 is attained]. Rests are same as Fig. 1

decreased, thus expiration time increases. In general, in air trapping (like emphysema), expiration time is prolonged; and in decreased compliance or severe hypoxia (like ARDS), inspiration time is prolonged. Altered I:E ratio or inverse ratio ventilation is not physiological. Thus, the patient may be in distress. Hence, in these cases, sedation is needed. Sedation may be given with midazolam, fentanyl, the preceding two drugs in combination, propofol, etc.

- *Respiratory rate:* Normally, in adults, this is kept 10–14/min. Only in ARDS cases, when tidal volume is kept low, the respiratory rate may have to be increased to maintain the minute volume. If respiratory rate and inspiratory flow are controlled, the I:E ratio automatically becomes fixed. Some ventilators have "Inspiratory Time" option (for PCV mode). This is also a way to fix the I:E ratio.
- *PEEP:* The PEEP is normally kept at 3–5 cm of H_2O. However, in ARDS, the PEEP needs to be higher (discussed latter).
- *Volume cycled (VCV) or pressure controlled (PCV)?:* This is another issue where intensivists are divided into different opinionated groups. In general, the physician should remember that pressure controlled ventilation is much more difficult from maintenance point of view. Often, there is need of deep sedation with or without N/M blockade. A Spanish study, done in 2000, found that VCV versus PCV modes did not have any difference in mortality in ARDS patients.[6] So, the physician should use the ventilation mode in which he/she is comfortable.

Besides these, there are numerous other settings (like trigger sensitivity or rise time). But those intricate details are best left to the intensivists.

Recruitment Maneuvers[7]

After the Covid-19 experience, the use of recruitment maneuvers has become the buzzword in critical care. This is a specialized technique, mostly done by intensivists well versed in respiratory care. Some common procedures include:

- Airway pressure release ventilation
- Continuous positive airway pressure (CPAP) maneuver (putting the ventilator in CPAP mode and increasing the pressure to 30 cm H_2O for 30–40 seconds)
- Prone positioning

Prone positioning is a good method and if used early, it can have considerable benefit in ARDS. But the enthusiastic young medicine resident who plans to use prone positioning must remember the following:

- Prone positioning has to be maintained for 12–16 hours/day. For this to be successful, 1:1 nursing care is a must
- Usually these patients need continuous sedation
- Proper preventive care for decubitus ulcers must be given

Observation Panel

The parameters mentioned in the previous section are input variables. Once we have set these parameters, we have to observe the patient data from output section of the touchscreen **(Fig. 3)**. This will tell us whether the respiratory mechanics are appropriate. There are many output variables like respiratory rate, peak pressure, and plateau pressure (in case of VCV) and minute ventilation. Also, the curves (pressure time, volume-time, flow-time, and flow-volume) have to be observed **(Fig. 4)**.

In addition, modern ventilators have special procedures to measure certain parameters like static compliance (by inspiratory hold).

Trouble Shooting

This has been depicted in **Table 1**.

Weaning

While connecting a patient to a ventilator for lifesaving, proper weaning is equally important. Delayed weaning may cause VAP, tracheomalacia, critical care induced neuropathy, and other problems.

The most important point that must be remembered for weaning is that the underlying disease must be quelled. There should not be any significant cardiac or pulmonary dysfunction at the time of weaning. For example, if the pneumonia is controlled but still, the patient is on vasopressor support, then weaning is unlikely to be successful.

The modern technique is to put the patient on spontaneous mode of ventilator from A/C mode. In spontaneous mode, the FiO_2 is slowly brought down to 21 and the pressure support is also reduced **(Fig. 5)**. If this is sustained, that is oxygen saturation is maintained and

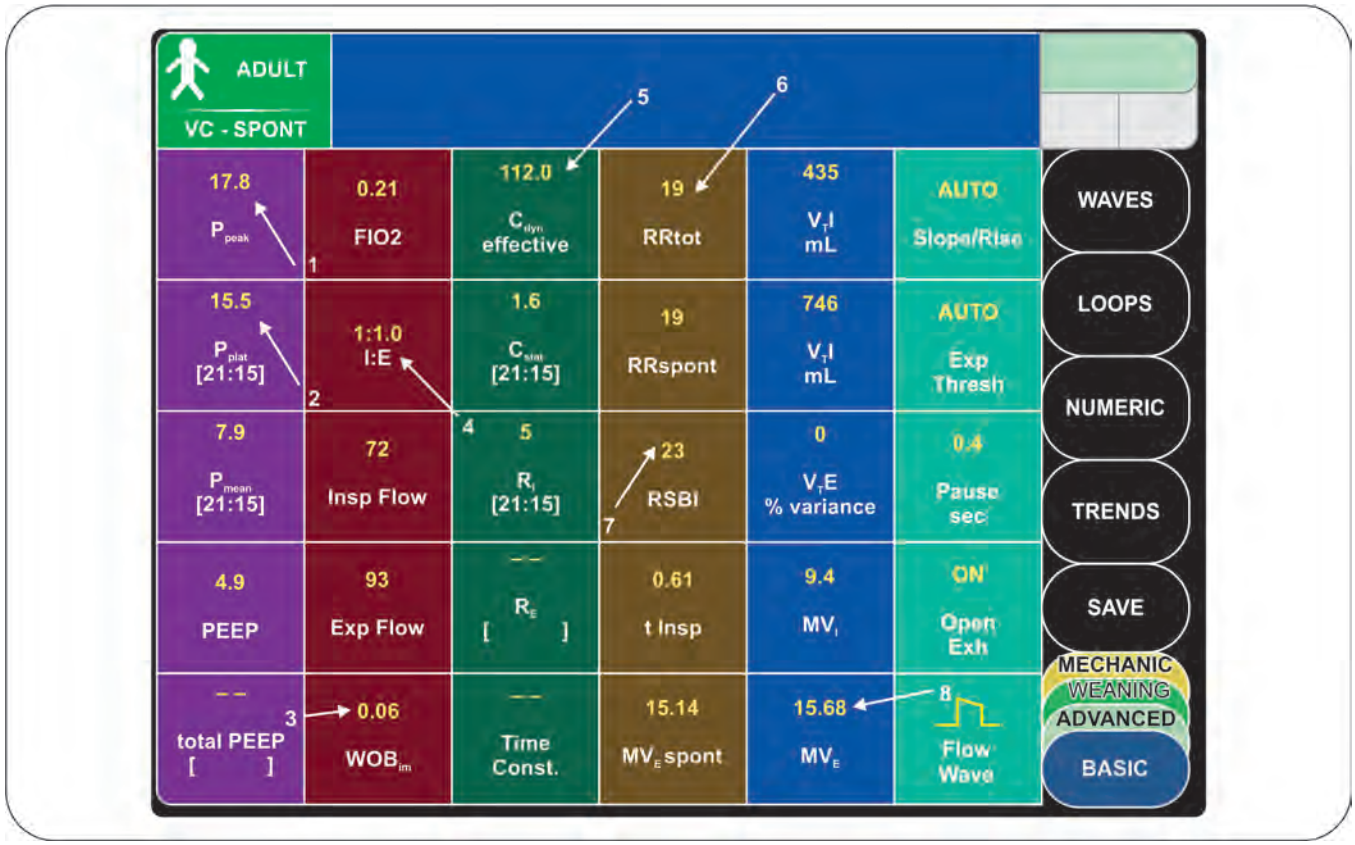

Fig. 3: The observation screen of a modern ventilator [1—peak inspiratory pressure; 2—plateau pressure; 3—work of breathing; 4—I:E ratio; 5—dynamic compliance (Normal: 50–70); 6—respiratory rate; 7—rapid shallow breathing index (this is important for weaning); 8—minute ventilation. This should be less than 10. Very high values indicate hyperventilation]. The recent ventilators may have even more parameters. Physicians should familiarize themselves with their machines

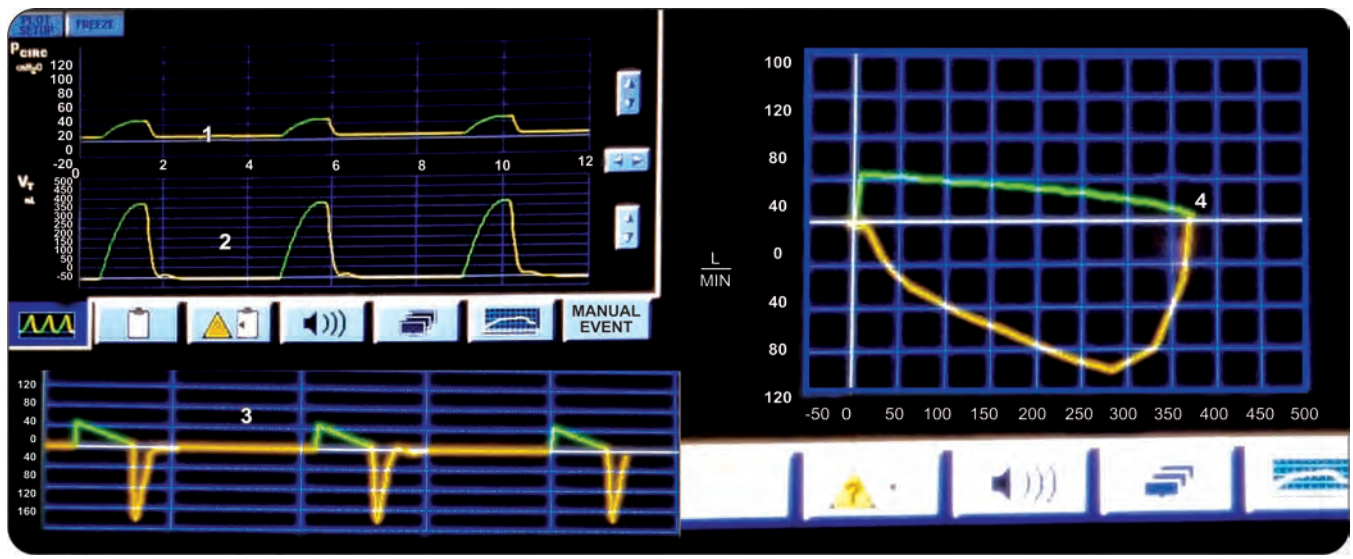

Fig. 4: The various graphs visible on ventilator screen [1—pressure-time; 2—volume-time; 3—flow-time; 4—flow-volume]

TABLE 1 Table showing some common problems faced during mechanical ventilation

Observation	*Possible causes*
Refractory hypoxia	• Oxygen source disconnected • Lung atelectasis • Airway block
Sudden hypotension	• Development of pneumothorax due to VILI • Too high PEEP • VAP with sepsis
Tachypnea	• Patient-ventilator dys-synchrony • Sepsis • Airway block

hemodynamic stability is attained, then T-piece trial can be given. The T-piece trial can be given for 30-60 minutes on the first day and then increased on subsequent days. If this is successful, extubation can be done. In some places, it is routine to put the patient on BiPAP or HFNC after extubation for some time. But this is not universal.

Difficulty in Weaning

In some cases, there is repeated weaning failure. Some common causes are: Hypokalemia, sepsis, underlying heart failure, hypothyroidism, severe anemia, massive ascites, etc. Thus, in such cases, these extra-pulmonary causes should be ruled out. Some rules of the thumb to assess suitability for weaning:

- RSBI<105 (RSBI=Respiratory rate/tidal volume in liters)
- 5<Respiratory rate<35
- Absence of significant acidosis (respiratory or metabolic)
- Good mentation
- MV<10 L. Very high minute ventilation means the patient is hyperventilating and respiratory muscles are likely to be fatigued. In such cases, extubation should be delayed.

Ventilator Strategy in COVID-19[8]

Any discussion about MV in 2020 is not complete without a few words about Covid-19. Covid-19 is associated with rapidly progressive ARDS like picture and MV is the lifesaving measure in such cases.

Although there are some data on pulmonary thrombosis in Covid-19, the gross ventilator strategies remains similar to the ARDS protocol. Thus, low tidal volume (4–8 m/kg), plateau pressure less than 30 cm of H_2O and

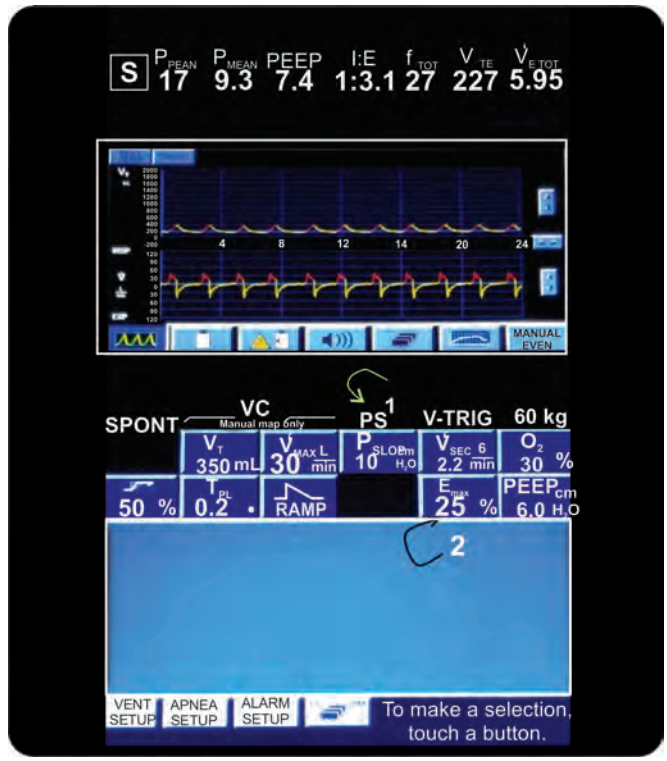

Fig. 5: Ventilator in spontaneous pressure support mode [1—the support pressure during inspiration; 2—expiratory sensitivity: this means when inspiratory flow drops to 25% of the peak value, the ventilator will switch to expiration]

conservative fluid strategy are advised. Also, a high-PEEP strategy is preferred and in severe hypoxemia, especially that which does not respond to optimum oxygenation, prone ventilation (12–16 hours/day) is recommended. A corollary of this last strategy is autoproning, which is now commonly practiced. Recruitment maneuvers can be done as needed, including staircase maneuvers (incremental PEEP).

Ventilator Strategy in COPD[1]

In COPD, there is obstructive airway disease. The patients have chronic respiratory acidosis. The ventilator strategy involves using an FiO_2 to target SpO_2 of 88–92%. The respiratory rate is kept at 10–14/min, not higher. This is because due to chronic respiratory acidosis, the HCO_3 levels are elevated as compensation. If respiratory rate is kept high, there will be quick CO_2 washout. This will precipitate metabolic alkalosis. The flow trigger is kept around 2 L/min. If this is lower, tachypnea may occur. I:E ratio is kept at 1:2.5 to 3.5. PEEP is started at 5 and then

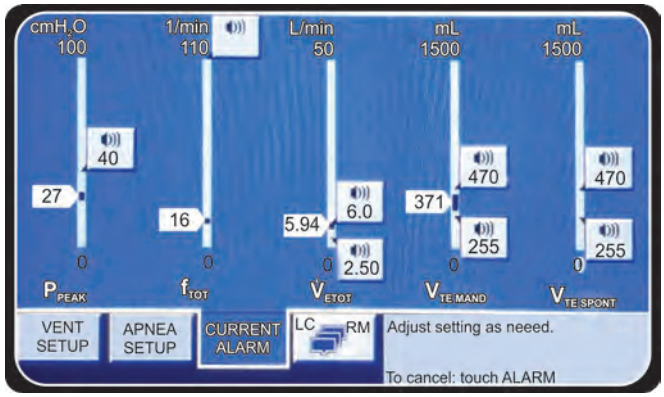

Fig. 6: The alarm settings of the ventilator. These are important because unless alarms are sounded at the right moment lives may be lost. Here, the respiratory rate alarm (f) is off. This is not correct

Fig. 7: The Apnea settings of a ventilator (top panel). This helps to save lives if there is sudden respiratory arrest in spontaneous mode

increased as needed. Expiratory sensitivity can be kept above the default setting of 25% to increase the time of expiration. Tidal volume is adjusted to maintain MV at less than 6 L. This prevents overinflation in emphysema.

Ventilator Strategy in DPLD[1]

At the outset, it must be explained to the patients' relatives that DPLD has a very poor prognosis in the CCU. The usual ventilator strategies are low tidal volume and high respiratory rate. If VCV is unable to maintain adequate minute ventilation (6–10 L/min) at acceptable plateau pressure (<30–35), then PCV mode may be used. High PEEP may be used to recruit the collapsed alveoli. I:E ratio may be kept at 1:1 or even 2:1. Prone ventilation may be used. Here, unlike COPD, high FiO_2 may be used to improve oxygenation but increasing the PEEP can also achieve that objective. Inspiratory hold technique may be used to determine lung compliance and if this is very low, recruitment may be tried (as described earlier). Failure to improve oxygenation by any means warrants the use of ECMO.

Interpretation of ABG in a Ventilated Patient

Often, the physician is asked to review the arterial blood gas (ABG) report of a ventilated patient. This is a crucial test to check the adequacy of ventilation. In an ABG report, the first parameter to check is the PaO_2. Low values indicate hypoxia and the need to increase FiO_2 or PEEP. Ideally, the PaO_2 should be around five times the FiO_2. That is, if FiO2 is 30%, the PaO_2 should be around 150. PaO_2/FiO_2<300 (where FiO_2 is expressed in decimal) is the cut-off for defining ARDS. The next parameter to be checked is $PaCO_2$. Low values indicate hyperventilation and the need to decrease minute ventilation. High $PaCO_2$ indicates inadequate ventilation. Other reasons for increased $PaCO_2$ are a high-carbohydrate diet and severe shock. ABG should be done 30–60 minutes after any change in ventilator settings.

Conclusion

- In VCV, the clinician should always look at the peak and plateau pressures during daily rounds. Persistent high pressures increases risk of barotrauma. But persistent high pressures can also mean the patient is biting the tube (thus sedation may have to be increased), or there is secretion clogging the tube (thus suction may be needed). Also, very high inspiratory flow rate may increase the peak pressure.
- A ventilated patient needs good nutrition. Otherwise, weaning will be difficult.
- If prolonged ventilation support is anticipated, early tracheostomy should be done.
- The alarm settings of a ventilator should be checked periodically to ensure that proper thresholds are set **(Fig. 6)**.
- In PCV mode, frequent suction should be avoided because it releases the alveolar pressure and can precipitate atelectasis.
- Apnea settings should always be active **(Fig. 7)**.

Acknowledgment: The pictures taken with the help of a highly skilled medical technologist, who wishes to remain anonymous for professional reasons.

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CHAPTER

103 ARDS in Viral Infections

Gagan Gunjan, Mohd Saif Khan, Krishna Kumar, DP Singh

Abstract

Introduction: Acute respiratory distress syndrome (ARDS) is an inflammatory lung parenchymal injury caused by various direct or indirect insults to pulmonary alveoli leading to exudative non-hydrostatic pulmonary edema. Ashbaugh and colleagues were the first to give a clinicopathological description of the ARDS in twelve adult patients. The ARDS Definition Task Force defined ARDS in 2012 (Berlin's criteria).

Pathophysiology: Pathophysiology of ARDS in patients with viral infections is not entirely clear. This is due to variable interaction between host factors and host immune response to viral antigen, which governs the severity of pneumonia or ARDS. Damage to alveolar endothelium results in increased endothelial permeability and recruitment and infiltration of leucocytes. Organ cross talk can occur through common language of pro-inflammatory cytokines and subsequently multi-organ dysfunction syndrome occur.

Management: Prognosis of ARDS in viral illness is poor with significant mortality and morbidity. Management is mainly supportive. Specific management includes anti-viral drugs, immunotherapies, and steroids. Supportive treatment has an important role to allow some time for specific treatments.

In this chapter, a focused review of ARDS caused by a variety of respiratory and non-respiratory viruses is presented along with cutting-edge developments in diagnostic and treatment modalities.

Introduction

Acute respiratory distress syndrome (ARDS) is an inflammatory lung parenchymal injury caused by various direct or indirect insults to pulmonary alveoli leading to exudative non-hydrostatic pulmonary edema. In 1967, Ashbaugh and colleagues were the first to give a clinicopathological description of the ARDS in 12 adult patients.[1] Clinically, ARDS is characterized by acute onset of dyspnea, hypoxemia, and appearance of bilateral diffuse radiological infiltrates, which are not explained by volume overload or cardiac dysfunction.[2] Severe sepsis is the most common cause leading to ARDS in about 50% of cases.[3] These infections can affect lungs directly (pulmonary ARDS) or indirectly (extrapulmonary ARDS).

Respiratory viruses that can cause ARDS can be of two types:

- Pandemic and
- Non-pandemic respiratory viruses.[4]

Influenza viruses (H5N1 and H1N1), Severe Acute Respiratory Syndrome Corona viruses (SARS-CoV), and Middle East Respiratory Syndrome (MERS) Corona viruses are notable examples of pandemic respiratory viruses, which can result in severe form of ARDS compared to non-pandemic respiratory viruses.[5-7] SARS was reported first time in 2002, originated in southern China and eventually involved more than 8,000 persons worldwide. H1N1 influenza pandemic started in 2009 from California, through Mexico, the United States spread

globally affecting mostly children and young adults. Recent addition to the list of pandemic respiratory virus is the SARS-CoV-2, which has been attributable to Corona Virus Dieases-19 (COVID-19).[8] Exact incidence of ARDS caused by viral diseases is unknown. Nevertheless, with the advent of multiplex nucleic acid amplification assays for the detection of viral pathogens, increasing numbers of viral etiologies are elucidated among the critically ill patients. In this chapter, a focused review of ARDS caused by a variety of respiratory and non-respiratory viruses is presented along with cutting-edge developments in diagnostics and treatment modalities.

Epidemiology

Incidence of ARDS varies extremely from country to country, being lowest in Brazil (10.1 per 100,000 person-years) to highest in the USA (78.9 per 100,000 person-years).[9,10] Unfortunately there is no population survey based data published from India showing incidence of ARDS. According to a multinational observational study representing a large data from 29,144 ICU patients across 50 countries, ARDS was present in 10.4% of patients admitted to ICU and 23.4% of patients on mechanical ventilator.[11]

Infections are the most common causes of ARDS, in which bacterial especially Gram negative microbial pathogens are the most common isolates from microbial cultures described in ARDS patients.[12] Exact incidence of ARDS caused by viral infections is not known. The most common viruses detected from viral pneumonia were Influenza and Rhinovirus. Respiratory syncytial virus infection is common in pediatric age group. Despite viral detection in critically ill patients, their role in pathogenesis in ARDS is debatable.

Etiology and Risk Factors of ARDS Caused by Viral Illness

Respiratory viruses can cause ARDS in those who are immunocompromised, in extreme of ages, having severe comorbidities, hematopoietic cell transplant recipients, and acquired human deficiency syndrome and in those with exaggerated host response. Most common types of viruses causing pneumonia are divided according to genetic material they contain and their pandemicity **(Table 1)**.

Pathophysiology of ARDS Due to Viral Infections

Pathophysiology of ARDS in patients with viral infections is not entirely clear. This is due to variable interaction between host factors and host immune response to viral antigen, which governs the severity of pneumonia or ARDS. Respiratory virus first invades nasal and bronchial epithelium, this invasion causes injury to respiratory airway and alveolar endothelium, cytokine release syndrome, which in worse case can take the form of cytokine storm. There is disruption in surfactant synthesis, which leads to alveolar collapse. Organ cross talk can occur through common language of proinflammatory cytokines and multi organ dysfunction syndrome occurs. In lungs, diffuse alveolar damage (DAD), a pathological hallmark of ARDS, has been observed in direct viral invasion of cells and lytic effects. Damage to alveolar endothelium results in increased endothelial permeability and recruitment and infiltration of leukocytes, which stimulate production of reactive oxygen species and nitric oxide that damage the epithelial-endothelial barrier. Few components of coagulation and fibrinolytic system are also activated in viral induced lung injury. These pathological events are translated to high incidence of both hemorrhagic and venous thromboembolic events.[20] Another unique difference in viral and bacterial etiology of ARDS is the small lymphocytes as predominant immune cells at the site of lung injury.[21] Due to cytokine-induced lymphocytic sequestration, lymphopenia ensues.

Few viruses (HSV, VZV, and CMV) remain in dormant state in ganglia or reticuloendothelial tissue and may become reactivated in the state of immunosuppression, especially in later stage of prolonged sepsis, characterized by immune-paralysis stage. Interestingly, in cases where ARDS results from inflammatory host response rather than direct cytopathic effect of virus, the antiviral therapy alone has limited value as has been observed in case of COVID-19 where SARS CoV-2 primarily injures the vascular endothelium.[22,23]

Clinical Features

Clinical features of virus induced ARDS are often nonspecific, vague, and overlapping. It is not uncommon for such patients to present with features of both ARDS as well as underlying cause. Symptoms appear within

TABLE 1 List of viruses causing pneumonia and ARDS

Name of virus	*Genetic material*	*Pandemicity of virus*	*Clinical characteristics*
Influenza A	RNA	Pandemic, H5N1 in 1997, H1N1 in 2009	Most common viral cause of pneumonia. Multiple subtypes of Influenza A Avian flu (H5N1) and swine flu (H1N1) have caused pandemics
Parainfluenza viruses 1–4	RNA	Non-pandemic	Rarely, parainfluenza virus may result in severe pneumonia and ARDS, especially in hematopoietic cell transplant recipients
Human Metapneumovirus	RNA	Non-pandemic	Sporadic cases with ARDS have been reported in severely immunocompromised, hematopoietic cell transplant recipients, and acquired human deficiency syndrome and in those living long-term care facilities
Human Rhinovirus	RNA	Non-pandemic	Main risk factors of ARDS are elderly age and immunosuppression
Ebola virus (EBOV)	RNA	Outbreak 2013–2016	22% patients infected with EBOV developed ARDS. High levels of EBOV RNA in bronchoalveolar lavage (BAL) is suggestive of EBOV induced ARDS[13]
SARS-CoV-1	RNA	Pandemic in 2002	The prevalence of ARDS in SARS can be high 20%
MERS-CoV	RNA	Pandemic in 2012	Despite virological similarity, MERS-CoV showed highest case fatality rate (34.4%) among coronaviridae
SARS-CoV-2	RNA	Pandemic in 2019-20	About 20% of hospitalized patients may develop ARDS within 8 days of symptom onset[14]
Respiratory Syncytial virus (RSV)	RNA	Non-pandemic	Common in infants and young children. Severe illness may develop in immunocompromised patients, bone marrow transplant recipients, underlying cardiopulmonary disease, and age more than 65 years[15]
Adenoviruses	RNA	Non-pandemic	Important cause of ARDS in immunocompromised adults and infants[16]
Hantavirus	RNA	Non-pandemic	Unexplained reason of ARDS linked to known exposure to special variety of rodents (deer mouse) residing in recently opened old building
Cytomegalovirus (CMV)	DNA	Non-pandemic	CMV pneumonia has been detected in 6–30% ICU patients. Immunosuppression, hematological malignancies, and prolonged mechanical ventilation are recognized risk factor for development of CMV pneumonia and viremia[17]
Herpes Simplex virus (HSV)-1	DNA	Non-pandemic	Rare cause of severe pneumonia and ARDS. However, HSV-1 has been detected in 5–64% cases of ARDS in ICU[18]
Varicella-zoster virus (VZV)	DNA	Non-pandemic	Pneumonia is the most common complication. Characteristic skin rashes help in diagnosis[19]

few days after the exposure to inciting factor and is often characterized by fever, cough, sore throat, myalgia, chills, or rigors. Watery diarrhea is also common along with abdominal pain, nausea, and vomiting, especially in illness caused by enterovirus and corona viruses.

Progressive symptoms of breathlessness, escalating requirement of oxygen, increased work of breathing, and alveolar infiltrates on chest imaging within 6–72 hours of an inciting event, ARDS should be highly suspected. On examination, patients may have tachypnea, tachycardia, and diffuse crackles, wheeze. In severe case, confusion, respiratory distress, cyanosis, and diaphoresis may be evident.

Differential Diagnosis and ARDS Mimics

There are a number of conditions that may present as acute hypoxemic respiratory failure with bilateral alveolar opacities and mimic ARDS. Some of the important mimics are being mentioned here.

- *Acute cardiogenic pulmonary edema:* It usually involves left ventricular systolic or diastolic dysfunction, but it may also occur due to fluid overload, hypertension, or severe renal disease. It can be distinguished from ARDS by evidence of cardiac dysfunction, elevated right-sided filling pressures, or related radiographic abnormalities. BNP or NT-proBNP is usually elevated.

In doubtful cardiac involvement, bedside transthoracic echocardiography may be performed to seek evidence of cardiac dysfunction.

- *Diffuse alveolar hemorrhage (DAH):* Almost two-thirds patients with DAH will present with hemoptysis. On fiber optic bronchoscopy (FOB), frothy hemorrhagic secretions are visible throughout the airways. Bronchoalveolar lavage (BAL) cytology, though nonspecific, may show hemosiderin-laden macrophages.
- *Inflammatory or autoimmune conditions:* Several specific acute inflammatory conditions may mimic ARDS, which mainly include acute eosinophilic pneumonia, pulmonary vasculitis, acute interstitial pneumonitis, acute fibrinous organizing pneumonia, cryptogenic organizing pneumonia. These conditions can be ruled out by serology, BAL specimens, ANA, C-ANCA, P-ANCA, or lung biopsy.
- *Malignancy:* Hematological malignancies, such as leukemia, lymphoma, and pulmonary secondaries of solid tumors may be mistaken for ARDS.
- *Others:* Few embolic syndromes (fat embolism syndrome and amniotic fluid embolism syndrome) may present with hypoxemia and bilateral opacities. BAL examination may reveal fat or amniotic fluid debris. Air embolism can be suspected when patients experiencing sudden-onset respiratory distress in the setting of a known risk factor, intravenous catheter insertion, or trauma.[24]

Diagnostic Criteria

The ARDS Definition Task Force has defined ARDS in 2012 known as Berlin's criteria,[25] which consist of rapid onset (within 7 days) of ARDS, impaired oxygenation status (PaO_2/FiO_2 ratio <300 mm Hg with positive end expiratory pressure, PEEP ≥5 cm H_2O), characteristic radiological opacities (diffuse, bilateral, and fluffy), and non-cardiac origin of pulmonary edema (not explained by cardiac dysfunction or fluid overload). Out of these four criteria, oxygenation status defines grading of severity of ARDS. Mild ARDS is said when PaO_2/FiO_2 ratio is in between 200 and 300 mm Hg, moderate ARDS is signified by a PaO_2/FiO_2 ratio between 200 and 100 mm Hg. Value of PaO_2/FiO_2 ratio ≤100 mm Hg corresponds to severe ARDS, which is associated with highest mortality rate.

Microbiological Tests

In the past, viral infections were purely clinical and the diagnosis of exclusion. Association of ARDS to viral etiology is confirmed by isolation of intact virus particles from cell culture or viral antigen detection by immunofluorescence, or multiplex RT-PCR. Among all these, most commonly performed and most rapid test is the multiplex RT-PCR, which gives comparable diagnostic accuracy compared to cell line culture (gold standard) and immunofluorescence techniques.[26] The best sample for highest diagnostic yield is BAL collected during FOB, which is not always possible due to highly infectious nature. Bacterial and fungal culture, lung histopathology should also be performed to find coexisting infections leading to ARDS.

Laboratory Tests

Hematological profile may reveal leukopenia, lymphopenia and thrombocytopenia, which are markers of severity of viral illness. Arterial blood gas (ABG) analysis shows hypoxemia, which is often initially accompanied by acute respiratory alkalosis (due to compensatory hyperventilation), which later is replaced by hypercapnic respiratory acidosis (due to contraction of baby lung of ARDS). Metabolic acidosis (HCO_3 <15 mEq/L) with hyperlactatemia may also develop due to the precipitating sepsis or associated organ injury.

Routine biochemical examination may manifest the evidence of organ injury (acute kidney injury or liver dysfunction) reflective of severe hypoxemia or associated shock and systemic inflammation (hypoalbuminemia and raised C-reactive protein). The prothrombin time (PT) and activated partial thromboplastin time (aPTT) may be prolonged, and D-dimer is elevated in severe viral illness and ARDS, suggesting prognostic importance of coagulation parameters.[27]

Imaging Studies

Radiological findings in viral ARDS are variable and nonspecific and graded according to the severity of ARDS. The initial chest radiograph may be normal or may reveal typically bilateral diffuse alveolar opacities with dependent atelectasis. Computed tomography (CT) of the chest may show widespread patchy and/or coalescent airspace opacities that are usually more apparent in the dependent lung zones. The opacities can be subtle (e.g.,

patchy ground glass), particularly in early ARDS, but can become consolidative in appearance as severity worsens. Lung ultrasound has emerged as noninvasive, radiation free, reproducible and promising tool with reportedly higher sensitivity (83–92%) for the diagnosis of ARDS compared with CT chest.[28]

Management

Management of ARDS in viral illness is mainly supportive. Specific management includes antiviral drugs, immunotherapies, and steroids. Supportive treatment has an important role to allow some time for specific treatments.

Respiratory Support

Main issue in ARDS is worsening gas exchange and hypoxemia due to development of intrapulmonary shunt. Therefore, reversal of hypoxemia is the key principle in the management, which can be accomplished by respiratory support in the form of various oxygen delivery devices.

Role of NIV and HFNOT: Both NIV and HFNOT are noninvasive oxygen delivery devices, which are associated with improved outcomes in acute hypoxemic respiratory failure (AHRF) patients compared to invasive mechanical ventilation. Before intubating an ARDS patient who has moderate hypoxemia, a trial of NIV or HFNOT may be warranted.

Ventilatory settings for ARDS lung include low tidal volume (TV) protective lung ventilation (TV, 4–8 mL/kg of predicted body weight) and frequently monitoring and maintaining plateau pressure (Pplat) below 30 cm H_2O to ensure safety to baby lung. Severe hypoxemia in ARDS (<150) should trigger institution of more aggressive approach such as prone position ventilation, extracorporeal membrane oxygenation (ECMO), and use of lung recruitment maneuver. Proning improves PaO_2 and decreases CO_2 retention in patients with severe ARDS. A multicentric trial (PROSEVA) has shown significant mortality improvement with proning when performed for the duration of 16 hours a day.[29-31]

Fluid Management in ARDS

The Society of Critical Care Medicine, 2020, guidelines recommend to use restricted fluid and to use dynamic tests of fluid responsiveness to determine the need of fluid.

Role of Corticosteroid

In H5N1 and H1N1 influenza ARDS, routine use of steroid was discouraged citing higher rate of nosocomial infections. Similarly, corticosteroids did not show any benefit but led to delayed viral clearance in a multicenter study performed in patients (n=309) with the MERS. Recently Oxford University released findings of RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial in which dexamethasone reduced the mortality by one-third in the patients on mechanical ventilator.[32]

Antiviral Treatment

Antiviral treatment can reduce the viral load, viral shedding, and reduce the disease transmission to close contacts. It has also shown proven benefit in radiologic clearance in ARDS. However, the efficacy of antiviral is maximized if administered within 48 hours of symptom onset. Specific antiviral drugs have been listed in **Table 2**.

Following respiratory virus is detected in respiratory or blood sample, antiviral treatment may be started. In pandemic times, empirical antiviral without waiting for result is warranted to improve outcome.

Antimicrobial Treatment

In critically ill patients, due to presence of various indwelling catheters, prevention and treatment of nosocomial infection is of equally importance while managing virus induced ARDS. Therefore, considering local antibiogram and host risk factors, empirical antibacterials may be indicated.[34]

Other Pharmacological Treatment in ARDS Patients

Anti-cytokine Drug

Two drugs, Aviptadil (concentrated in the lung 40%) and Remestemcel-L are being repurposed and investigated as therapeutics in COVID-19 ARDS (CARDS). Both down-regulate the synthesis of proinflammatory cytokines in the lung.

Immunotherapies

Palivizumab (monoclonal antibody) with intravenous immunoglobulin (IVIG) has been recommended in preventing Respiratory Syncytial virus (RSV) induced

TABLE 2 Antiviral drugs in viral induced ARDS

Antiviral drug	*Indication*	*Further information*
Ganciclovir	CMV induced ARDS	Combination therapy with immunoglobulins can reduce the mortality in ARDS
Acyclovir or Valacyclovir	HSV or VZV induced ARDS	Dose of acyclovir is 10 mg/kg IV q8h for 7 days. Combination with varicella-zoster immune globulin (VZIG) therapy may be considered
Oseltamivir	H1N1 ARDS	Oral dose of 150 mg twice daily for 10 days is recommended
Zanamivir	Oseltamivir resistant H1N1 ARDS	Compassionate use of intravenous Zanamivir or add Ribavirin for Oseltamivir resistant cases
Peramivir	Investigational use in H1N1 ARDS	Compared to Oseltamivir, it has higher affinity for the influenza virus, and only single dose intravenous infusion is enough.[33] Evidence is limited in critically ill
Favipiravir	H1N1 resistant to Neuraminidase inhibitors (NAIs) and SARS CoV-2	Favipiravir is an oral antiviral, approved in Japan for the treatment of influenza. Trials are ongoing for its use in COVID-19
Ribavirin	Respiratory Syncytial virus (RSV), Metapneumovirus, Parainfluenza virus, Measles, and Hantavirus	Intravenous formulation is available for use in critically ill patients. Ribavirin nebulization may be used in ARDS
Remdesivir	SARS CoV-2	It inhibits viral RNA polymerases broad-spectrum antiviral activity, emergency use authorization (EUA)
Cidofovir	Adenovirus induced ARDS	Dose of Cidofovir is 5 mg/kg/wk for 2 weeks, then every 2 weeks. Another dosing schedule is 1 mg/kg IV thrice a week
Lopinavir–Ritonavir	SARS CoV-1	400 mg and 100 mg, respectively twice a day for 14 days. No impact on SARS CoV-2

severe pneumonia in high-risk infants and young children. Interferons-alpha-2a with ribavirin has been shown to improve survival in severe MERS-CoV infection. Convalescent plasma, due to its immunotherapeutic potential, has been successfully used in SARS, MERS, Ebola virus disease, and COVID-19.

Conclusion

Prognosis of ARDS in viral illness is poor with significant mortality and morbidity. Mortality increases with poor oxygenation status (46% with severe ARDS), late presentation, requirement of mechanical ventilation, presence of comorbidity, and higher age. However, survival has improved with advances in critical care management and early supportive measures.[35] Patients, who survive ARDS, suffer long-term consequences, which include significant weight loss, poor functional status, and poor quality of life.

Recent viral pandemics have deepened our understanding of pathophysiology and management of ARDS. Clinical features are nonspecific and overlapping with viral illness as well as ARDS, but helpful in diagnosis. Multiplex RT-PCR of respiratory sample is confirmatory for viral ARDS. Supportive management include NIV or HFNOT initially and invasive lung protective ventilation in later more severe stage of ARDS.

Specific management includes antiviral and corticosteroid, which should be started early in the course of viral illness for the maximum therapeutic benefit. Other therapies are adjunctive and still investigational.

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CHAPTER

104 ABG Analysis: Physicians' Perspective

Ravindra Kumar Das

Abstract

Background: Analyzed report of Arterial Blood Gas is indicated in almost all patients admitted through emergency department (ED). ABG measurements are widely used in hospitals nowadays. Its use is particularly confined in ICU as monitor due to lack of test of accuracy and availability of simple method of analysis, management if started after correlating the clinical diagnosis with that of ABG diagnosis, mortality is reduced and discharge is improved.

Method: Prospective randomized controlled trial had been done over 136 patients of ED. Allocation ratio was 1:1. One group was managed in the background of analyzed ABG measurements and the control group was managed according to the traditional method. The ABG measurements were analyzed according to "rkdas Indian 2017 method of ABG interpretation". The primary and secondary outcomes were assessed statistically. Patients and outcome access were blinded.

Result: The percentage of death in the study group is significantly less than the control group (p-value 0.22) with 95% confidence interval (3.08–17.52). The percentage of discharge is significantly more in study group than control group (p-value 0.036) with 95% confidence interval (50.25–73.35).

Conclusion: Management in the background of interpreted ABG decreases the mortality and improves the number of discharge.

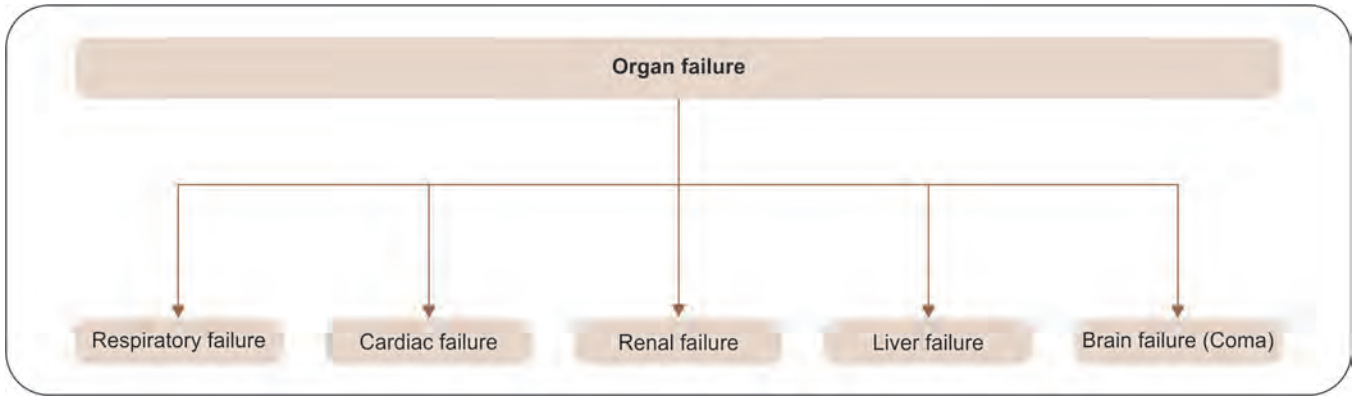
Introduction

Arterial blood gas (ABG) is the most accurate test possible without restriction. It is widely used in hospitals particularly in ICU as a monitor.[1] For physicians it is indicated in almost all patients who are admitted through emergency department (ED). Analyzed report is the ultimate representation of patients' clinical status. Correct interpretation can lead to quicker and reliable changes in the plan of care. A sensitive physician is always interested to have analyzed ABG report before planning of management.

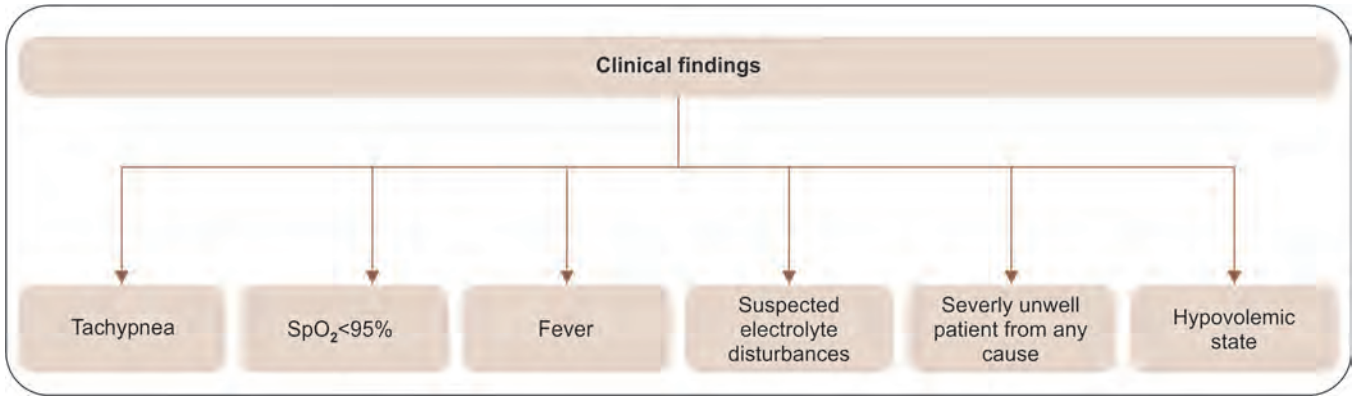
It helps the clinician in diagnosis and in some cases prognosis. Management started in the background of ABG significantly decreases the mortality. Failure to improve and deterioration of ABG parameters during management suggests early referral of the patients. In mixed disorder (multi-organ involvement) where mortality is high and complete clinical diagnosis at a glance is difficult, analyzed report of ABG helps the physicians. Wide utility of ABG is restricted in ICU as a monitor due to lack of absolute method of analysis and reliable test of its accuracy. Whenever clinical diagnosis does not match with ABG analysis, clinician often categorizes it imprecise. This difficulty has been overcome by new method of ABG interpretation.

A randomized control trial has been done and outcome is enthusiastic. Mortality is significantly decreased and

Flowchart 1: Organ failure



Flowchart 2: Clinical finding



discharge is improved when management is started after ABG correlation of clinical diagnosis.

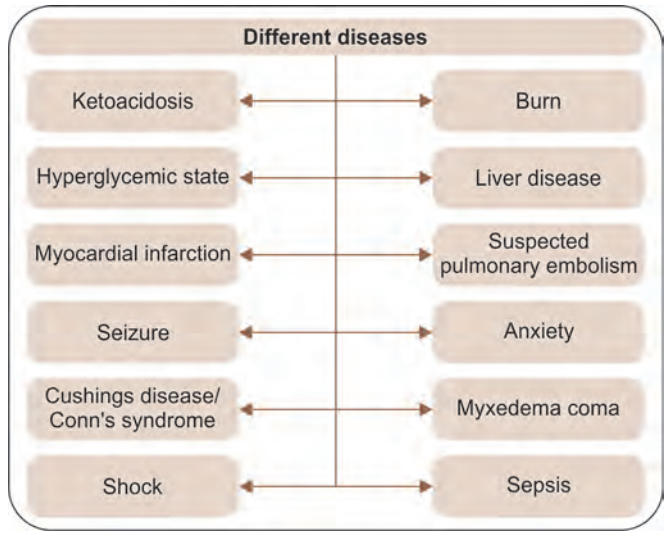
Indications

- Organ Failure **(Flowchart 1)**
- Multi Organ Failure
- Poisoning/Drug Toxicity/Alcohol Intoxication
- Clinical Findings **(Flowchart 2)**
- Different Diseases **(Flowchart 3)**
- Monitor in Ventilated Patient

Method

It was a prospective randomized control trial that was done in ED of Darbhanga Medical College, Laheriasarai. After getting ethics approval and consent form duly signed. Patients were randomized in two groups by simple

Flowchart 3: Different diseases



random allocation. Around 136 patients admitted in ED were randomized in 17 blocks and each block were allotted 8 patients with allocation ratio 1:1. Patients and outcome accesses were blinded. Arterial blood from 68 patients were taken before start of management and measurement were done by cobas b 121 machine.

Primary outcome (mortality and discharge) and secondary outcome (total days of stay in hospital) were recorded. Referral and LAMA were also considered. Statistical analysis was done by SPSS and standard method applied. Analysis of measured ABG data were done according to the method mentioned below.

"rkdas Indian 2017 Method of ABG Interpretation"[2]

- Accuracy of ABG:
  - Base excess (BE) method
  - Relation of pH to H^+ as already established[3]
  - Relation of Hb% measured through CBC and ABG
  - Relation of SpO_2% derived by machine and measured by pulse oximeter
- Gas analysis:
  - SpO_2%
  - PaO_2 mm Hg
  - Relation between PaO_2 & SpO_2 from Hb% dissociation curve
  - $PaCO_2$ mm Hg
  - Decide type of respiratory failure
  - Derivation of $PAO_2 = 150–1.25 \times PaCO_2$ mm Hg
  - P (A–a) O_2 value mm Hg
  - Cause of hypoxemia decided by algorithm[4]
  - P/F, i.e., PaO_2/FiO_2, i.e., hypoxemia index to decide ARDs and its severity
  - Oxygen content (CaO_2) in patients having anemia
  - $CaO_2 = Hb\ (gm/L) \times 1.34 \times SPO_2/100 + 0.003 \times PaO_2$
- Electrolyte analysis:
  - Osmolality = $2 \times Na\ (mEq/L) + \frac{\text{Plasma glucose (mg/dL)}}{18} + \frac{\text{BUN (mg/dL)}}{2.8}$
  - $BUN = \frac{\text{Blood urea (mg/dL)}}{2.14}$
  - Blood volume = $\frac{2L}{Hct\ (\%)}$ in cases of having no anemia or polycythemia
  - The cause of K^+ derangement is correlated with pH[5]
  - Chloride generally changes in parallel with plasma Na^+
  - Free calcium level
  - $AG = (Na^+ + K^+) – (Cl^- + HCO_3^-)$ mmol/L
  - Delta Gap (Δ gap) = anion gap – 12
  - Gap-Gap ratio = delta gap/HCO_3^- defict (24-HCO_3^-)
  - Δ gap + HCO_3^-
- Acid-Base analysis:
  - pH&H^+ value
  - HCO_3^- value
  - Direction of movement of H^+ and HCO_3^- to know about primary cause from rule of thumb[4]
  - Find out the compensatory change from knowing the primary cause
  - Movement of $PaCO_2$ and HCO_3^-
  - Calculate delta gap, gap-gap ratio, and delta gap + HCO_3^- in a patient of high anion gap metabolic acidosis to decide associated non anion gap metabolic acidosis and/or metabolic alkalosis
  - In case of primary respiratory cause decide:

    $\frac{\Delta H +}{\Delta CO_2}$, if < 0.3 – Chronic cause

    If > 0.8 – Acute cause

    If 0.3-0.8 – Acute on chronic respiratory cause
  - Decide complex disease:
    - If $PaCO_2$ and HCO_3^- moves in opposite direction
    - In a respiratory cause if there is associated metabolic cause or vice versa
    - In a respiratory cause if anion gap is >20
    - In a respiratory cause if base excess is ≥±5
    - In a high anion gap metabolic acidosis there is associated non-anion gap metabolic acidosis and/or metabolic alkalosis
  - In ABG, if pH = 7.4 ± 0.04; $PaCO_2$ = 36–45 mm of Hg; HCO_3^- = 22–26 mmol/L then no acid base disorder
  - Diagnosis of acid-base analysis.
- Complete diagnosis

Result

In the study and control group female to male were 31(45.6%) to 37(54.4%) and 36(52.9%) to 32(47%), respectively, which were not significant. Also (mean age

TABLE 1 Clinical characterization

	Case N (%)	*Control N (%)*	*p-Value*	*Significance*
Respiratory	10(14.71)	9(13.24)	0.805	Not significant
Gastrointestinal	3(4.41)	3(4.41)	1.000	Not significant
Cardiovascular	6(8.82)	5(7.35)	0.753	Not significant
Sepsis	1(1.47)	7(10.29)	0.026	Significant
Cerebrovascular accident	5(7.35)	12(17.65)	0.066	Not significant
Cardiopulmonary	4(5.88)	6(8.82)	0.510	Not significant
Multiorgan disease	9(13.24)	0(0)	0.001	Significant
End stage renal disease	1(1.47)	2(2.94)	0.559	Not significant
CKD with HF	1(1.47)	1(1.47)	1.000	Not significant
Hepatobiliary disease	2(2.94)	3(4.41)	0.648	Not significant
DM	1(1.47)	1(1.47)	1.000	Not significant
Diabetic complication	9(13.24)	4(5.88)	0.142	Not significant
Others	16(23.53)	15(22.06)	0.838	Not significant

± SD) between the two groups were (49.34±17.29) and (49.50±16.99), which were also not significant. So far as clinical characterization is concerned, in both the groups the differences in percentage of systematic involvement in all the categories were not significant except in sepsis of study group and multi-organ disease in control group **(Table 1)**.

On analysis of ABG measurement it was found that 12(17.6%) ABG were inaccurate by BE method. When the relation between pH&H^+ were matched in table, all 12 ABG were found accurate **(Table 2)**.

Moderate to severe hypoxemia were found in 10(14.72%) of patients. Type I respiratory failure were present in 5(7.35%) of patients. Type II respiratory failure were found in 9(13.2%) patients out of which 4(5.9%) were due to hypoventilation alone, 4(5.9%) with severe hypoxemia and 1(1.5%) with moderate hypoxemia.

Hyponatremia was present in 58(85.3%) patients and conspicuously one had hypernatremia. 13(19.17%) patients had hyperkalemia. Hypocalcaemia was a common finding. Hypochloremia was present in 4(6.2%) of patients.

Discussion

In my study, 17.6% of ABG were inaccurate by BE method while in general population difference between measured and derived HCO_3^- is 4.5% only.[6]

In my study, only 42.6% of patients had correct provisional diagnosis in ED. While in 80.9% of patients ABG diagnosis matched with the final clinical diagnosis. Around 19.1% of ABG were not compared to final clinical diagnosis because the patient either left or referred to higher center **(Table 3)**.

Different clinical characterizations of both groups were not significant except in sepsis and multi-organ disease group. Sepsis is a condition where there is multi-organ involvement commonly and in both the conditions mortality is high and almost equal[7] **(Table 1)**.

In 5.9% of severe hypoxemia pulse oxymeter was not useful.

The common acid-base disorders were respiratory 42(61.8%) among which the most common findings were acute or chronic respiratory alkalosis 21(50%). In the metabolic cause, acidosis was more than alkalosis **(Table 2)**. One (1.5%) of patients had no acid base disorder.

Acute exacerbation of chronic obstructive pulmonary disease (COPD) was provisionally diagnosed in 4.4% of patients, but only 1.5% had acute on chronic respiratory acidosis (acute exacerbation of COPD). Around 8.8% of patients were clinically diagnosed as COPD/cor pulmonale in which 3% had acute or chronic respiratory acidosis (acute exacerbation of COPD).

TABLE 2 ABG analysis

Accuracy of ABG (BE method)				Gas analysis											
	Accurate	Not accurate		Hypoxemia					Resp. Failure						
									Type I			Type II			
			Total	No	Mild	Moderate	Severe	Total	Yes	Cause		Yes	Cause		
										Mod.	Severe		Hypoventilation	Mod. Hypoxemia	Severe Hypoxemia
Frequency	56	12	58	35	23	6	4	68	5	5	0	9	4	1	4
Percentage	82.4	17.6	100%	51.5	33.82	8.82	5.9	100	7.35	7.35	0	13.2	5.90	1.5	5.9

Electrolyte analysis																
	Na^+ (mmol/L)				K^+ (mmol/L)				Ca^{++} (mmol/L)				Cl^-			
	Low	Normal	High	Total	Low	Normal	High	Total	Low	Normal	High	Total	Low	Normal	High	Total
Frequency	58	10	0	68	32	23	13	68	33	1	0	34	42	19	4	65
Percentage	85.3	14.7	0	100	47	33.8	19.1	100	97.1	2.9	0	100	64.6	29.2	6.2	100

Acid-base analysis												
	pH											
	Low	Normal	High	Total	Primary cause				Single acid-base disorder	Mixed acid based	No defect	Total
					Metabolic	Resp.	No defect	Total				
Frequency	13	23	32	68	25	42	1	68	16	51	1	68
Percentage	19.1	33.8	47	100	36.8	61.8	1.5	100	23.5	75	1.5	100

	Primary Resp. Cause							Primary Metabolic Cause					
	Acute Resp. Acidosis	Chr. Resp. Acidosis	Acute on Chr. Resp. Acidosis	Acute Resp. Alkalosis	Chr. Resp. Alkalosis	Acute on Chr. Resp. Alkalosis	Total	HAGMA	NAGMA	Metabolic Alkalosis	HAGMA + NAGMA	HAGMA + Metabolic alkalosis	Total
Frequency	0	4	3	6	8	21	42	3	2	11	8	1	25
Percentage	0	9.5	7.1	14.3	19	50	100	12	8	44	32	4	100

TABLE 3 Relationship between ABG diagnosis and clinical diagnosis

Match of ABG diagnosis to	*Frequency no.*	*Percent (%)*
Provisional diagnosis	29	42.6
Final clinical diagnosis	55	80.9
Not available to match the clinical diagnosis	13	19.1
Total	68	100

TABLE 4 Primary outcome

	Case			*Control*				
	Frequency	*Percent*	*95% Conf. Interval*	*Frequency*	*Percent*	*95% Conf. Interval*	*p-Value*	*Significance*
Death	7	10.3	3.08–17.52	17	25	14.71–35.29	0.022	Significant
Discharged	42	61.8	50.25–73.35	30	44.1	32.3–55.9	0.036	Significant
LAMA	10	14.7	6.28–23.12	7	10.3	3.08–17.52	0.436	Not significant
Refer	9	13.2	5.15–21.25	14	20.6	10.99–30.21	0.25	Not significant

In 13(19.1%) of patients, ABG diagnosis were not matched with the final clinical diagnosis due to LAMA and referral of patients.

Death in study group were 7(10.3%), while in control group it was 17(25%), p-value 0.222, significant. Around 42(61.8%) of patients discharged in study group while 30(44.1%) were discharged in control, p-value 0.036, significant. LAMA were 10(14.75%) and 7(10.3%) in study and control group, respectively. Around 9(13.2%) and 14(20.6%) patients were referred in study and control group respectively which is not significant **(Table 4)**.

Around 10.3% patients died during therapy compared to 25% in control group **(Fig. 1)**, ABG predicted in almost all cases about the seriousness of the disease. In 5.9% patients of acute heart failure 2.9% had metabolic acidosis and died,[8] 1.5% had normal pH and 1.5% had alkalosis, they survived.[8] There was 1.5% case of AMI and pH was 7.25. In acute coronary syndrome if pH <7.3, mortality is expected to be 100%.[9]Around 2.9% had arrhythmia with acidosis, they succumbed during therapy. Acidosis contributes to the development of arrhythmia, and the patient is resistant to therapy in acidosis. One patient had CVA with altered sensorium and PaO_2 was 50 mm Hg. Commonly in such type of patients with CVA there is hyperventilation and PaO_2 should not be low but this was due to associated aspiration pneumonia. Around 1.5% of patients who died were a case of complex disease with pH 7.50, mortality is high in complex disease and pH >7.55.

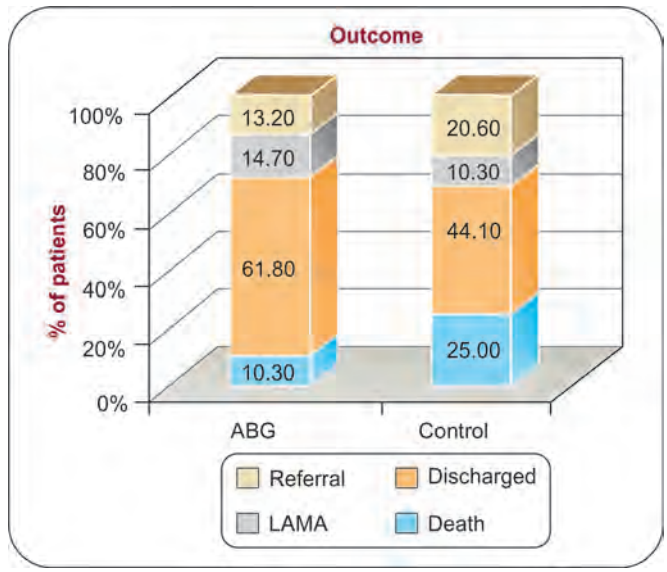


Fig. 1: Bar diagram of outcome in percentage

There were 4.4% of cases of acute exacerbation of COPD, 1.5% had pH 7.32 managed successfully with low FiO_2 and with Bi-Pap machine; 2(2.9%) patients had pH

7.12 and 7.21 in which 1 patient (1.5%) was associated with non-anion gap metabolic acidosis and treated with Bi-pap and improved; while the other needed ventilator but refused to give consent and left against medical advice.

Around 14(20.6%) patients were suffering from type I and type II respiratory failure together. Their causes were decided by algorithm and managed accordingly. ABG acted as monitor in all the 75% mixed disorder patients.[1] The outcome of the two groups shows that patients managed in the background of ABG findings had mortality less by 14.7% than control group, which is significant. The overall stay of the discharge patients were less in study group.[10]

Conclusion

Accuracy of ABG should be tested by different methods, if BE method fails. In this study, all ABG measurements were accurate. At ED in the hand of even an expert physician only about 50% of provisional diagnosis is correct. Around 81% of final clinical diagnosis matched with ABG diagnosis. From the time of admission proper management is started with ABG support in almost all cases, which may be a cause of better outcome. Almost all patients admitted through ED had ABG changes and thus indicated in all patients. In multi-organ disease (complex disease), the mortality is high. Measuring SpO_2 through pulse oxymeter become difficult in severe hypoxemia and only ABG can say about hypoxemic state of patients.

Respiratory alkalosis is common ABG finding. Around 21% patients were of respiratory failure and their cause is easily decided by algorithm and thus managed accordingly. Around 13% of patients admitted in ED are of COPD out of which 33% is diagnosed as acute exacerbation of COPD and when ABG matching is done 33% of them were wrong. ABG is accurate method to decide acute exacerbation of COPD.

ABG also acts as monitor even outside of ICU, particularly in mixed disorders. Management in the background of analyzed report of ABG reduces mortality significantly.

Analyzed report of ABG in ED is physician's necessity for management. In other word physician can proclaim ABG as "gold standard in ED."

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CHAPTER

105 Hyperkalemia in ICU

SV Ramana Murty, TVSP Murthy, DJK Chakravarthy

Abstract

Hyperkalemia is a medical emergency and potentially life-threatening electrolyte disturbance. It usually presents in clinical setting of acute kidney injury, tumor lysis syndrome, major tissue damage like road traffic accidents or rhabdomyolysis. People above 60 years and those taking drugs like NSAIDs, Betablockers, and ACE inhibitors are at high risk. High index of clinical suspicion is required to diagnose hyperkalemia, since it may often be asymptomatic. All care should be taken while sending blood sample for serum potassium levels, since we may encounter pseudohyperkalemia. ECG changes usually correlate well with severity of hyperkalemia. Urgent measures are required when serum potassium is more than 7.5 mEq/L. Measures include immediate stabilization of myocardium with intravenous calcium gluconate and shift of Potassium from ECF to ICF by salbutamol nebulizations. Oral administration of ion exchange resins will reduce the serum potassium levels but slowly. We may have to go for hemodialysis in acute and severe cases. Simultaneously we have to address the original cause.

Introduction

Hyperkalemia is a medical emergency and potentially life-threatening electrolyte disorder especially in patients with renal disease, heart failure, and people using certain drugs like angiotensin converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), beta-blockers, or non-steroidal anti-inflammatory drugs (NSAIDs). It is rare in healthy general population. Certain groups are at greater risk.

Why is It to be Addressed?

Acute severe hyperkalemia would become a life challenging and leads to dangerous cardiac arrhythmias and death if not attended to earliest.

Historical Background

- Sir Humphry Davy (1807), a British Chemist, coined the element, Potassium. It is called kalium in (Latin).
- However, Kalium is renamed as potassium. But in Periodic Table its symbol is retained as "K."
- Atomic number: 19; Element classification: Metal; Period number: 4; Molecular weight: 39.098 g/mol; and Valance: +1.

Etymology

- Derived from modern Latin word "*potassa*"
- *Potassa* + *ium*

Definition

- Hyperkalemia is defined as a plasma potassium level more than 5.5 mmol/L.
- There is no internationally accepted definition for hyperkalemia; The "European Resuscitation Council" defines hyperkalemia as a plasma level more than 5.5 mmol/L and severe hyperkalemia as more than 6.5 mmol/L.[1]

Basics

- Potassium is the principal intracellular cation 140–150mEq/L.
- The plasma (serum) potassium is 3.5–5.0 mEq/L, while the whole blood contains 50 mEq/L.
- Dietary potassium is absorbed cent percent through GIT and 90% is excreted through urine and 10% through faces.
- It maintains intracellular osmotic pressure.
- It is required for regulation of acid base balance and water balance in the cells.
- It is required for the activity of the enzyme "Pyruvate kinase."
- It is essential for transmission of nerve impulse, cardiac muscle activity, and biosynthesis of proteins by ribosomes.

Note:[2]

- The factors that enhance cell uptake of potassium from ECF compartment include: insulin, alkalosis, beta catecholamines, hyperosmolality, and cell damage.
- The factors that impair cell uptake of potassium from ECF compartment include: acidosis, chronic kidney disease, diabetes mellitus, and alpha catecholamines.

The Clinical Spectrum of Hyperkalemia Presenting in ICU, Requiring Immediate Care

Acute kidney injury, acute on chronic kidney disease, MODS **(Fig. 1)**, Acute necrotizing pancreatitis **(Fig. 2)**, septic abortion, burns, snake bite, muscle injury (rhabdomyolysis), Tumorlysis syndrome, sepsis, disseminated intravascular coagulation, metabolic acidosis, and hemolysis.

Epidemiology

- Most cases in hospitalized patients are due to chronic drug use and renal compromise.
- Risk factors include advanced age, significant prematurity and the presence of diabetes mellitus, heart failure, and sepsis.
- Hyperkalemia has been reported in 1.1–10% of all hospital admissions.[3]

Pseudohyperkalemia[4-6]

- Pseudohyperkalemia represents an artificially elevated potassium concentration in the plasma. This is due to movement of potassium (K^+) from the cells immediately prior to or following venepuncture.
- Pseudohyperkalemia is suspected when hyperkalemia is reported by laboratory in an asymptomatic individual with no obvious underlying cause and no ECG abnormalities.
- Faulty blood collection procedure, like excessive clenching of fist, prolonged tourniquet application during blood drawing, moisture in storage and delay in testing the blood sample, and gross change in room temperatures are some of the responsible factors.

Fig. 1: Male 45 years with thrombocytopenia, Hyperkalemia, MODS

Fig. 2: Male 38 years with acute pancreatitis, AKI, hyperkalemia, and MODS

Causes of Hyperkalemia

- Increased intake:
  - High potassium containing foods
  - Potassium containing drugs
  - Intravenous fluids containing potassium
- Tissue breakdown:
  - Catabolic state
  - Hemolysis
  - Rhabdomyolysis
  - Tumorlysis syndrome
  - Bleeding into soft tissues, body cavities
- Shift of potassium into extracellular fluid:
  - Metabolic acidosis
  - Tissue damage
  - Uncontrolled diabetes mellitus
  - Hyperkalemic periodic paralysis
- Impaired excretion:
  - Acute kidney injury
  - Potassium sparing diuretics
  - Reduced tubular excretion: Addison's disease
  - Reduced circulatory volume

Common Risk Factors

- Premature infants probably due to renal prematurity
- Males are more affected because of excess muscle mass
- Elderly people >60 years
- Military recruits, drug abusers, Sickle cell anemia; conditions with high risk for rhabdomyolysis
- Peripheral vascular disease

Drug use:

- Excess and chronic use of NSAIDs[7]
- Use of potassium sparing diuretics, beta-blockers, ACE inhibitors, ARBs especially with renal compromise[8]
- Direct renin inhibitors (e.g., Aliskiren)
- Cyclosporine or tacrolimus[9]
- Antibiotics (e.g., pentamidine and cotrimoxazole)
- Oral contraceptive pills
- Heparin therapy in bed ridden people

Foods Rich in Potassium (Fig. 3)

Vegetables: Potatoes, tomatoes, pumpkin, cooked spinach, Brussels sprouts

Fruits: Orange, banana, honey dew, prunes, raisins, other dried fruits

Other foods: Chocolate, nuts, seeds, peanut butter, onion, yogurt, bran products

Grading of Severity of Hyperkalemia

Hyperkalemia can be graded according to the serum concentration of potassium into:

- Mild 5.5–6.5 mmol/L
- Moderate 6.5–7.5 mmol/L
- Severe >7.5 mmol/L

Clinical Presentation

- Hyperkalemia is often asymptomatic, hence it can be called silent killer.
- Most patients are relatively asymptomatic with mild and even moderate hyperkalemia.
- Presentation may be nonspecific: with fatigue and vague muscular weakness. The patient may complain of tingling around lips or in fingers.

Physical Examination Findings

Physical signs vary as per the etiology and also serum potassium concentration:

- Pulse slow and usually irregular
- Hypertension and edema in the setting of renal disease
- Signs of hypoperfusion
- Shortness of breath, palpitations, chest pain, nausea, vomiting, and paresthesias
- Distension of abdomen and absent bowel sounds in case of acute necrotizing pancreatitis
- Muscle tenderness may be present in patients with rhabdomyolysis
- Jaundice may be seen in patients with hemolytic conditions, acute cholecystitis

Note:

- Symptoms usually develop at levels of 6.5–7 mEq /L
- But the rate of change is more important than the numerical value
- Individuals with chronic hyperkalemia may be asymptomatic relatively at higher level
- Whereas patients with a sudden rise of plasma potassium may develop severe symptoms relatively at lower values of potassium
- Neuromuscular manifestations include paresthesias and fasciculations in the arms and legs

Fig. 3: Fruits and vegetables rich in potassium

- As the serum K^+ continues to rise, an ascending paralysis with eventual flaccid quadriplegia supervenes. Classically, trunk, head, and respiratory muscles are spared. Cranial nerves least affected. However, respiratory failure can rarely occur.

ECG Manifestations of Hyperkalemia (Figs. 4A and B)[10]

Typical ECG findings in hyperkalemia include progress from tall, "peaked" T waves and a shortened QT interval to lengthening PR interval and loss of P waves, and then to widening of the QRS complex culminating in a "sine wave" morphology and death if not treated.

Diagnosis

Diagnosis of hyperkalemia depends on:

- Clinical suspicion
- Serum potassium concentration
- Characteristic ECG manifestations

Note:

- Beware of pseudohyperkalemia
- Then etiology should be recognized

Hence the investigations should envisage:

- Whether true hyperkalemia is present?
- How much severe it is?
- What is its etiology?
- Risk factors if any?

Investigations

- Serum electrolytes: Sodium, potassium, magnesium, calcium, chloride
- Blood urea, serum creatinine, bicarbonate (when Tumorlysis syndrome is suspected)
- Creatine kinase (especially when Rhabdomyolysis is suspected)
- Serum amylase, liver enzymes
- Baseline 12 lead ECG, and later repeat ECGs
- Serum cortisol levels
- Arterial blood gas report
- Ultrasound scan of abdomen
- CT scan abdomen, MRI abdomen depending on the clinical setting
- Urine complete analysis, urine electrolytes
- Complete blood counts
- Microbiological tests depending on suspected multiple organ failure or sepsis
- Blood hematology, if disseminated intravscular coagulation is suspected

Note: Clinical setting along with comorbid history, should guide the investigations required for workup of a case toward assessing the severity of hyperkalemia, and clinical background

Transtubular Potassium Gradient (TTKG)[11]

- Estimation of TTKG can reveal whether hyperkalemia is due to renal cause or extra renal cause and mineralocorticoid bioactivity in people with hyperkalemia
- TTKG value <6 suggests renal cause
- TTKG value >6 suggests extra renal cause
- Typical TTKG on normal diet is 8–9
- TTKG <5 in presence of hyperkalemia may indicate mineralocorticoid deficiency

$$\text{TTKG} = \frac{\text{Urinary } K^+}{\text{Serum } K^+} \times \frac{\text{Serum osmolality}}{\text{Urine osmolality}}$$

Emergency Management

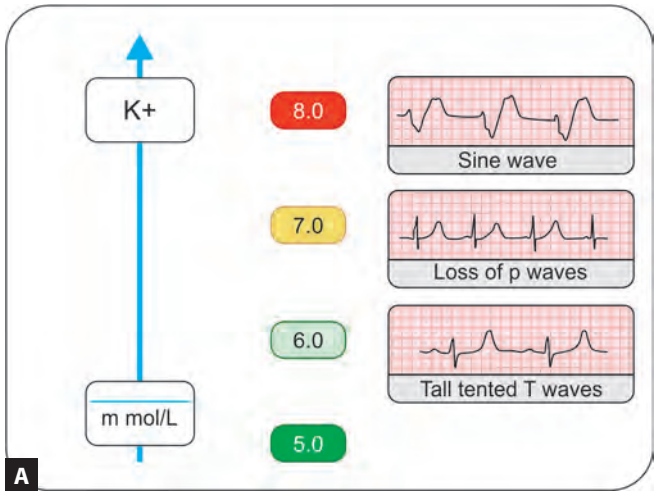
- Acute rise in serum potassium is a medical emergency
- Urgent treatment is required in cases of potentially fatal hyperkalemia, that is, serum K^+ >7.5 mEq/L

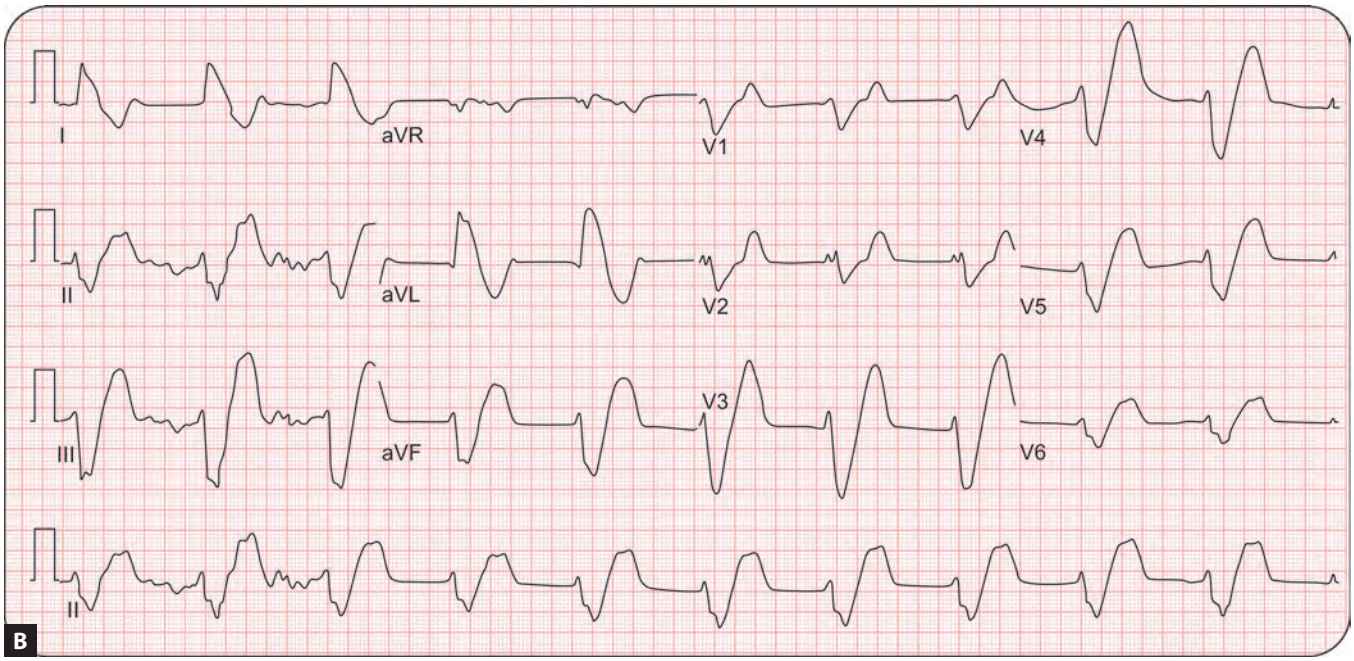
Basic principles of acute management of severe hyperkalemia in ICU:

- Stabilization of myocardium
- Shift of extracellular fluid (ECF) potassium to intracellular fluid (ICF)
- Removal of the excess potassium from the body

Stabilization of myocardium (to be done under cardiac monitoring) to prevent dangerous ventricular arrhythmias:[12]

- Inj. Calcium gluconate (10% solution) 10– 20 mL to be given iv over 5–10 minutes, or
- Inj. Calcium chloride 5 mL of 10% solution over 2 minutes
- However, calcium chloride can cause tissue necrosis if it extravasates and requires a central line
- The dose can be repeated after 5–10 minutes, if there is no change in ECG





Figs. 4A and B: (A) Typical ECG changes in Hyperkalemia (Serial changes as the serum potassium raises). (B) ECG showing changes of Hyperkalemia (Sine wave pattern) in male 45 years, DKA with serum potassium 7.9 mmol/L

- Calcium antagonizes the cardiac and neurological effects of hyperkalemia and prevents cardiac toxicity and dangerous cardiac arrhythmias
- It should be noted that calcium gluconate does not reduce plasma potassium

Shift of ECF potassium to ICF:

- Insulin and glucose infusion
- Beta 2 adrenergic agonists
- Alkalinizing agents

Insulin and glucose infusion:[13]

- Administer regular insulin 10 units as iv bolus + 50% dextrose 50 mL as iv bolus
- Onset of action is within 15–30 minutes and action lasts for 2–6 hours
- Initial bolus of glucose insulin should be followed by continuous infusion of 5% dextrose at 100 mL/hour to prevent late hypoglycemia
- Insulin—dextrose is treatment of choice in case hyperkalemia with end stage renal disease (ESRD)

- The plasma potassium concentration will fall by 0.5–1.5 mEq/L. This effect begins in 15 minutes and usually lasts for 4–6 hours
- In diabetic patients avoid extra dextrose infusion

Alkalinizing agents:

- One ampoule of sodium bicarbonate 7.5% providing 44.6 meq is given over 5 minutes or better added to 5% glucose infusion
- Onset of action is within 5–10 minutes and the effect lasts for 1–2 hours
- However, the use of alkalinizing agent is controversial and contra indicated in patients with ESRD

Note:

- When there is associated metabolic acidosis like in Tumorlysis syndrome alkali therapy can be used
- It should not be advocated in cases of ESRD

Beta 2 adrenergic agonists (Salbutamol, Ventolin, or Albuterol):[14]

- Salbutamol is given in a nebulized form
- 5 mg of salbutamol mixed with 3–4 mL of normal saline and administered through a high flow nebulizer over 10 minutes
- It generally becomes effective in 30–60 minutes and its effect persists for 2–4 hours
- It lowers serum potassium by 0.5–1.5 mEq/L

Rationale

Beta 2 agonists such as salbutamol promote cellular uptake of potassium and effectively lowers serum potassium level

Removal of the Excess Potassium from the Body

- Loop or thiazide diuretics
- Cation exchange resins
- Dialysis

Loop diuretic:

- Fruesimide 40–80 mg iv, the onset of action within 15 minutes, lower value of K^+ maintained for 2–3 hours
- Hydrochlorothiazide can be given in mild cases
- Potassium sparing diuretics contraindicated

Cation exchange resin:[15]

- Cation exchange resins, such as sodium polystyrene sulfonate (SPS) (kayexalate) promote the exchange of sodium for potassium in gastrointestinal tract
- Each gram binds 1 mEq of potassium and releases 2–3 mEq of sodium
- When given orally the usual dose is 25–30 gm mixed with 100 mL of 20% sorbitol 3–4 times daily (sorbitol prevents constipation)
- Onset of action more than 2 hours, and maintained for 4–6 hours
- It can also be given as retention enema consisting of 50 gm of resins and 50 mL of 70% sorbitol mixed in 150 mL of water every 4–6 hourly
- In general each enema can lower the plasma potassium concentration by 0.5–1.0 mEq/L within 1–2 hours and effect will last for 4–6 hours

Adverse effects of resins:

- Anorexia, nausea, vomiting, and constipation
- Intestinal necrosis typically of colon or ileum is a rare but fatal complication of SPS. Intestinal necrosis is more common in patients with reduced intestinal motility (in postoperative state)

Note: Patiromer is a non-absorbed polymer provided as a powder for suspension which binds potassium in exchange of calcium.

Dialysis[16]

- Emergency dialysis is a final measure for lethal hyperkalemia that has not responded to more conservative measures or for patients who had chronic renal failure.
- The most rapid and effective way of lowering the plasma potassium concentration is hemodialysis, which can produce a 1 mEq/L drop in serum potassium after 1 hour, and 2 mEq/L drop after 3 hours.
- Peritoneal dialysis also removes potassium but is only 15–20% as effective as hemodialysis.
- Patients with acute kidney injury require temporary but urgent venous access for hemodialysis.

Conclusion

In ICUs, we often come across electrolyte disturbances. Hyperkalemia may sometimes present silently. Hence, one should have a high index of clinical suspicion and act accordingly. Calcium gluconate, for membrane stabilization and β2-agonists, and insulin with glucose to be used in the treatment of hyperkalemia to induce a redistribution of K^+, and dialysis to be reserved for cases with severe hyperkalemia and renal compromise. The workup depends more so on the clinical background.

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Section 8

Section Editor: **Rajendra Prasad**

Respiratory Disease

CHAPTER

106 Allergic Bronchopulmonary Aspergillosis: Diagnosis and Treatment

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Abstract

Aspergillus is ubiquitous, occurring in mycelial form and grows at 15–53°C and humid conditions. Pulmonary aspergillosis is a clinical spectrum of lung disease caused by the fungus Aspergillus. ABPA is the commonest disease among allergic bronchopulmonary mycosis. The exact prevalence of ABPA is not known but contemporary estimates suggested that ABPA complicates 1–11% of all chronic cases of bronchial asthma. The basic underlying immuno-pathophysiologic process in ABPA is a hypersensitivity reaction to fungus in the bronchial tree. Patients are usually atopic with previous history of bronchial asthma. The onset is insidious with constitutional symptoms like anorexia, fatigue, weight loss, headache, generalized aches and pains, and low-grade fever. It is characterized by repeated episodes of exacerbation with periods of remission, if untreated may progress to fibrotic lung disease. Patients with chronic fibrotic disease may present with cyanosis, cor pulmonale, and respiratory failure. Radiologically fleeting shadows are characteristic of ABPA. Bronchiectasis, centrilobular nodules and mucoid impaction are main features of ABPA seen in CT scan thorax. Oral corticosteroid remains the cornerstone for the treatment of ABPA. Optimization of baseline asthma therapy is essential. Early diagnosis and proper treatment may alter the prognosis of disease and further prevent end stage lung fibrosis.

Introduction

Aspergillus is a ubiquitous fungi, which most commonly occurs in mycelial form, is thermo tolerant and grows at 15–53°C, the optimum being 37–40°C, and favoring humid conditions. Pulmonary aspergillosis is a clinical spectrum of lung disease caused by the fungus Aspergillus. The classification of pulmonary aspergillosis includes saprophytic aspergillosis in the form of pulmonary aspergilloma, immune disease in the form of allergic bronchopulmonary aspergillosis (ABPA), IgE mediated asthma, hypersensitivity pneumonitis, allergic Aspergillus sinusitis (AAS), and infectious disease in the form of invasive and semi-invasive pulmonary aspergillosis.[1] ABPA is considered to be the commonest manifestation amongst allergic bronchopulmonary mycosis. ABPA is characterized by a hypersensitivity immunological reaction which is most commonly caused by *Aspergillus fumigatus* in about 95% of the cases and rarely by *Aspergillus flavus, Aspergillus niger, Aspergillus oryzae, Aspergillus sydowi, Aspergillus terreus, Aspergillus glaucus, Aspergillus nidulans,* and *Aspergillus clavatus*. Other fungi such as Candida, Helminthosporium, Curvularia, Drechslera, Pseudallescheria boydii, and Fusarium vasinfectum have also been found to cause an identical syndrome.[2] ABPA clinically manifests as chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis.[3-11] The condition has immunologic features of immediate hypersensitivity (Type I), antigen-antibody complexes (Type III), and eosinophil-rich inflammatory cell responses (Type IVb), based on the revised Gel and Coombs classification of immunologic hypersensitivity.[12,13] ABPA was first reported in England[14] in 1952 and in India[15] in 1971. Since then, a

large number of cases have been reported from various parts of the world. Concomitant occurrence of ABPA and AAS is now being increasingly recognized which is also called as "sinobronchial allergic mycosis" syndrome.[16] ABPA is commonly associated in patients with chronic bronchial asthma and cystic fibrosis but can also occur in non-asthmatics.[17] The aim of the present write-up is to discuss the prevalence, clinical presentation, diagnosis, and treatment of ABPA.

Prevalence of Allergic Bronchopulmonary Aspergillosis

The prevalence of ABPA is highly variable complicating 1–11% of all chronic cases of bronchial asthma.[18-26] A very recent study from India, however, found a higher prevalence of Aspergillus sensitization (39.5%) and ABPA (27%) in 564 patients with asthma.[27] A study by Alok Nath et al. on 350 patients found the prevalence of Aspergillus hypersensitivity (AH) and ABPA to be 35.1% and 21.7%, respectively.[28] The condition is being increasingly recognized and the estimated prevalence rates in recent publications have been reported ranging from 5.9% to 20.5% for ABPA and 38% to 43% for AH.[29,30] A study in northern India was conducted to determine the prevalence of ABPA in patients of bronchial asthma where 244 patients were recruited consecutively over a period of 3 years and were analyzed prospectively by clinical evaluation, chest radiography, skin test, sputum culture for fungus, and serum precipitin test. Those patients with further suspicion of ABPA were further investigated by serum titers of specific IgG and IgE against *A. fumigatus*. The diagnosis of ABPA was made on predetermined major and minor criteria, where at least five major criteria had to be present. ABPA was seen in 7.4% patients with bronchial asthma.[26]

Immunopathology of Allergic Bronchopulmonary Aspergillosis

Majority of patients with ABPA are atopic with history of bronchial asthma. The pathogenesis of ABPA circles around a hypersensitivity reaction to the fungal spores and mycelial fragments of *A. fumigatus* present in the bronchial tree. Atopic individuals after inhalation of fungal spores in the bronchi result in the fungi to germinate and form vegetative elements (hyphae). Local immunologic reactions and stagnation of tenacious sputum in bronchial airways favor the trapping of fungal spores and further colonization. Antigenic substance of the fungus stimulates formation of IgE, IgG, and IgA antibodies. ABPA is immunologically classified as it gives both Type I (immediate) and Type III (Arthus, antigen-antibody immune complex) hypersensitivity reactions. Type I reaction is IgE mediated and responsible for accumulation of eosinophils, bronchospasm, edema leading to acute symptoms of diseases. Type III reaction results in polymorph aggregation, inflammation of bronchial, and peribronchial tissues and is responsible for the radiological features of ABPA. Recently, possible role of Type IVb[12,13] hypersensitivity reaction has also been observed in patients with ABPA and the presence of parenchymal granuloma and mononuclear cell infiltration seen on histopathology. Long-standing involvement of the bronchial tree leads to bronchiectasis, fibrosis, lung contraction, and lobar shrinkage.[9]

Clinical Presentation

The clinical picture of ABPA is dominated by asthma and recurrent exacerbations. The onset is insidious with constitutional symptoms like anorexia, fatigue, weight loss, headache, generalized aches and pains, and low-grade fever. Asthma is generally uncontrolled with usual anti-asthmatic therapy. It is characterized by repeated episodes of exacerbation with periods of remission in between and if untreated may progress to end stage fibrotic lung disease. It may occur at any age but is usually more prevalent in the age group of 20–40 years. Patients with chronic fibrotic disease may present with cyanosis, cor pulmonale, and respiratory failure. However, symptoms have little or no relationship to severity or chronicity of the disease, as one-third patients may be relatively asymptomatic in spite of extensive radiological shadows.[31] Expectoration of brownish mucus plugs is characteristic and has been reported in 5–54% of cases.[25] These plugs consist of fungal hyphae with eosinophils and mucous. Cough, breathlessness, and wheezing are common symptoms seen in ABPA. Hemoptysis has been reported in approximately 34–85% of cases, while pleuritic chest pain may be present in 50% of cases. In one of his study author found that hemoptysis was found in 28.6% of patients.[32] Chronic cases of ABPA may rarely present with symptoms of bronchiectasis.

On clinical examination of chest, wheezing and diffuse crepitations are the common findings but tachypnea, cyanosis, features of cor pulmonale, and sometimes hypertrophic osteoarthropathy may be seen. The disease is often misdiagnosed as tuberculosis, bronchiectasis, and bacterial pneumonia.[9] Almost half of the ABPA patients are initially misdiagnosed as pulmonary tuberculosis.[27]

Diagnostic Approach

ABPA should be suspected in any patient with asthma and parenchymal infiltrates on chest radiograph accompanied with peripheral blood eosinophilia. Not all features are required in order to diagnose ABPA. The important diagnostic criteria are the presence of recurrent pulmonary infiltrates, peripheral blood eosinophilia and positive skin test to Aspergillus antigen or positive specific IgE against *A. fumigatus*.

Radiological Features

Chest X-ray

Radiological features in patients of ABPA may be transient (acute) or permanent (chronic). Transient shadows may clear with or without steroid therapy and are mainly due to pulmonary infiltrates and stagnation of mucus in damaged bronchi.[33,34] Transient shadows are perihilar infiltrates mimicking adenopathy, air fluid levels from dilated central bronchi filled with fluid and debris. Parenchymal abnormalities are more common and present in 80–90% patients of ABPA as ill-defined homogenous shadows without evidence of loss of volume which may be of 5–15 mm in size or more as massive/lobar in extent, may be unilateral or bilateral, more in upper lobes, resolve (fleeting/migratory shadows) often after expectoration of bronchial plugs but tends to recur in same/other places. Sometimes pulmonary shadows may mimic carcinoma. Fleeting opacities are characteristic of ABPA. Author in one of his studies found that 66.7% patients had fleeting shadows. Author described "walking pneumonia" as a clue to diagnosis of ABPA.[35] Bronchial abnormalities occur in 50–70% of episodes of acute ABPA consists of tramline, parallel lines, ring shadows, and toothpaste shadows which represent normal or abnormal bronchial wall. The impacted bronchus may appear as full wine glass having an open upper end with tapering lower end,[36] gloved finger 2–3 centimeter long and 5–8 mm wide, and inverted V, Y, or toothpaste shadows. Gloved-finger shadows are due to distally occluded bronchi filled with secretions. Tram lime shadows are the thickened walls of undilated bronchi, so the distance between lines is that of a normal bronchus while parallel lines shadows represent walls of bronchiectatic bronchi, the distance between walls is greater than normal. Permanent (chronic) changes reflect histological abnormalities secondary to repeated acute episodes of ABPA, and are often associated with physiologic abnormalities. Rarely cavitations, local emphysema, pulmonary fibrosis or contracted upper lobe, honeycombing, collapse due to mucous impaction, and spontaneous pneumothorax.

Computed Tomography

High resolution computed tomography (HRCT) has been shown to be more sensitive than the plain chest radiograph and might be useful in the assessment of extent of disease. It is a sensitive noninvasive technique for the recognition of ABPA. Central bronchiectasis occurs due to the deposition of immune complex in proximal airways. Bronchiectasis, centrilobular nodules and mucoid impaction are main features of ABPA.[37] Central bronchiectasis with ABPA may be seen in 40% patients [38] and is characterized by string of pearls and signet ring appearance as described by Webb et al.[39] Central bronchiectasis (in 2nd, 3rd, 4th order large bronchi) is an important diagnostic feature of ABPA with normal small bronchi and bronchioles.[40] Because of the lack of specificity of central bronchiectasis in diagnosis of ABPA and the fact that a significant proportion of patients with ABPA have "peripheral" bronchiectasis, the term central has been suggested to be removed by the recent expert group.[38] An important HRCT finding, considered pathognomonic for ABPA, is airway plugging with high attenuation mucus (HAM).[41-45] HRCT of the chest is found to be normal in a third of the patients; in that case they are labeled as ABPA-S.[27]

Radiological Classification of Allergic Bronchopulmonary Aspergillosis

Serological ABPA (ABPA-S) (mild), ABPA-central bronchiectasis (ABPA-CB) (moderate), and ABPA-CB-other radiologic findings (ORF).[46] In ABPA-S all the diagnostic features of ABPA are present except evidence of central bronchiectasis on HRCT. It is believed that patients with ABPA-S have milder clinical course and

less severe immunological findings when compared to ABPA-CB. In ABPA-CB all findings of ABPA including central bronchiectasis on HRCT present however in ABPA-CB-ORF all findings of ABPA and CB along with other radiological features such as pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cyst, fibrocavitory lesions, Aspergilloma, ground glass appearance, collapse, mediastinal lymph node, pleural effusion, and pleural thickening. Newly proposed radiological classification of ABPA based on computed tomography chest findings, categorizes ABPA as ABPA-S, ABPA with bronchiectasis, ABPA with HAM and ABPA with chronic pleuropulmonary fibrosis.

Laboratory Investigations

- A peripheral blood eosinophil count >1,000 cells/μL has been used as a threshold in the diagnosis of ABPA. However, as many as 60% of patients with ABPA present with a eosinophil count <1,000 cells/μL at diagnosis, and a quarter of ABPA patients have a count <500 cells/μL. In a recent study, the sensitivity and specificity of eosinophil count >1000 cells/μL were found to be approximately 30% and 93%, respectively, for the diagnosis of ABPA among asthmatics.[47] Due to the poor sensitivity of this cut off, an eosinophil count >500 cells/μL is proposed as the limit in the recent diagnostic criteria.[48]
- *Serological tests:* Increase in total IgE and specific IgE and IgG precipitating antibodies against *A. fumigatus*. Both total and specific IgE levels are high during development of pulmonary infiltrates and decrease after remission. The total IgE levels are >1,000 IU/mL may be as high as 20,000 IU/mL in acute cases except in cases that are in remission or on steroids therapy. Precipitating antibodies against *A. fumigatus* are present in most of cases of ABPA with pulmonary infiltrates and diminished after steroid therapy.
- *Skin test:* Positive skin tests (Type 1 and Type 3) are more reliable than precipitin tests. Immediate type 1, skin reaction is positive in most of the cases but also positive in 25% of asthmatics without ABPA. Late onset (Type 3) erythema and edema occur usually after 4–6 hours and reache at peak within 8 hours and subside by 24 hours due to deposition of IgE, IgM, IgA, and complement components.
- *Sputum smear and culture for Aspergillus:* Nearly two-thirds of patients of ABPA show positive smear and culture for Aspergillus, positive culture with Aspergillus species in sputum has been reported in 58% cases of ABPA.[9]
- *Pulmonary function test:* Is neither sensitive nor specific and does not help to define the extent of disease or exclude it, during remission patient may have normal lung function even in presence of bronchiectasis. The status depends upon the stage at which they are performed. Acute and chronic pulmonary function changes in ABPA have been described. In acute episodes obstructive changes are observed, while during irreversible stages with bronchiectasis and fibrosis restrictive changes are found. In chronic-cases diffusion capacity is reduced.

Classical Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis[4]

Major Criteria

Bronchial asthma, radiological pulmonary infiltrates, immediate skin test positivity to *A. fumigatus* antigen, elevated total serum IgE, precipitating antibodies against *A. fumigatus* antigen, peripheral blood eosinophilia, elevated serum IgE and IgG against *A. fumigates*, and central/proximal bronchiectasis with normal tapering of distal bronchi.

Minor Criteria

History of expectorating golden brown plugs in sputum, positive sputum smear and culture for Aspergillus species and Type III (Arthus) skin reactivity to *A. fumigatus*.

The presence of six of eight major criteria makes the diagnosis almost certain and latest criteria do not differentiates in major and minor, eight diagnostic criteria are laid down to detect ABPA suggested by Patterson et al. 1997[6] are: Asthma (mild or severe) or cystic fibrosis, immediate cutaneous reactivity to Aspergillus antigen, current or previous pulmonary infiltrates, elevated total IgE concentration (>l mg/L), precipitin antibodies to *A. fumigatus*, peripheral blood eosinophilia, elevated serum IgE and/or IgG-against *A. fumigatus* and central bronchiectasis.

Since, previous ABPA diagnostic criteria lacked a consistent case definition, International Society for

Human and Animal Mycology (ISHAM) criteria for ABPA diagnosis in asthmatics was published in 2013, which included:[48]

- Obligatory criteria (both should be present):
  - Total IgE >1,000IU/mL
  - Positive Aspergillus specific (Af) IgE or skin prick test
- Other criteria (2 out of 3):
  - Raised Af IgG or precipitins
  - Eosinophils >500 cells/uL
  - Radiological features consistent with ABPA

Staging of Allergic Bronchopulmonary Aspergillosis

Five stages of allergic bronchopulmonary aspergillosis have been described according to Patterson et al.:[6]

- *Acute stage:* Symptoms consistent with ABPA and fulfilling the diagnostic criteria of ABPA.
- *Remission:* Control of respiratory symptoms with radiological clearing and decline in IgE levels.
- *Exacerbation:* Clinical and/or radiological deterioration associated with an increase in IgE by >50%.
- *Steroid dependent asthma:* Patient requires oral or parenteral glucocorticoids for the control of asthma.
- *Fibrosis:* Manifestations of fibrotic lung disease.

Also, a revised classification was proposed by Agarwal et al. in 2013, which divided ABPA into seven stages:[48]

- *Stage 0 asymptomatic:* No previous diagnosis of ABPA with well controlled asthma and fulfilling the diagnostic criteria of ABPA.
- *Stage 1 acute:* Symptoms consistent with ABPA and fulfilling the diagnostic criteria of ABPA. *Stage 1a:* With mucoid impaction on thoracic imaging. *Stage 1b:* Without mucoid impaction on thoracic imaging.
- *Stage 2 response:* Clinical and/or radiological improvement with decline in total serum IgE level by ≥25%.
- *Stage 3 exacerbation:* Clinical and/or radiological deterioration associated with an increase in IgE by >50%.
- *Stage 4 remission:* Sustained clinical and radiological improvement with total serum IgE levels persisting at or below baseline for ≥6 months off treatment.
- *Stage 5a (Treatment dependent ABPA):* Two or more exacerbations within 6 months of stopping therapy or clinical and/or radiological worsening, along with increase in total serum IgE levels. *Stage 5b (Glucocorticoid dependent asthma):* Patient requires oral or parenteral glucocorticoids for the control of asthma.
- *Stage 6 advanced ABPA:* Extensive bronchiectasis on chest imaging along with either cor pulmonale and/or chronic type II respiratory failure.

Treatment of Allergic Bronchopulmonary Aspergillosis

Oral corticosteroid remains the cornerstone for the treatment of ABPA.[49] The goal of therapy is to achieve symptom resolution, clearance of radiographic infiltrates, and establishment of a stable baseline serum level of total IgE. There are two dose schedules of oral glucocorticoid therapy, low dose, and high dose. In low dose oral glucocorticoid therapy, prednisolone 0.5 mg/kg/day is given for 2 weeks, then on alternate day for 6–8 weeks and then tapered 5–10 mg every 2 weeks and then discontinued. In high dose glucocorticoid therapy, prednisolone 0.75 mg/kg is given for 6 weeks, followed by 0.5 mg/kg for 6 weeks, then taper 5 mg every 6 weeks to continue for a total of at least 6–12 months. Repeat chest X-ray in 1 month should demonstrate clearing of the infiltrates. The total serum IgE level also regresses along with the infiltrates. The failure of the total serum IgE level to decrease suggests continuation of active disease and requires additional corticosteroids. The total serum IgE level, chest X-ray, absolute eosinophil count should then be followed at 6–8 weeks of interval regularly. The goal of glucocorticoid therapy is not normalization of total serum IgE but reduction in total serum. IgE by 35–50% from baseline defines remission by 6 weeks. Serial total serum IgE levels are important for follow-up care.[48] Patients who have remission of ABPA may discontinue prednisone. The remission may last for years or may be permanent. In patients with recurrent flares of ABPA or in those with severe persistent asthma, long-term corticosteroid therapy may be necessary to control their symptoms. Patients in the fibrotic stage of ABPA may have increased sputum volume as a result of infection. Measures such as postural drainage and antibiotics may be useful, but with deterioration, exercise tolerance decreases, and oxygen therapy may be needed. Optimization of baseline asthma therapy is essential with inhaled corticosteroid and β2

agonists. In addition, prophylactic measures should be instituted when indicated to prevent the adverse effects of long-term corticosteroid treatment such as osteoporosis. Thus, patients who take prednisolone for more than 2–3 months should be considered for bone mineral density analysis to direct commencement of calcium/vitamin D supplementation with or without bisphosphonates.[50]

Alternative to Corticosteroid Treatment

Even though oral corticosteroid is the treatment of choice in ABPA, the fact that it is associated with numerous adverse effects cannot be neglected. Inhaled corticosteroids are associated with fewer side effects, and hence considering them as a viable treatment option for ABPA seems appropriate. Not a lot of studies have been conducted to evaluate the role of inhaled corticosteroids in the management of ABPA. Inhaled corticosteroids, while useful for concomitant asthma management in patients with ABPA, do not control the pathophysiology or clinical manifestations of ABPA.[51-53] In contrast to the inhaled corticosteroid therapy "pulse" therapy (10–20 mg/kg/day IV methylprednisolone infused on three consecutive days every 3–4 weeks) was found out to be generally safe and effective in two open labeled series of thirteen steroid dependent ABPA CF patients.[54,55]

Anti-fungal Drugs

The most efficacious alternative to long-term oral corticosteroids is the use of antifungal agents either in conjunction to the steroid therapy or even as a standalone therapy. Use of antifungal therapy in the treatment of ABPA is based on the assumption that allergic inflammatory responses arise in part from noninvasive airway fungal infection. Pooled analysis showed that itraconazole could significantly decrease IgE levels by >25% when compared to placebo, reduction in steroid dose by ≥50%; increase in exercise tolerance by ≥25%, improvement of ≥25% in results of spirometry, resolution of pulmonary opacities but failed to reach statistical significance, and did not cause significant improvement in lung function. Itraconazole modified the immunologic activation associated with ABPA and improve clinical outcome at least over the period of 16 weeks. The effectiveness of itraconazole in the treatment of ABPA was also demonstrated in two randomized, double-blind, placebo controlled trials in patients with asthma.[56,57] Also, a randomized trial of itraconazole versus prednisolone in acute stage ABPA found out that oral glucocorticoids were more effective than itraconazole monotherapy in producing treatment response.[58] At present, itraconazole should be limited in cases where oral steroids are contraindicated or refused by patients. The use of azoles for ABPA in asthma patients was reviewed by the Cochrane collaboration which suggested that itraconazole modifies the immunologic activation associated with ABPA and improves the clinical outcome, at least over a period of 16 weeks, though adrenal suppression with inhaled corticosteroids and itraconazole is a potential concern.[59] Newer generation triazoles such as voriconazole and posaconazole have also been reported as beneficial in the treatment of ABPA. Treatment with voriconazole as a monotherapy was shown to be associated with improvements in clinical status, lung function, and serologies.[60] A newer agent isavuconazole has been shown to be effective in a study conducted by Jacobs et al. in a patient of ABPA who was successfully treated with marked improvement and minimal adverse effects.[61]

Alternatives to Azoles

Amphotericin deoxycholate has been frequently used via inhalational route in the treatment of pulmonary fungal infection, primarily in the setting of cancer treatment and lung transplantation. Amphotericin B can be delivered via nebulization to the lower respiratory tract in doses which are capable enough to exceed the minimal inhibitory concentration of Aspergillus in the epithelial lining.[62] However, data regarding the efficacy of amphotericin B is pretty scarce as of now and thus more studies need to be conducted in order to determine its actual role in the treatment of ABPA.

Omalizumab

Omalizumab is a recombinant humanized IgG1 monoclonal antibody that binds IgE with high affinity and has been associated with improvement in symptoms, reduction in exacerbations, asthma hospitalizations, improvement in lung function, and reduction in dose of oral steroids.[48] However, a recent retrospective series conducted in France has found variable results in 32 patients of ABPA with cystic fibrosis, which though reported a reduction in the steroid need over a 21-month observation period, but there was no significant improvement in the lung function or the use of antibiotics.[63]

Conclusion

Presently ABPA is one of the important emerging immunologically mediated respiratory diseases, commonly presenting in patients of asthma. It should be highly suspected in patients presenting with history of asthma, peripheral blood eosinophilia, recurrent pneumonitis, or transient (fleeting) pulmonary infiltrates mimicking pulmonary tuberculosis. In such suspected patients, detailed evaluations are needed to prove the diagnosis. Early diagnosis and proper treatment may alter the prognosis of disease and further prevent end stage lung fibrosis.

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CHAPTER

107 Obstructive Sleep Apnea

Puneet Rijhwani, Aviral Gupta

Abstract

Obstructive sleep apnea is a severe form of sleep disordered breathing, which affects over 9% of middle aged urban Indians. Male sex, obesity, age, upper airway and craniofacial anomalies, genetic, and other environmental factors, particularly ambient air pollution are risk factors for OSA. These factors result in upper airway collapse during sleep, leading to obstructive respiratory events and symptoms of OSA, such as excessive daytime sleepiness, nocturnal breathing disturbances, morning headaches, and many more. Home sleep apnea testing or polysomnography is diagnostic. A plethora of complications can result from OSA, including metabolic, cardiovascular, cerebrovascular, and neuropsychiatric complications. Obese patients with OSA should be encouraged for weight loss, and other lifestyle modifications. Positive airway pressure therapy is the cornerstone of management of the disease; with only some patients requiring surgical management.

Introduction

Sleep disordered breathing is an umbrella term, consisting of disorders characterized by an abnormal respiratory pattern during sleep, which may coexist with other respiratory, cardiovascular, nervous, or endocrine diseases. It encompasses conditions ranging from snoring at the mild end of the spectrum to obstructive sleep apnea (OSA) at the severe end.

There are three main types of sleep apnea:

- Obstructive sleep apnea (OSA), seen in more than 80% of sleep apnea patients, occurs due to blockage of air from entering and leaving the lungs.
- *Central sleep apnea (CSA)*, occurs when the brain stops responding to breathe until it senses a lack of O_2 and/or a increased level of CO_2 that needs to be exhaled.
- *Complex sleep apnea* is a combination of these two.

OSA or hypopnea syndrome is the most common sleep-related breathing disorder. It is caused by repetitive collapse of the upper airway during sleep and is characterized by obstructive apneas, hypopneas, and/or respiratory effort related arousals (RERA). It leads to daytime sleepiness, behavioral problems in children, increases cardiovascular risk in adults, and can be factor in work place or motor vehicle accidents.

Epidemiology and Risk Factors

The prevalence of OSA is high and on a rising trend due to the increasing rates of obesity in the world.[1] A literature-based analysis to estimate the global prevalence of OSA suggested that nearly 1 billion adults in the age group of 30–69 years were affected, with India standing at the fourth spot among the countries with the highest burden.[2]

Male sex is a major risk factor, with the prevalence of sleep disordered breathing estimated at 24% for men and 9% for women aged 30–60 years,[3] with 4% of men and 2% of women meeting the minimal diagnostic criteria for sleep apnea syndrome;[4] later estimates reaching up to 4%

for women and 9% for men.[3] An Indian study conducted among middle-aged urban Indians estimated an overall prevalence of OSA at 9.3% (Men—13.5%; Women—5.5%).[5] OSA is thus two to four times more common in males than females, but the risk appears to become similar to men in postmenopausal women.[6]

Obesity is the second major risk factor for development of OSA. Up to 60% of patients with OSA are overweight or obese.[7] A high body mass index (BMI) is associated with a higher risk for OSA, with BMI being more strongly associated to OSA in younger adults.[1] A substantial decrease in OSA severity following weight loss has been demonstrated, and longitudinal analysis indicate that a 10% increase in weight leads to sixfold increase in the risk of developing moderate to severe OSA, and a 32% increase in Apnea-hypopnea index (AHI).[8] Almost 90% of the patients with obesity hypoventilation syndrome have coexistent OSA.

Age is another important risk factor for the development of OSA, the prevalence increasing from young adulthood up to the sixth or seventh decade, and then it plateaus.[7,9] Age is an independent associated risk factor for OSA, with odds ratio reaching 34.5 for the 60–80 year age group as compared to 20–29 year age group.[7]

Upper airway abnormalities (such as enlarged tonsils or adenoids, small nasal cavity) and craniofacial anomalies (such as micrognathia, retrognathia, a wide craniofacial base) have also been implicated in increasing the risk of OSA.[10] Another study noted that a majority of Asian men who had severe OSA, were non-obese and differences in craniofacial anatomy was considered an important risk factor in this population (vs. White men).[11]

Genetic factors that produce the OSA phenotype usually affect body fat distribution, craniofacial morphology and neuromuscular factors. Relatives of patients with sleep apnea have two- to fourfold greater risk of sleep apnea and familial factors can explain up to 40% of the variance in AHI.[12]

Other risk factors associated with a higher risk of OSA are smoking, menopause (hormonal differences could account for the sex differences in OSA, with hormonal replacement being protective), nasal congestion,[10] and ambient air pollution (particularly nitrogen dioxide and PM 2.5).[13] A number of comorbid conditions are also associated with a higher prevalence of OSA, although whether this association is etiological or simply reflects the common risk factors of these conditions is still under evaluation. These conditions include diabetes, hypertension, congestive heart failure, stroke, coronary artery disease, atrial fibrillation, chronic lung disease, pregnancy, endocrine disorders (hypothyroidism, acromegaly), end stage renal disease, gastroesophageal reflux, and many others.[10]

Pathophysiology

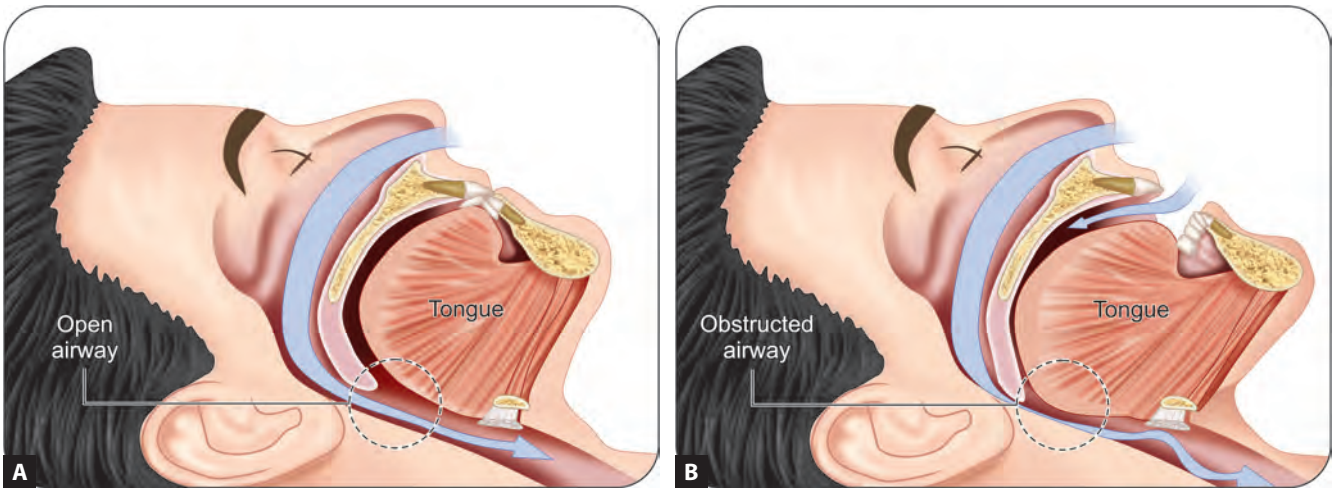
The pathogenesis of OSA is not fully understood. The upper airway collapse during sleep results from an interplay of several factors. Unfavorable upper airway anatomy (small airway due to obesity, genetics, age, craniofacial, or upper airway abnormalities) may lead to its collapse when subjected to a collapsing transmural pressure **(Figs. 1A and B)**.[14]

Decreased central respiratory output during sleep, which reduces tonic upper airway dilator muscles activity can predispose to such a collapse.[15] Upper airway caliber decreases normally during sleep and has a higher compliance. Upper airway and nervous system reflex activity is also impaired during sleep, leading to inability to maintain ventilation and increasing arterial carbon dioxide levels.[16] However, patients with OSA are observed to have a low arousal threshold, waking up frequently to increased carbon dioxide levels and hyperventilating. The resultant hypocapnia can further decrease the respiratory drive and reducing tonic muscular output, leading to airway collapse and apneic episode.[15,16] Neuromuscular incoordination and diseases that lead to it may also play a role in the pathogenesis of apnea.

Lung volume decreases with increasing age, obesity, and during sleep; which removes the caudal traction on the upper airway applied by the inflated lung, increasing airway collapsibility.[15,16] Rostral fluid shifts during sleep, particularly in conditions with extracellular volume overload, can also narrow the airway.[15]

Clinical Features

Patients with OSA often complain of daytime symptoms such as inability to remain fully awake or alert, fatigue (more common in women), tiredness, and poor focus; referred to as daytime sleepiness.[17] They do not wake up feeling refreshed (non-restorative sleep). A quantitative assessment of the sleepiness and fatigue can be done by the Epworth Sleepiness Scale.



Figs. 1A and B: Mechanism of obstructive sleep apnea

Bed partners of patients with OSA report that the patient has nocturnal breathing disturbances such as snoring, gasping, choking, snorting, or breathing pauses while sleeping. A systematic review of 42 studies noted that nocturnal gasping or choking was the single most useful clinical symptom for identifying patients with OSA (likelihood ratio 3:3); and while snoring was a frequent complaint, it had no value in suggesting OSA as a single finding (likelihood ratio 1:1).[18] For the diagnosis of OSA, snoring had a higher sensitivity (80%), but a lower specificity (50%) as compared to gasping or choking (sensitivity—52%, specificity—84%).[18]

Other symptoms found in patients with OSA are morning headaches (12–18% of patients), lasting for several hours after waking up on most days of the week.[19] There is also a high prevalence of insomnia in patients with OSA (up to 30%), and females had more insomnia symptoms as compared to males.[20] Up to 40% patients experience nocturia (even correlating with severity OSA in patients <50 years of age); treatment with continuous positive airway pressure (CPAP) significantly reduces the number of night-time urinations **(Fig. 2)**.[21]

Physical evaluation of patients with OSA reflects the comorbid conditions and etiological factors for the disorder. The most common clinical finding is obesity, particularly central obesity. Patients often have large waist circumference and neck circumference (>17 inches for men and >16 inches for women).[22] Oropharyngeal examination can indicate craniofacial abnormalities and crowded upper airway. Mallampati classification and Friedman tongue position can be used to rapidly assess the severity of airway narrowing; a meta-analysis indicating it positively correlated with predicting OSA severity.[23] Associated conditions and complications that can be found in patients with OSA are systemic hypertension, heart failure, and pulmonary hypertension.

Diagnosis

The American Academy of Sleep Medicine (AASM) has established guidelines for the diagnosis of OSA.[24] Diagnostic testing should be performed in patients with excessive daytime sleepiness and the presence of at least two of the following features—habitual loud snoring, witnessed apnea or choking or gasping during sleep, and systemic hypertension; patients fulfilling these criteria are at high risk of moderate to severe OSA.[24]

The AASM recommended against the use of clinical tools, questionnaires, and prediction algorithms to diagnose OSA in adults, in the absence of polysomnography or home sleep apnea testing.[24] Examples of such tools include the Berlin questionnaire, STOP-Bang questionnaire, the NoSAS score (which performed significantly better than the previous two[25]), the Multivariable Apnea Prediction instrument (MVAP), etc.

The use of home sleep apnea testing (HSAT, also known as out-of-center sleep testing or OCST) or polysomnography (PSG) is recommended for the diagnosis of OSA.[24] An in-laboratory PSG is considered

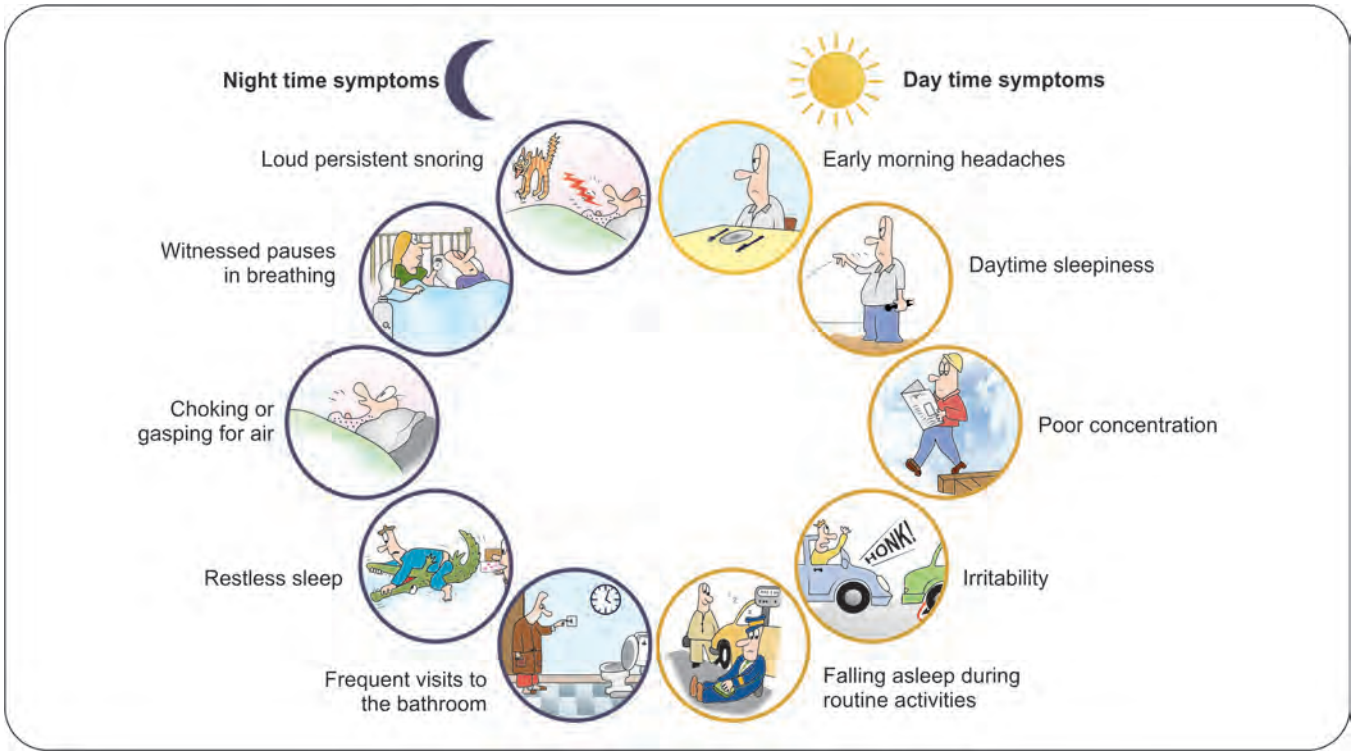


Fig. 2: Symptoms of obstructive sleep apnea

the gold standard for diagnosis, and should be performed in cases where HSAT is negative, technically inadequate, or inconclusive.[24] The diagnostic criteria for OSA, as per AASM, International Classification of Sleep Disorders (ICSD), 3rd edition are:[26]

- ≥15 predominantly obstructive respiratory events per hour of sleep during PSG or OCST, in the absence of associated symptoms or disorders
  OR
- ≥5 predominantly obstructive respiratory events per hour of sleep during PSG or OCST, with ONE or more of the following:
  - Complains of sleepiness, non-restorative sleep, fatigue, or symptoms of insomnia
  - Waking up with breath holding, choking, or gasping
  - Habitual snoring, breathing interruptions, or both noted by a bed partner or other observer
  - Comorbidities—hypertension, type 2 diabetes mellitus, coronary artery disease, atrial fibrillation, congestive heart failure, stroke, cognitive dysfunction, or mood disorder

The respiratory events include obstructive apnea (≥90% reduction in airflow for >10 seconds with continued respiratory effort), hypopnea (a ≥30% reduction in airflow for ≥10 seconds with arousal or ≥3% desaturation) and respiratory effort-related arousal, that is, RERA (arousals associated with decrease in airflow lasting at least 10 seconds, that do not meet criteria for apnea or hypopnea). The quantitative data generated from sleep study can be expressed in the form of two indices:

- Apnea-hypopnea index (AHI)—Number of apneas plus hypopneas per hour of sleep
- Respiratory disturbance index (RDI)—Number of apneas plus hypopneas plus RERAs per hour of sleep

RDI is the preferred index[24,27] and can be used to classify the severity of OSA into mild (5–14 events per hour), moderate (15–29 events per hour), and severe (≥30 events per hour).

Differential Diagnosis

Conditions that can mimic OSA and should be kept as a differential diagnosis include:

- Primary snoring—Most patients with OSA snore, but not all patients who snore have OSA
- Pulmonary disease—Asthma, chronic obstructive pulmonary disease
- Insufficient sleep
- Other sleep disorders—Central sleep apnea, narcolepsy, periodic limb movement disorder, restless legs syndrome
- Neurological disorders leading to daytime sleepiness
- Neuromuscular disorders
- Medical diseases—Hypothyroidism, end stage renal disease, hepatic encephalopathy
- Medications—Sedatives (benzodiazepines, barbiturates, non-benzodiazepines, antihistamines, antidepressants, etc.), opioids, etc.
- Psychiatric disorders (depression, anxiety) and substance abuse (alcohol, narcotics, etc.)
- Gastroesophageal reflux disease

Complications

OSA can lead to several cardiovascular, cerebrovascular, and metabolic complications, which can lead to adverse clinical outcomes and even premature death **(Fig. 3)**.

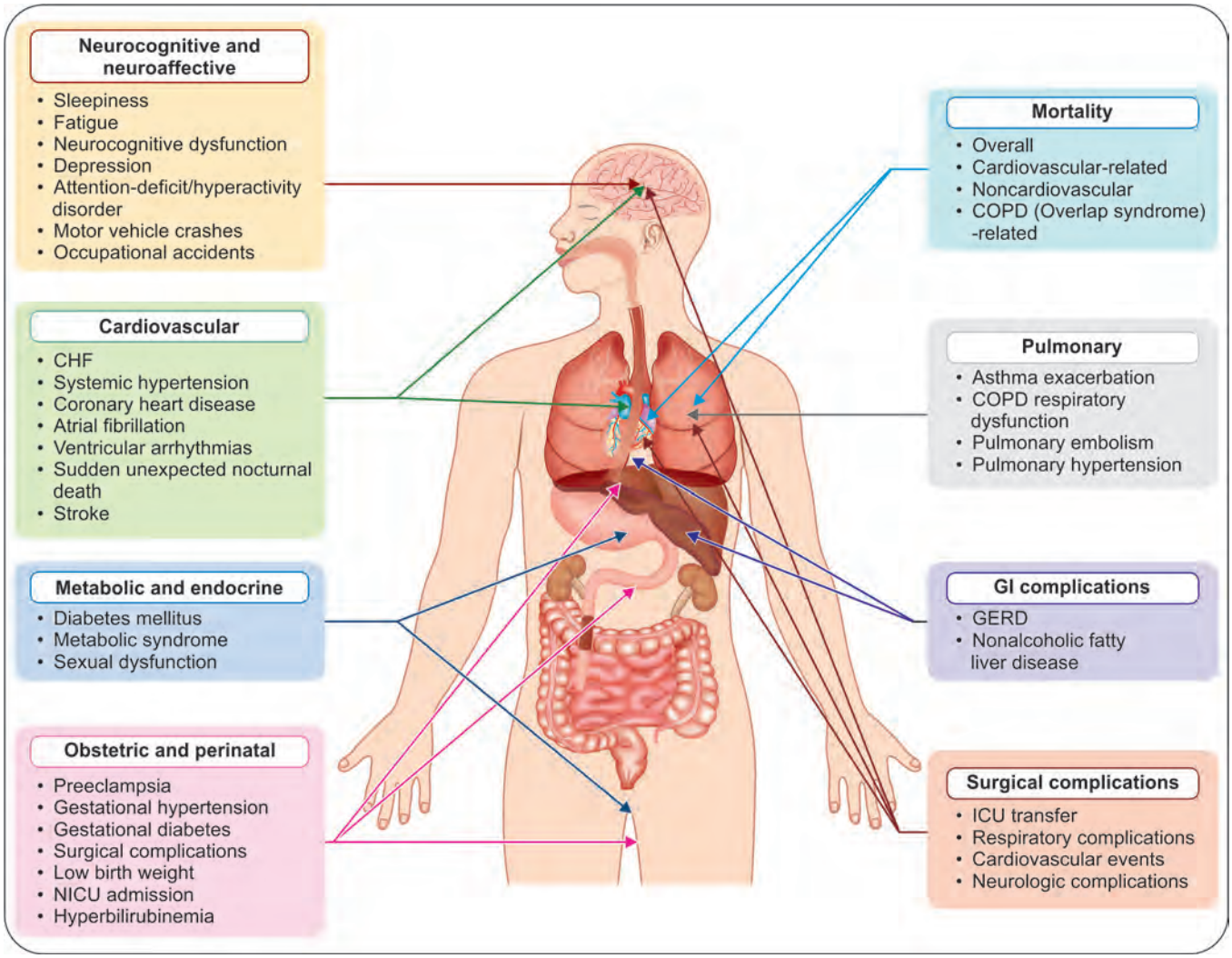


Fig. 3: Adverse outcomes of OSA

The repeated arousal events associated with intermittent hypoxia in OSA, leads to increased sympathetic activity, hemodynamic changes, inflammation, metabolic changes, and endothelial dysfunction.[28] There is increased incidence of hypertension, cardiovascular events (myocardial infarctions, heart failure, etc.), coronary artery disease, atrial fibrillation, QT prolongation, pulmonary hypertension, and even venous thromboembolism.[28]

It has been noted that patients with OSA tend to have a "non-dipping" pattern of blood pressure (lack of the typical 10% drop in blood pressure during sleep).[29] A meta-analysis of 31 articles indicated that CPAP therapy resulted in a small, but statistically significant reduction of blood pressure in patients with OSA.[30]

There was also an increased incidence of stroke in patients with OSA, particularly in men.[31] OSA has also been implicated in causing two times the increased risk of depression,[3] risk being higher in women than men.[32] Other neuropsychiatric complications include memory and cognitive defects, difficulty in maintaining attention;[33] which combined with the excessive daytime sleepiness, can lead to motor vehicle and workplace accidents.

The reported prevalence of pulmonary hypertension in OSA patients varied between 17% and 70%.[34] OSA associated pulmonary hypertension is classified under group 3 pulmonary hypertension and most of these cases are only of a mild degree.[34]

Metabolic alterations and complications are frequent in patients with OSA. Studies have demonstrated an increased prevalence of type 2 diabetes mellitus and its complications, which is independent of the shared risk factors (e.g., obesity) of both the diseases. An increased incidence of diabetes was independently and significantly associated with OSA severity (30% higher hazard with AHI >30), time spent with oxygen saturation under 90%, and the AHI in rapid eye movement (REM) sleep.[35] Sleep disordered breathing is also independently associated with metabolic dysfunction such as insulin resistance and glucose intolerance, its severity correlating with the RDI and the degree of sleep related hypoxemia.[36]

The prevalence of moderate to severe OSA in patients with metabolic syndrome is very high (60%), the combination of OSA, and metabolic syndrome (syndrome X) being called "Syndrome Z". Independent association of OSA with increased triglyceride and glucose levels, inflammatory markers, atherosclerosis, and arterial stiffness in patients with metabolic syndrome has been observed.[37] Effective treatment with CPAP reduces several components of metabolic syndrome in these patients.[37] The chronic intermittent hypoxia in OSA is also a potential candidate for leading to progression of fatty liver in obesity.[37]

Management

Patient education and behavior modification is the initial step in management of all patients with OSA. They should be educated about the natural history, risk factors, potential complications, and the increased risk of accidents due to drowsiness.[22] Overweight and obese patients should be encouraged for weight loss via dietary therapy, exercise, drug therapy, or even bariatric surgery.[8,22] Patients who suffer from OSA primarily in the supine sleep position on PSG, should be initiated on positional therapy (use of a positioning device, monitoring and sometimes the use of an objective position monitor).[22] All patients should be instructed to avoid alcohol and medications, which have an inhibitory effect on the nervous system or cause weight gain.

The mainstay of therapy for OSA in adults is positive airway pressure therapy, delivered in continuous (CPAP), bi-level (BiPAP), or autotitrating (APAP) modes. CPAP prevents upper airway collapse, which leads to respiratory events.[15] CPAP treatment is indicated in treatment of any severity of OSA.[22] It reduces AHI, excessive daytime sleepiness, lowers blood pressure, and improves quality of life,[38] but its effect on mortality remains to be demonstrated.

Other strategies include the use of oral appliances such as mandibular repositioning appliance or tongue retaining device, which enlarge the upper airway and improve its patency.[22] These devices have lower efficacy than CPAP, but have better compliance rates.[39] They are indicated for use in mild to moderate OSA, patients who fail behavioral measures, or fail or do not respond to or are not appropriate candidates for CPAP.[22]

Patients with a surgically correctable obstructive lesion of the upper airway (e.g., adenoid hypertrophy, tonsillar hypertrophy, craniofacial abnormality) can be considered for primary surgery and correction of the obstructive lesion.[22] Surgery can also be a secondary therapy if there is intolerance or failure of positive airway pressure (PAP) or oral appliance therapy.[22] Hypoglossal nerve stimulation may be considered in selected OSA patients (failed CPAP,

BMI <32 kg/m^2), a meta-analysis indicating a statistically significant reduction in AHI and daytime sleepiness at 12 months of therapy.[40] Tracheostomy eliminates OSA by bypassing the upper airway, but reduces the quality of life substantially.[15,22]

Currently no pharmacologic agent with proven long-term effectiveness is available for replacement of above therapies for OSA. A Cochrane review on drug therapy for OSA, concluded that out of the 25 drugs reviewed, only 10 drugs had some effect on the severity of OSA, but long-term outcomes of these drugs is still unknown.[41] Dronabinol (a synthetic cannabinoid) has been shown to reduce AHI in moderate to severe OSA, but it is not yet recommended in OSA, and needs further Phase III trials to support its efficacy.[42]

OSA patients continuing to have residual daytime sleepiness, despite effective PAP therapy may benefit from the addition of modafinil or armodafinil (central nervous system stimulants), after other causes of residual sleepiness are ruled out.[22]

Conclusion

Obstructive sleep apnea, the most common sleep disordered breathing, affects almost a billion people worldwide. India stands fourth among countries with the highest burden and the increasing obesity and air pollution rates worldwide will only serve to increase its prevalence. It leads to morbidity and mortality due to its cardiovascular, cerebrovascular, and metabolic complications; and impacts the patient's quality of life. Management relies upon lifestyle modification, positive airway pressure therapy, and other strategies (sometimes including surgery) for successful treatment. No pharmacotherapy is yet approved for primary therapy.

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CHAPTER

108 Interstitial Lung Disease in Connective Tissue Diseases: An Update

Nirmal Garabadu

Abstract

Multiple connective tissue diseases (CTDs) manifest interstitial lung disease (ILD) and cause significant morbidity and mortality. Till date, there is no effective therapy. There are new evolving concepts of pathogenesis and rapid progress in identifying the effector cells. Serum biomarkers provide new insights for early diagnosis and disease progression. But management of patients with CTD-ILD remains sub-optimal. Multi-disciplinary clinics are now established for early diagnosis, improved management, and effective therapy.

Introduction

Connective tissue diseases (CTDs) are a group of diseases with heterogeneous systemic features and show immune-mediated multi-organ dysfunction. The respiratory tract can be affected in virtually every CTD. Interstitial lung disease (ILD) is a potential complication in many of the CTDs. In ILD a group of parenchymal lung disorders share common radiologic, pathologic, and clinical manifestations. There are six most common and important forms of ILD namely smoking related, connective tissue or autoimmune disease related, hypersensitivity pneumonitis, occupation related, medication related, and idiopathic pulmonary fibrosis (IPF). The CTDs associated with ILD are as follows:

- Systemic Sclerosis (SSc)
- Rheumatoid Arthritis (RA)
- Polymyositis/Dermatomyositis (PM/DM)
- Sjögren's Syndrome
- Systemic Lupus Erythematosus (SLE)
- Undifferentiated CTD
- Mixed CTD

Sometimes they are asymptomatic and require high-resolution computed tomography (HRCT) of lungs or pulmonary function testing (PFT) for detection. Lung involvement is a decisive contributor to mortality in CTD. The fibrosing forms are often incurable and lead to significant morbidity and mortality.

ILD associated with CTDs share a common clinical presentation such as cough (non-productive), shortness of breath to progressive dyspnea. At times ILD may be the presenting feature that predates the CTD. Prevalence of ILD in CTDs appears to be higher than previously thought. In order to initiate proper treatment early recognition of pulmonary involvement is very important.

An accurate ILD diagnosis requires thorough medical history and physical examination along with autoimmune serologic testing, high resolution chest tomography imaging, and lung biopsy (if necessary). Severity of disease and response to treatment is assessed by restrictive pattern of ventilatory defect and abnormal diffusion capacity (DLco). Frequency of ILD in different CTDs is shown in **Table 1**.

Pathogenesis of CTD-ILD

Three factors interplay in the pathogenesis. They are vascular injury, inflammation, and autoimmunity. It is characterized by a combination of

TABLE 1 Frequency of ILD in different CTDs

Connective tissue diseases	*Frequency of ILD (%)*
Rheumatoid arthritis	20–30
Systematic sclerosis	45
Sjögren's syndrome	Up to 25
Polymyositis/dermatomyositis	20–50
Systemic lupus erythematosus	2–8
Mixed connective tissue disease	20–60

- chronic inflammation within the lungs consisting of an accumulation of chronic inflammatory cells and increased levels of numerous proinflammatory cytokines, chemokines, and cell surface molecules;
- varying degrees of fibrosis.

In the pathogenic process of pulmonary fibrosis initially there is microvascular injury, which leads to endothelial or alveolar epithelial damage. Then proinflammatory and profibrotic extra cellular mediators like chemokines, cytokines, growth factors, lipids, and prostanoids come into play. The pivotal mediator of fibrosis is the Cytokine Transforming Growth Factor Beta (TGFbeta). TGFbeta along with platelet derived growth factor, endothelin-1 (ET-1) play the key role in fibroblast production **(Flowchart 1)**.

Histology

In response to lung injury in CTD associated ILD, three major histopathologic patterns occur. They are:

- Usual interstitial pneumonia (UIP),
- Non-specific interstitial pneumonia (NSIP), and
- Organizing pneumonia (OP).

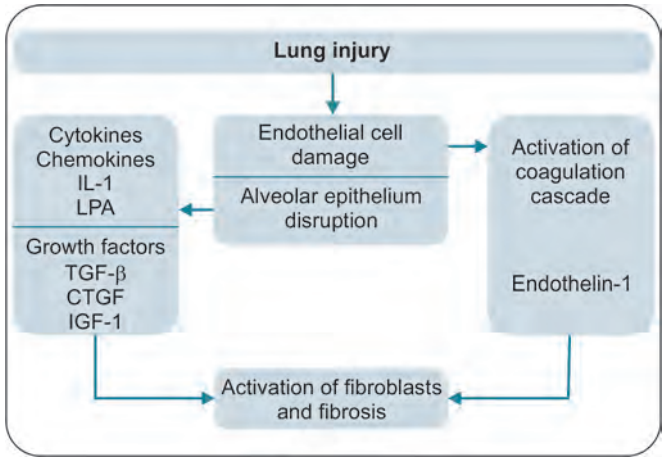
UIP is recognized by dense fibrotic areas heterogeneously distributed with areas of normal lung architecture, numerous microscopic cysts filled with mucus called honeycomb change and fibroblastic foci juxtaposed to honeycomb cysts.

NSIP shows diffuse cellular inflammation and/or fibrosis in the lung interstitium. The distribution is homogeneous pattern throughout the lungs.

OP is recognized by multiple round or oval deposits consisting of extra cellular matrix proteins and myofibroblasts.

Treatment and prognosis in ILD is determined by the etiology of ILD rather than a specific histologic pattern.

Flowchart 1: Mechanisms involved in pulmonary fibrosis. Endothelila and alveolar epithelial injury initiates activation of coagulation cascade, release of various growth factors and cytokines. This leads to activation of fibroblast and development of fibrosis



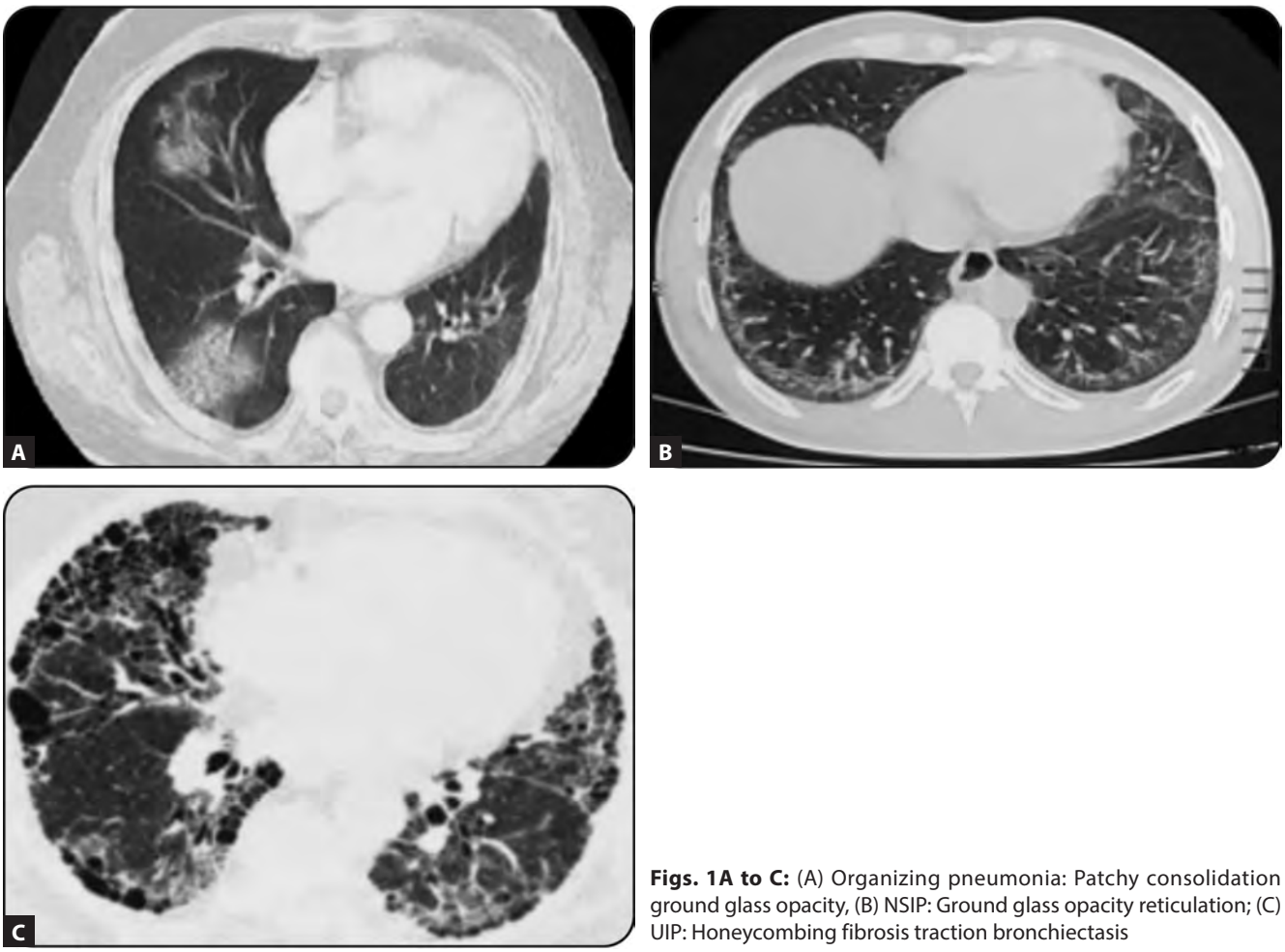
CFG, connective tissue growth factor; IGF-1, insulin like growth factor 1, LPA, lysophosphatidic acid, TGF-β, transforming growth factor β

Therefore, biopsy is not advocated unless absolutely necessary.

Radiology/HRCT Imaging

HRCT imaging of chest is essential for making accurate ILD diagnosis. Three features of chest imaging deserve specific mention.

- Distribution of opacities within the lungs—upper lobe versus lower lobe, peripheral versus central/peribronchiolar, and whether spare extreme periphery. Specific forms of ILD have characteristic distributions and no known explanation for that.
- Next, findings of fibrosis be recognized-reticular opacities often seen in periphery of the lungs, traction bronchiectasis (dilated and distorted bronchi and bronchioles due to traction by surrounding fibrosis) and honeycomb change (clusters of small cysts in extreme periphery) and volume loss. Honey combing and traction bronchiectasis occur in advanced fibrosis. These findings portend poor prognosis irrespective of etiology.
- Lastly, presence of ground glass opacities and/or consolidation—areas of hyperattenuated lung considered to be inflammatory in nature and likely to be reversible.



Figs. 1A to C: (A) Organizing pneumonia: Patchy consolidation ground glass opacity, (B) NSIP: Ground glass opacity reticulation; (C) UIP: Honeycombing fibrosis traction bronchiectasis

Imaging pattern on HRCT is characterized by reticulation associated with fibrotic features, architectural distortion, traction bronchiectasis and honeycombing.

UIP pattern on HRCT shows peripheral and basal predominant involvement. There is reticulation associated with fibrotic changes and also includes traction bronchiectasis and honeycombing.

In NSIP pattern ground-glass opacity and reticulation with traction bronchiectasis is seen predominantly, basal and bilateral OP pattern consists of patchy, subpleural, peripheral, and peribronchiolar consolidation[1] **(Figs. 1A to C)**.

Relative Frequency of Pattern of Involvement in ILD Associated with CTDS

See **Table 2**.

Autoantibodies in the Diagnosis of CTD-ILD

In specialized ILD clinics detection of autoantibodies assist diagnosing unrecognized CTD-ILD. These autoantibodies tests change the diagnosis (in about 4–19% cases) from idiopathic ILD to CTD-ILD. Distinguishing idiopathic interstitial pneumonia from CTD-ILD is absolutely important as regards prognosis and management. The major autoantibodies and their associated CTDs are given in **Table 3**.

Prognosis of CTD-ILD

High mortality and more aggressive disease is seen in male sex, a history of smoking, older age, South Asian ethnicity and UIP pattern. Another survival analysis showed disease

TABLE 2 Relative frequency of radiological and histological patterns in connective tissu disease associated ILD

CTD	UPI	NSIP	OP	LIP
Systemic sclerosis	+	+++	+	–
Rheumatoid arthritis	+++	++	++	+
Sjögren's syndrome	+	++	–	++
Polymyositis/dermatomyositis	+	+++	+++	–
Systemic lupus erythematosus	+	++	+	++
Mixed connective tissue disease	+	++	+	–

TABLE 3 Major autoantibodies and their associated CTDs

CTD	Autoantibody
Rheumatoid arthritis	High-titer RF, anti-CCP
Systematic sclerosis	Anti-centromere, anti-topoisomerase (Scl-70), anti Th/To, anti-nucleolar ANA
Systemic lupus erythematosus	ANA, anti-dsDNA, anti-ribonucleoprotein
Sjögren's syndrome	RF, anti-LA, anti-RO
Polymyositis/dermatomyositis	Anti-JO, non-JO, anti-MDA-5
Mixed connective tissue disease	Anti-ribonuleoprotein

course and intensity of ILD lesions at baseline as critical indicator for survival. In yet another study of 359 patients with median follow-up time 4 years, there were 85 deaths (23.7%).

Connective Tissue Diseases Associated with ILD

Systemic Sclerosis

Systemic sclerosis (SSc) is a rare CTD and is characterized by immune dysfunction, vasculopathy, cellular inflammation, and fibrosis of skin and multiple internal organs. Initial tissue injury is followed by excessive collagen deposition. Nearly one-half of cases develop clinically significant ILD and is a leading cause of death in these patients. Risk of ILD is greater in African-American ethnicity and in those with more extensive skin involvement (diffuse SSc).[2]

Risk factors for the development of progression of ILD are older age at disease onset, shorter disease duration and the presence of anti-Scl-70 (anti-topoisomerase antibody) and absence of anti-centromere antibody.[3] But none of these risk factors is absolute. All the patients diagnosed as systemic sclerosis should have assessment of respiratory symptoms, HRCT scan of chest and PFTs to ensure early identification of ILD. The risk of developing ILD is greatest early in the course of disease. PFTs and DLco are very useful to monitor the progression. Therefore, suggested to repeat the tests every 4–6 months for 3 years. Most patients will show a slow decline in lung function, but some have rapid progression.

Certain biomarkers serve as indicators of disease and predictors or progression. Serum levels of surfactant proteins A&D (SP-A and SP-D) and glycoprotein KL-6 were elevated when compared to healthy controls. Recently a novel biomarker chitinase-like protein YKL-40 is gaining interest.

Most of the cases show NSIP pattern in HRCT scan and histopathology. Some with advanced disease with severe fibrosis may show UIP pattern. The utility of HRCT is sufficient to make the diagnosis of UIP/IPF in about 50–60% cases.

Management/Treatment Considerations of SSC-ILD

There are no approved drugs. Current approach to treatment include routine follow-up alone in mild disease

with no signs of progression. On the other hand in patients with progressive ILD active immunosuppression is advocated along with monitoring. Based on available data, decisions for treatment is made case by case basis. All do not need treatment. Decline in lung function, progression of fibrosis on HRCT or worsening respiratory symptoms due to ILD will require active drug treatment.

In early stage of disease (requiring treatment) evidence of inflammation is commonly present, and therefore therapies target inflammatory response. Corticosteroids, cyclophosphamide, azathioprine and mycophenolate mofetil are the immunosuppressive agents used. Corticosteroid therapy is generally ineffective. Others show modest benefit.

Oral cyclophosphamide at 2 mg/kg/day was tried for 12 months in Scleroderma lung study. It showed slowing of decline in lung function, improvement in dyspnea and skin thickening. At 24 months only benefit of reduction in dyspnea remained.

Mycophenolate mofetil is a less toxic and better tolerated drug as compared to cyclophosphamide. Therefore, this drug is a better option for long term use.

Azathioprine is an alternative agent for those who do not tolerate cyclophosphamide. Data suggests Azathioprine for maintenance therapy following intravenous cyclophosphamide.

Endothelial-1 receptor antagonists (Bosentan)—BUILD-3 study did not reduce morbidity and mortality. As regards 6-minute walk test it was no better than placebo.

Tyrosine kinase inhibitors (Imatinib) blocks platelet derived growth factor receptor. A recent large multicenter randomized controlled trial showed no significant benefit in treatment of IPF.

Pirfenidone has both anti-inflammatory and anti-fibrotic effect. It inhibits collagen synthesis & TGFbeta production. It improved exercise capacity and showed no radiological progression of disease.

Nintedanib completely inhibits tyrosine kinase, fibroblast proliferation, migration & transformation. It is recommended for use in IPF where forced vital capacity (FVC) is less than 80% of predicted. Though Pirfenidone and Nintedanib are both approved for use in IPF there is no recommendation for use in SSc-ILD. Results of ongoing Scleroderma Lung Study III and SENSCIS trial may guide us regarding their use in progressive and fibrotic variety.

Lung transplantation is an option in SSc-ILD patients who fail to respond to pharmacotherapy.

Rheumatoid Arthritis (RA)

ILD is seen in 20–30% cases of RA and is second leading cause of death. Development of ILD is associated with shortened survival. Smoking, older age, severe joint affection, high rheumatoid factor, and MUC5B gene association are the risk factors. Between 3–5% of patients showed ILD prior to RA diagnosis. Although RA is more common in females, RA-ILD occurs more frequently in males.

Pathogenesis of ILD in rheumatoid arthritis patients is not clear. Both rheumatoid factor and anti-CCP antibodies in high titers are linked to development of ILD. There is growing evidence suggesting perhaps rheumatoid arthritis starts in lungs. Because some patients with high anti-CCP antibodies do not have any articular manifestation. Cigarette smoking plays a role in inducing antibody production. Smoking may promote citrullination of lung proteins particularly those having HLA-DRB1 shared epitope.

HRCT scans in RA patients show a variety of patterns. UIP pattern is most common which occurs in 40–62% cases. NSIP is second most common pattern. Patients with UIP pattern on HRCT scan have worsened survival as compared with those having NSIP pattern. Therefore, all RA patients should undergo annual screening for ILD and if ILD is suspected HRCT scan be obtained.

Optimal therapy of RA-ILD is not known. Corticosteroids and immunosuppressants though widely used show limited benefit in RA-UIP. In NSIP or organizing pneumonia corticosteroids are the mainstay of therapy. Cyclophosphamide and azathioprine have been used with varying success. Mycophenolate mofetil is another option for treatment. In fibrotic group, immunosuppressants along with Nintedanib/Pirfenidone may be used.[4]

Five-year survival in RA-UIP patients is less than 50%. Lung transplant is a reasonable option for these patients.

Polymyositis/Dermatomyositis (PM/DM)

ILD is common and found in 25–45% cases of PM/DM. In 18–20% cases ILD presents prior to myositis. ILD markedly influences the disease course of inflammatory myositis. The strongest predictive factor is the presence of specific autoantibodies. Most important are JO-1 and KL-7 (associated with anti-synthetase syndrome) and MDA5 (associated with Amyopathic dermatomyositis). ILD associated with those Myositis specific autoantibodies

is severe, rapidly progressive, and non-responsive to treatment, and therefore have very poor prognosis.[4] Pattern of radiological involvement is NSIP, UIP, Cryptogenic organizing pneumonia or diffuse alveolar damage.

There are no large controlled trials to confirm the efficacy of treatments in ILD-PM/DM. Treatment is designed differently for chronic progressive and rapidly progressive cases. In RP-ILD treatment protocol is aggressive. About 20–40% of RP-ILD with anti-MDA5 patients die within 6 months of diagnosis even if treated intensively.

Corticosteroid is the mainstay of therapy along with steroid sparing immunosuppressants. Tacrolimus, mycophenolate mofetil, rituximab, and iv immunoglobulin also show benefit in some series.

Sjögren's Syndrome

ILD is associated in about 25% cases of Sjögren's syndrome and is an important extra glandular manifestation. Subclinical lung disease is even more frequent.

Association of lymphocytic interstitial pneumonia was first described in 1973. However, NSIP in its fibrosing variant is the most common manifestation. Organizing pneumonia, usual interstitial pneumonia, and lymphocytic interstitial pneumonitis are the other types of ILD. Dyspnea and cough are the main symptoms. Presence of anti-SSA is a predisposing factor.

The course of NSIP is unpredictable. It may progress, remain stable, reverse, or can be progressive and irreversible even with treatment. UIP pattern shows irreversible lung disease and has worse prognosis than NSIP.

Corticosteroid is the mainstay of treatment along with azathioprine and cyclophosphamide in NSIP. Immunosuppressive drugs do not benefit patients with UIP. There is no standard regimen of treatment. ILD is a significant cause of death.

Systemic Lupus Erythematosus (SLE)

In SLE pleuropulmonary involvement is not uncommon. But prevalence and severity of ILD is lower. Two important pulmonary manifestations of SLE are acute lupus pneumonitis and diffuse ILD. ILD is seen in about 3–8% of cases. The presenting symptoms are dyspnea, cough, fever, and pleuritic pain. These two conditions have major impact on morbidity and mortality. Therefore, it is essential to recognize and treat them properly. HRCT scan of chest and pulmonary function tests help in diagnosis.

Predominant lung pathology determines the treatment. High dose corticosteroids are the mainstay of treatment. Other agents such as cyclophosphamide, azathioprine, iv immunoglobulin, and rituximab are used if there is no prompt improvement. In acute lupus pneumonitis, weekly rituximab shows rapid improvement in PFT and symptoms.

Mixed Connective Tissue Disease (MCTD)

Pulmonary impairment is not evident clinically in early stage of disease. In a study published in 1976, 80% cases of MCTD had pulmonary disease but 69% were asymptomatic. The most relevant autoantibody associated is U1RNP.

Although MCTD is characterized by overlap features of SSC, PM/DM, and SLE the HRCT findings appeared remarkably homogeneous. NSIP is the most common pattern in MCTD. More than 50% of patients of MCTD have abnormality in DLco.[5] Lung fibrosis is associated with increasing mortality. About 47% patients respond well to corticosteroid 2 mg/kg/day monotherapy or combination of corticosteroid and cyclophosphamide.

Undifferentiated Connective Tissue Disease (UCTD)

Undifferentiated CTD defines clinical entities with features suggestive of CTD and yet do not meet the criteria of a specific single disease.[6] Patients with established UCTD lung involvement usually appears as a complication. About 88% cases have NSIP pattern. Lung involvement is associated with worse prognosis. Treatment is same as other CTD-ILD with NSIP pattern.

Conclusion

ILD is a frequent and serious complication of CTDs. Accurate and early diagnosis is challenging, but crucial to offer appropriate treatment. Lack of international guidelines to standardize clinical, radiologic, histopathologic, and biologic parameters is a great hurdle. There is no consensus regarding drugs to be used, duration of treatment, and optimal timing. Multi-disciplinary clinics involving pulmonologists, rheumatologists, radiologists, and pathologists are necessary to design treatment modalities for optimal outcome.

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CHAPTER

109 Superior Vena Cava Syndrome—Revisited

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Abstract

Superior vena cava syndrome is clinically manifested by dyspnea, facial swelling and facial edema, venous engorgement of neck and chest wall due to extrinsic, and/or intrinsic obstruction of superior vena cava causing reduction in venous return from head, neck, and upper extremities. It may develop quickly or gradually depending on underlying etiology which may compress, invade, or thrombose a thin-walled vessel in superior mediastinum.

Introduction

Superior vena cava syndrome (SVCS) is clinically manifested by dyspnea, facial swelling, and facial edema, venous engorgement of neck and chest wall due to extrinsic and/or intrinsic obstruction of superior vena cava causing reduction in venous return from head, neck, and upper extremities. It may develop quickly or gradually depending on underlying etiology which may compress, invade or thrombose a thin walled vessel in superior mediastinum.

Historically, it was first described in 1757 by William Hunter in patient of syphilitic aortic aneurysm.[1] Nearly two hundred years later Schechter described more than 200 patients of SVCS, out of which 40% were due to syphilitic aortic aneurysm or tubercular mediastinitis.[2] Subsequently, advances in antibiotics decreased infectious causes considerably and currently malignancy is the leading cause of SVCS.

Anatomy

It's large, valveless and thin walled vein formed by union of right and left brachiocephalic veins at first costal cartilage in superior mediastinum; traverses through middle mediastinum behind second costal cartilage and terminates into right atrium within pericardial sac at level of third costal cartilage. Azygos vein, which is main tributary enters at T4 level and drains upper lumbar and thoracic wall. It is surrounded by relatively rigid structures of thorax including sternum, trachea, right main bronchus, aorta, pulmonary artery, and perihilar and paratracheal lymph nodes. It's easily compressible by any space occupying process in surrounding. Its diameter is around 2 cm and length around 6–8 cm. Its low pressure vessel draining venous blood from head, neck, upper extremities, and upper thorax.

Pathophysiology

Superior vena cava can be partially or completely obstructed through:

- Extrinsically by benign or malignant tumors
- Intrinsically by thrombus or aneurysm
- Combination of both processes

Gradual obstruction ensures formation of collateral/s mainly through azygous vein, internal mammary veins, lateral thoracic veins, paraspinous veins, and esophageal venous network. It is manifested as engorged superficial

subcutaneous veins with diverted blood flow direction. Despite collateral systems, venous pressure is raised up to 300 mm of saline in severe cases.[3]

Etiology

Malignant Causes (60%)

- Lung cancer, small cell (SCLC), and squamous cell (50%)
- Non-Hodgkin lymphoma (5%)
- Other malignancies (5%)
- Metastatic tumor mostly from breast cancer
- Mediastinal germ cell tumors
- Hodgkin's lymphoma
- Thymoma

Benign Causes (40%)

- Intravascular devices including central venous access devices, pacemaker/defibrillator leads, etc.
- Benign tumors including teratoma and dermoid cyst
- Cardiac causes including pericarditis and atrial myxoma
- Vascular causes including aortic aneurysm, vasculitis (Behcet's syndrome)
- Infectious causes including tuberculosis, histoplasmosis, and syphilis
- Fibrosing mediastinitis due to prior irradiation

Malignant causes predominate, especially lung cancer including SCLC and squamous cell carcinoma owing to central predisposition.[4] In young males, lymphoma especially large cell variants like diffuse large B cell lymphoma, lymphoblastic lymphoma, and primary mediastinal lymphoma may cause rapidly progressing SVCS. Rarely germ cell tumors may be found in young males. In recent years prevalence of benign causes is on rise due to expanding use of central venous catheters.

Epidemiology

Right sided tumors tend to involve superior vena cava. SVCS develops in 5–10% of right sided tumors. Exact Indian data of SVCS is lacking but considering 5% of lung cancer and lymphoma incidence gives a rough estimate of around 5,000 cases per annum. As lung cancer has preponderance in males, malignant SVCS is also common in males while benign causes are equally distributed in both sexes. Most cases of SVCS are diagnosed between 50 and 70 years of age owing to high incidence of lung cancer in that age group.

Clinical Features

Signs and symptoms depend on the following:

- Degree, site, and rapidity of obstruction of superior vena cava
- Underlying etiology
- If malignant etiology then its subtype and overall tumor burden

Partial obstruction may not manifest clinically and patient may remain asymptomatic. Few subtle signs may go unnoticed. Gradually developing obstruction allows adequate time for collateral development delaying the manifestations to appear in advanced stages. Obstruction proximal and distal to azygous vein will exhibit differently.

The most common symptom of SVCS is dyspnea followed by neck and facial swelling/fullness of head.[5] Other symptoms include cough, arm swelling, chest pain, dysphagia, hemoptysis, epistaxis, dizziness, syncope, and lethargy. Symptoms may aggravate by bending forward or lying down due to obstruction to outflow of blood from head and neck. The most common sign of SVCS is venous distention of neck and chest wall followed by facial edema, cyanosis, plethora of face, and edema of arms in descending order of frequency.

Signs may progress through four stages which may considerably overlap:

- Due to increased venous pressure, swelling of neck, face, upper extremities manifests initially, which may be demonstrated through Pemberton's sign (though classically described in retrosternal goitre). Bilateral arms elevation above head for 2 minutes manifesting as above due to decreased venous outflow aggravating obstruction is considered as positive sign.
- Involvement of cardiorespiratory system may manifest as dyspnea, cough, and hoarseness and suggest severe airway and vascular obstruction. Risk of cardiac arrest and respiratory failure is high in patients receiving sedatives or general anesthetic agents.
- As venous stasis progresses, neurological symptoms manifest, including headache, dizziness, syncope, visual disturbances due to cerebral edema, which entails poor outcome. Seizure is more likely due to brain metastases rather than cerebral edema. Small

cell lung cancer with SVCS is more likely to have brain metastases than without SVCS.

- Life threatening manifestations include stridor (due to laryngeal edema which is poor prognostic sign), syncope without aggravating maneuvers, confusion, and hemodynamic instability. All of these require emergent intervention.

"Downhill" varices where direction of blood flow is from cephalad to caudal is indicative of esophageal varices due to collateral formation. Venous obstruction proximal to azygous vein leads to varices in upper third of esophagus in contrast to distal obstruction, which causes varices in entire length of esophagus.[6]

Life expectancy is unchanged in benign causes in contrast to malignant etiology, where it is dependent on tumor histology. Lymphoma has better survival than small cell lung cancer after irradiation and disease-specific treatment.

Investigations

SVCS is a clinical diagnosis with characteristics manifestations. Current treatment is directed toward underlying etiology. Hence, work up is individualized to ascertain etiology. The most commonly employed initial modality is chest X-ray, which shows superior mediastinal widening and right sided pleural effusion in around one-fourth patients. Pleural effusions are mainly exudative in nature and exceptionally chylous, especially in lymphoma.[7]

Contrast enhanced computed tomography (CECT) scan is a modality of choice, which delineates detailed anatomical information regarding superior vena cava and its tributaries with respect to other critical structures like trachea, bronchi, esophagus, and spinal cord. CT suggests reduced or absent opacification of central venous structures and collateral venous circulation.[8] Magnetic resonance imaging (MRI) is indicated only when CECT is contraindicated in renal dysfunction.

Integrated whole body positron emission tomography-CECT is the preferred modality of choice in lymphoma and lung cancer patients as it helps in complete staging, and hence intent of treatment (definitive vs. palliative).

Histopathological evidence of malignancy is essential and it may be obtained through endobronchial fine needle aspiration, CT guided needle biopsy, mediastinoscopy, or thoracotomy (if all other modalities fail). Mediastinoscopy and thoracotomy have minimum complications and high tissue yield.[9] Thoracocentesis in pleural effusion can also establish diagnosis in two-thirds of patients.

Management

Treatment Deciding Factors

SVCS treatment entails a judicious use of available measures on a case by case basis. There are no evidence-based guidelines or recommendations available. Various factors guiding the management decision algorithm include:

- Etiology
- Treatment responsiveness of the underlying disease
- Grade of severity
- Nature of underlying disease
- Overall prognosis
- Goals of therapy

Treatment Modalities

Overall treatment is a mix and match of various available modalities in individualized sequences and combinations. Various therapeutic modalities include nursing in semi-inclined position, securing the airway, fluid restriction, avoiding upper body cannulation, diuretics, inhaled oxygen, steroids, radiotherapy, chemotherapy, removal of the foreign body (viz., catheter), endovascular thrombectomy, intravascular pharmacological or mechanical thrombolysis, stent placement, oral or parenteral anticoagulation, and surgical venous bypass.

Treatment in Various Clinical Settings

SVCS with Life-threatening Symptoms

It is not uncommon to see aggressive malignancies like acute hematological malignancies and small cell lung cancer present with stridor, respiratory failure, or altered sensorium. It is a medical emergency.

Symptomatic Management

Place the patient in semi-inclined position and access lower limbs for venous cannulation. Following securing airway and addressing issues like dyselectrolytemia and tumor lysis syndrome (TLS), emergency endovenous recanalization (e.g., mechanical or pharmacologic thrombolysis and balloon angioplasty), and SVC stenting

should be the preferred modality depending on the availability of equipment and expertise. This will be accompanied by other supportive modalities including fluid optimization, diuretics, steroids, oxygen, and anticoagulation. If the SVCS is only due to stenosis without accompanying thrombosis, the role of anticoagulants is debatable.

Definitive Management

Before commencing definite management, an adequate tissue biopsy is must.[10] Steroids should be used carefully in lymphomas as they may melt the tumor jeopardizing the biopsy findings. They may also aggravate the tumor lysis syndrome, which is again another medical emergency, needing expeditious management. It includes treating the primary pathology by surgery, radiation, or chemotherapy depending on the type and extent of disease.

SVCS without Life-threatening Symptoms

Symptomatic Management

Symptomatic management is almost same in all non-emergent cases. Upper limb, neck, or subclavian cannulation should be avoided. Depending on the severity of symptoms, diuretics may be used to reduce venous congestion in SVC drainage area including brain. Fluid intake should be optimized to avoid worsening of edema and to overcome dehydration. This is even more relevant in cases likely to have TLS. Malignancy related SVCS is frequently associated with thrombosis as well as a risk of DVT; hence, anticoagulants should be initiated in all cases unless proved otherwise. Oxygen supplementation should be reserved for cases having respiratory compromise. Steroids are important component of chemotherapy in NHL, but caution should be taken about the risk of worsening TLS and should only be started after obtaining the tumor tissue biopsy. Use in cases other than NHL is questionable.[11]

Definitive Management

Since malignancy is the most common cause of SVCS. It is pertinent to discuss treatment in two parts: malignancy related and SVCS due to other causes.

Malignant SVCS: It incorporates treating the primary malignancy with surgery, radiation, or chemoradiation. In most cases, after this, SVCS disappears; however, in case of persisting symptoms, endovascular interventions or surgical venous bypass may be used. As an example, SVCS in case of a large thymoma may be corrected by surgical venous bypass. Non-Hodgkin lymphoma is a chemosensitive tumor. The most common subtype is diffuse large B cell lymphoma, if localized then treated with radiation therapy and in advance stages treated with chemotherapy mainly anti CD20 chimeric monoclonal antibody Rituximab in combination with cyclophosphamide, adriamycin, vincristine, and prednisolone. Responses are quick within 7 days. Patient must be watched and treated for tumor lysis syndrome. SCLC is chemosensitive and radiosensitive tumor. SVCS related to SCLC is treated with chemotherapy alone or in combination with thoracic irradiation. Response rates are to the tune of 73–93%.[12] Within 1–2 weeks relief from SVCS is achieved. Chemotherapy agents of choice are etoposide and platinum. Non-small cell cancer response rates with chemotherapy (59%) and radiation therapy (63%) are comparable.[13] Nearly one-fifth patients are destined to have recurrence from SVCS.

Non-malignant SVCS: The treatment is cause dependent. Most cases are iatrogenic due to some kind of catheter. They are managed with urgent removal of the catheter followed by anticoagulation. The rare cases due to chronic inflammatory processes may be managed by endovenous stenting. Overall survival in benign causes is unchanged if timely diagnosed and treated. Recent times have shown increase in use of central venous catheters, and hence superior vena cava thrombosis. It can be treated with streptokinase, urokinase, or recombinant tissue type plasminogen activator. Heparin and oral anticoagulants reduce progression of thrombus. Removal of catheter should be considered along with anticoagulation. In case of pacemakers, electrode wires should be changed.

Complications and Care of SVCS Treatment Modalities

Bleeding risk: Thrombolytic and anticoagulants are associated with significant risk of bleeding. Patients should be regularly monitored for the same.

Stent migration: Stent migration into the heart and pulmonary vasculature may be immediately life threatening. A high index of suspicion is warranted.

Pulmonary embolism: Tumor, thrombus fragment, or rarely a stent can embolize and cause a catastrophe.

Stent occlusion: Long-term anticoagulation is a need in a patient with a stent. Hence, its long-term safety in benign causes is questionable.

Tumor lysis syndrome: As explained earlier, it may be aggravated by the use of steroids. Hence, it again requires a high index of suspicion.

Conclusion

Superior vena cava syndrome may expedite to life threatening emergency if not treated urgently. Early institution of underlying etiology has curative potential in nonmetastatic solid malignancy, advanced lymphomas, and nonmalignant causes. Tissue diagnosis and appropriate imaging is essential in management of SVCS. Palliation of symptoms can be done with diuretics, steroids, stenting, and anticoagulation as indicated.

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CHAPTER

110 Asthma—COPD Overlap: Challenges in Diagnosis and Management

M Sabir

Abstract

As such overlap of asthma and COPD is not a new clinical condition but had been discussed since long in context with patients having obstructive airway disease, where it was difficult to decide whether it is asthma or COPD. Asthma-COPD overlap (ACO), previously referred as asthma-COPD overlap syndrome (ACOS), is characterized by persistent airflow limitation consistent with COPD, together with several distinguishing features of asthma.

Till date there is no universally accepted definition of ACO, but in recent past there is increasing recognition and stress on better diagnosis, management, and prevention of asthma-COPD overlap. It is difficult to define it as a single disease entity, as it is a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms. It has been observed that ACO patients as compared to asthma or COPD have more rapid decline in lung functions, frequent exacerbations, worsening quality of life, higher mortality rate, and are difficult to treat.

In this chapter, attempt will be made to discuss briefly salient features of ACO.

Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are two obstructive airway diseases, responsible for significant morbidity and mortality; creating serious global health problem. Although asthma and COPD are clinically two distinct disease entities, having diverse etiopathogenesis, management protocols, and response to treatment, but some features at some point are overlapping and compatible with both diseases leading to a mixed picture of overlapping clinical presentation and comorbidities creating difficulties in differentiating weather it is asthma or COPD. These patients are labeled as Asthma-COPD overlap (ACO); previously referred to as asthma-COPD overlap syndrome (ACOS).[1]

Definition

As such overlap of asthma and COPD is not a new clinical condition but had been discussed since long in context with patients having obstructive airway disease, where it was difficult to decide whether it is asthma or COPD.

As early as in 1961, Prof. Orie and colleagues proposed that all obstructive airway diseases, including asthma, emphysema, and chronic bronchitis, should be considered as different manifestation of a single disease with common genetic origins. Although it generated lot of controversy but discussion at different levels on this hypothesis (Dutch hypothesis) is still continue.[2,3]

In 1995, COPD guidelines from American Thoracic Society defined asthma, chronic bronchitis, emphysema, COPD, and other clinical situations having airflow limitation **(Fig. 1)**, and identified 11 distinct clinical entities related to obstructive airway diseases dominated by COPD and asthma and overlap between two or more conditions as depicted in **Table 1**.[4-6]

Further guideline developed for asthma and COPD had placed more emphasis on recognizing them as two distinct

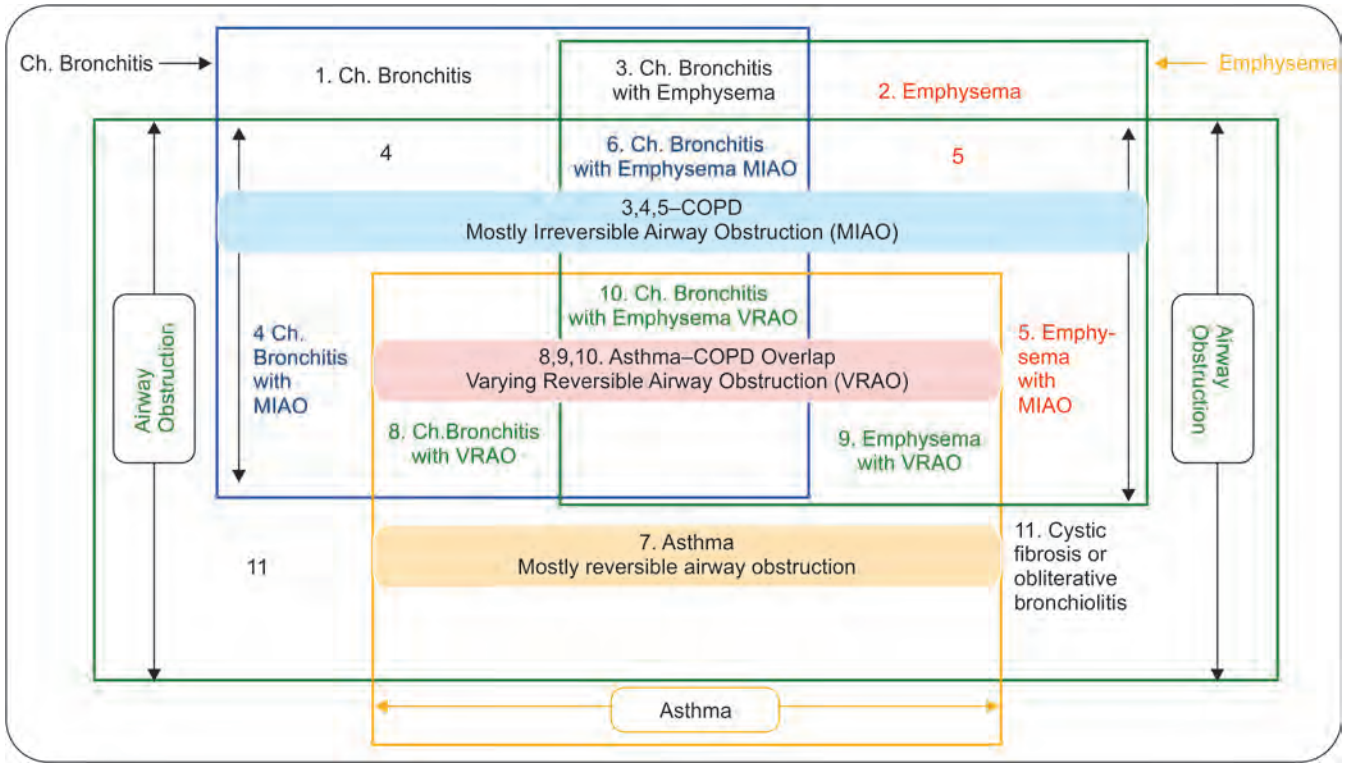

Fig. 1: Overlapping of clinical entities with obstructive airway diseases (non-proportional diagrammatic representation)
MIAO, mostly irreversible airway obstruction; VRAO, varying reversible airway obstruction

diseases where complete or incomplete reversibility of airflow obstruction is the defining characteristic. This is useful as it facilitate easier recognition of asthma and COPD, but obstructive airway diseases other than these two entities, for example, having ACO and others received less attention especially during clinical evaluation, management, and research.

In recent past there is increasing recognition and stress on better diagnosis, management, and prevention of asthma—COPD overlap.

'ACO,' also labeled as 'asthma + COPD' are terms used to collectively describe patients who have persistent airflow limitation together with clinical features that are consistent with both asthma and COPD.[1]

It is difficult to define it as a single disease entity, as it is a descriptive term for clinical use that includes several different clinical phenotypes reflecting different underlying mechanisms.

Till date there is no universally accepted definition of ACO. The description proposed by Global Initiative for Asthma (GINA) and the Global initiative for chronic Obstructive Lung Disease (GOLD) committees jointly created the term ACOS later renamed it as ACO, to much extent is of help as diagnostic tool for clinician, managing obstructive airway diseases.[1]

Others academic groups/associations, for example, Spanish Society of Pneumology and Thoracic Surgery (SEPAR), Roundtable Groups, Czech Republic guidelines, Australian Asthma management Handbook have offered different definitions of ACOS, based on persistent airflow limitation as assessed by spirometry and bronchodilator response; documented history of asthma and atopy, exposure to tobacco smoke and/or biomass burning, peripheral eosinophil count, fraction of NO in the exhaled breath (FNO) and IgE levels in different combinations.[8-13]

Salient practical features of the GINA/GOLD (2020) and other recommendations related to definitions and parameters of ACO, COPD, and Asthma are summarized in **Table 2**.

TABLE 1 Clinical entities with airway obstruction

Clinical entities ***(Prefix Nos. as per Fig. 1)***	***Definition***	***Presentation***
1. Chronic Bronchitis	Symptomatic cough and sputum daily for at least 3 months over 2 years	Persons with chronic bronchitis and/or emphysema without airflow obstruction are not classified as having COPD
2. Emphysema	Abnormal airspace enlargement	
3. Chronic Bronchitis with Emphysema	Usually occur together	
7. Asthma	Mostly reversible airway obstruction, airway hyper-responsiveness with bronchodilator responsiveness	
4, 5&6. COPD	Persistent airflow limitation	
4. Chronic Bronchitis	Usually occur together	MIAO
5. Emphysema		
6. Chronic Bronchitis with Emphysema		
8, 9&10. Asthma - COPD Overlap	Clinical features that are consistent with both asthma and COPD	Varying incompletely reversible Airway Obstruction
8. Chronic Bronchitis with (VRAO)	Some patients with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough	Difficult to differentiate patients with asthma whose airflow obstruction is not completely reversible from persons with Chronic Bronchitis and/or emphysema that have partially reversible airflow obstruction with airway hyperreactivity
9. Emphysema with (VRAO)	Some patients with asthma who have developed fixed airway obstruction may have abnormal airspace enlargement	
10. Chronic Bronchitis with Emphysema with (VRAO)	Some patients with these two disorders may have clinical asthma	
11. Diseases with known etiology or specific pathology	e.g., cystic fibrosis or oblitrative bronchiolitis etc.	

MIAO, mostly irreversible airway obstruction; VRAO, varying reversible airway obstruction

Prevalence and Morbidity of Asthma-COPD Overlap

Globally more than 339 million people are living with asthma; and 65 million people have moderate to severe COPD.[1,14]

Prevalence rates for ACO have been reported to be in the range between 9% and 55% of those with either diagnosis of asthma or COPD. This variation reflects the different criteria used by different investigators at different places in the world. Concurrent doctor diagnosed asthma and COPD has been reported between 15% and 32% with one or other diagnosis.[1]

In a systematic review and meta-analysis, based on the random-effects model, the pooled prevalence of ACO was found to be 2.0% in the general population, 26.5% among patients with asthma, and 29.6% among patients with COPD, whereas the prevalence of asthma-only was 6.2% and COPD-only was 4.9%.[16] In one of the study it has been reported to be more common amongst females & young population.[15,16]

Studies suggest that patients having asthma-COPD overlap have frequent exacerbations,have poor quality of life,a more rapid decline in lung function, higher mortality,higher prevalence of comorbidities and greater use of healthcare resources as compared with patients with asthma or COPD alone.[1,7,17-19]

Risk Factors for Asthma-COPD Overlap

Cigarette smoking: Tobacco smoke may modify the small airway inflammation and remodeling associated with bronchial asthma. It is suggested that FEV1 decline in subjects with ACO is more due to air way inflammation so caused than the pulmonary emphysema.[20]

TABLE 2 Parameters in asthma, ACO, and COPD

Parameters	*Asthma*	*ACO*	*COPD*
Age in years	Any age	40 or above 40	Usually above 40
Exposure to tobacco smoke	Usually none	≥5 pack years or equivalent	≥10 pack years or equivalent
Exposure to Biomass burning	Usually none	Yes especially in women	Yes
Past medical history of "atopy" Asthma	Asthma (doctor diagnosed) allergies	Asthma (doctor diagnosed) Allergies	Usually none of these
Symptoms	Vary over time. Often triggers by exposure to dust or allergen, exercise change in weather, emotions, etc.	Usually persistent but may vary	Chronic, continuous, usually progressive
Course of disease	Often improves with treatment or spontaneously. In few patients may persists because of development of fixed airway obstruction	Partially or fully improve with treatment, slowly progressive, needs high doses of treatment	Usually progressive
Post bronchodilator response in FEV1	Almost always >12% & 200 mL increase Frequently >12% & 400 mL increase	Usually >12% and 200 mL increase Rarely >12% and 400 mL increase	Usually <12% and 200 mL increase in FEV1
X-ray chest	Usually normal	Same as COPD	Hyperinflation and other changes of COPD

Atopy: There is no direct evidence that atopy alone causes pulmonary emphysema or the chronic bronchitis typical in COPD. However, α1-anti-trypsin deficiency in airways may increase the likelihood of developing asthma. Some of the COPD patients may manifest allergic symptoms, but it is not clear whether this represents late-onset atopy or asthma.[21,22]

Age: Age is not definite risk factor for ACO. Decline in lung functions with ageing is a normal phenomenon, may create confusion while screening for ACO. Adults with asthma, especially if they are smokers, lose FEV1 more rapidly as compared to nonsmoking asthmatics. In one of the study patients with asthma tend to be younger (mean age: 51.3 years) than those with ACO (mean age: 66.7 years), and those with COPD (mean age: 72.4 years).[23]

A history of childhood or adult-onset asthma should be a major criterion for ACOS. As the prevalence of COPD increases after age 40 years, an age cutoff of 40 years is reasonable to improve the accuracy of the diagnosis.[21]

Pathogenesis/Mechanisms Underlying Asthma-COPD Overlap

Asthma and COPD are having distinct pathophysiology. ACO shares several pathological characteristics with both Asthma and COPD as it shares some of the clinical and spirometric parameters, but the mechanism underlying this overlap is not clear.

Whether ACO is simply the coexistence of asthma and COPD or a distinct phenotype related to fundamental pathogenic mechanisms of asthma and COPD remains to be determined and the mechanisms underlying the overlap between asthma and COPD remain controversial.

"Dutch hypothesis" proposes that asthma and COPD are manifestations of the same basic disease process, where asthma predisposing to COPD in due course of time in the process of aging; where ACO may be a stage of this disease process. On the contrary British hypothesis suggests that asthma and COPD are two distinct diseases generated by different pathophysiological mechanism.[2,7,24,25]

As depicted in **Figure 2**, pathogenic processes in asthma are known to include mast cell-mediated bronchoconstriction, inflammation due to local antibody production, and eosinophilic inflammation. These are mediated by complex processes involving number of different messenger molecules, including histamine, cysteinyl leukotriene, prostaglandin D2, interleukins (ILs), and chemokines ultimately producing airway obstruction.[25,26,28,29]

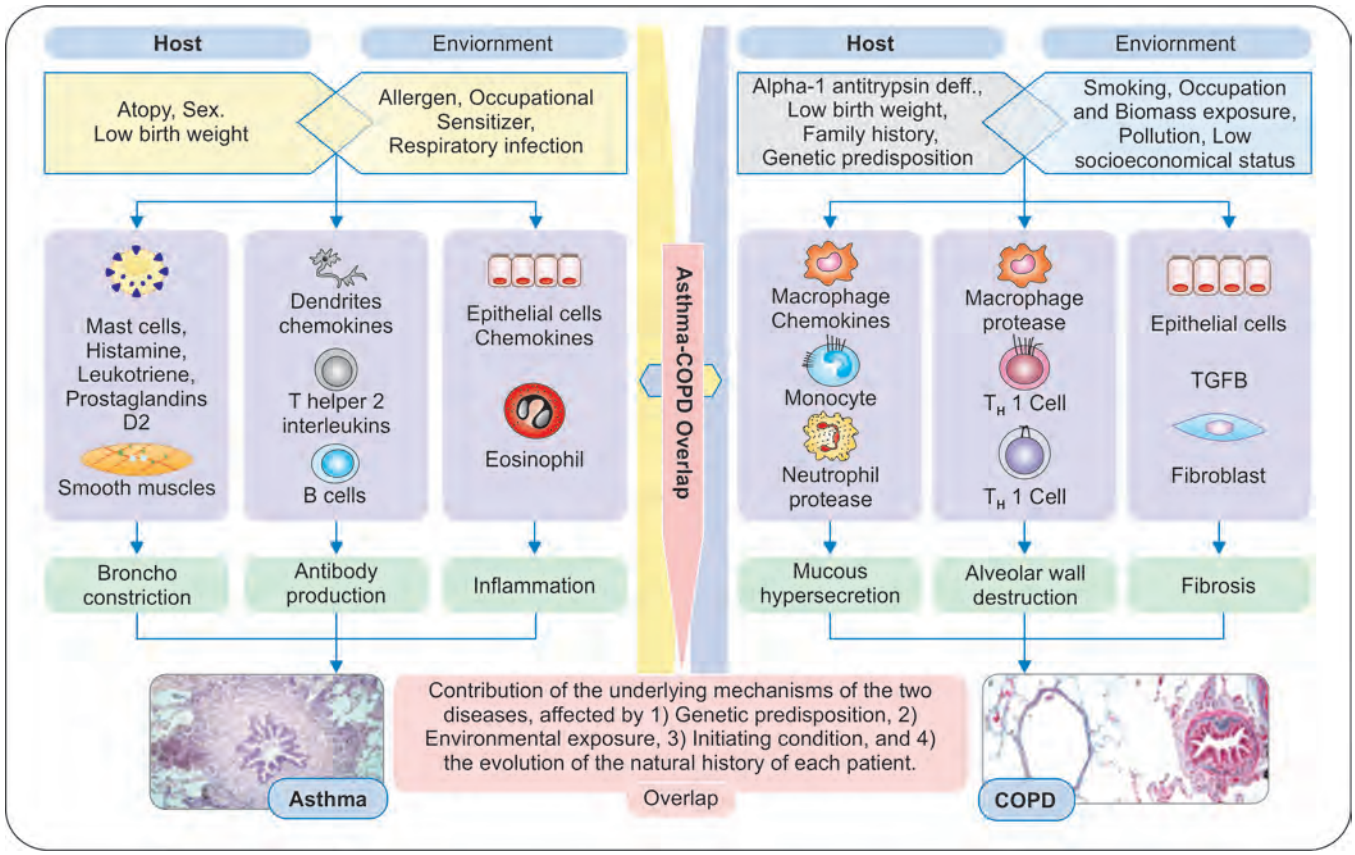

Fig. 2: Pathology of asthma, COPD, and their overlap[27]
TGFβ, tumor growth factor β; TH1, T-helper 1; TC1, type 1 cytotoxic T cells

In majority of asthmatics airflow obstruction so produced is typically reversible but in patients suffering from severe asthma it may partially or incompletely reversible (fixed airway obstruction) producing persistent airflow limitation.[30,25]

Inflammation in COPD patients is dominantly neutrophilic where involvement of inflammatory cells and messenger molecules, for example, epithelial cells, macrophages, chemokines, monocytes, neutrophils, T-helper cells, and type 1 cytotoxic cells typically producing bronchoconstriction, mucus hypersecretion, alveolar wall destruction, and fibrosis. In contrary to asthma airflow limitation in COPD is not completely reversible[30,31] **(Fig. 1)**.

In patients with overlap between asthma and COPD, the extent of the contribution of the underlying mechanisms of the two diseases may vary significantly amongst individuals, affected mainly by genetic predisposition, environmental exposure, the initiating condition, and the evolution of the natural history of each patient.

As in both asthma and COPD, the pathogenic processes are triggered by interactions between host and environmental factors; the same assumption is made in patients having ACO. In addition to the multiple risk factors as shown in **Figure 2**, evidence suggests that asthma itself is an independent risk factor for COPD especially amongst adults who had childhood asthma.[7,32] Tucson cohort study observed that asthmatic subjects were 12.5 times more likely to develop COPD than healthy individuals; and about half of the older patients with obstructive airway disease have overlapping diagnoses of both asthma and COPD.[33]

It has been observed that some asthmatic having long exposure to tobacco smoke and/or other environmental pollution, for example, biomass fuel smoke have more chances to develop COPD (asthma-COPD overlap). There

are conflicting data regarding the genetic component underlying ACO.[7,34-36]

It has been observed amongst longstanding asthmatics, that about 20% patients develops fixed airway obstruction, and by enlarge it is not reversible with bronchodilators. This group of patients with fixed airway inflammation and eosinophilic inflammation are often labeled as suffering from COPD and they are denied inhaled corticosteroids (ICS), on the contrary they may have ACO and expected to be benefited by ICS.[37,38]

Assessment

There is paucity of research data related to ACO, as these patients have been systematically excluded from clinical studies. Whatever few reports available are not exactly defining underlying mechanism, prevalence, clinical presentation, diagnosis, and management of ACO.[39]

Dyspnea, cough, expectoration, wheezing, and chest tightness are common symptoms in asthma and COPD, with some qualitative and quantitative variation; are also present in ACO on similar pattern. Patients of ACO usually experiences reduction in day-to-day activities, frequent need for reliever drugs, and recurrent acute exacerbations despite adherence to standard pharmacotherapy. Pattern of other parameters in clinical evaluation depends upon the dominance of the overlapping disease asthma or COPD **(Table 3)**.

Broad expected pattern of history and clinical evaluation of the patient suffering from obstructive airway diseases (Asthma, COPD, and ACO) have been summarize in **Table 3**.[1,21]

Investigations

Spirometry

Persistent expiratory airflow limitation with or without bronchodilator reversibility, as assessed by spirometric data are considered to be strongly suggestive of ACO[1] **(Table 4)**.

Biomarkers of asthma: Mostly used in research as there is little agreement about the most appropriate cutoff point for making a diagnosis.[11,40]

Blood or sputum eosinophil count—Measurement of blood eosinophil is well standardized and reproducible as compared to sputum eosinophil counts and are reported to be high in COPD patients with asthmatic features from 2% to 5%, or an absolute cell count 300 cells/uL^{-1}.

Fractional exhaled nitric oxide (FeNO)—Measurements of FeNO is another biomarker of asthma which is increased in asthma [50 parts per billion (ppb) in non-smokers].

Serum IgE titers—Levels are higher amongst asthmatic patients.

Carbon monoxide diffusing capacity (DLco): DLco is usually normal or low in ACO as compared to asthma (normal) and COPD (<80% predicted). DLco is a good indicator of functioning of gas exchange mechanism of lung, which is deranged in COPD.

Imaging Studies

X-ray chest—As such X-ray chest is not of much diagnostic significance for obstructive airway diseases (OAD) but of immense value in excluding other respiratory disease, for example, respiratory infections (especially tuberculosis), cystic fibrosis, obliterative bronchiectasis included in differential diagnosis of OAD.

CT scan chest—Valuable in assessing airway wall thickness and damage to peripheral lung tissues as seen in emphysema.

Blood tests—CBC, blood sugar, liver, and renal function studies to rule out systemic diseases included in differential diagnosis of OAD.

Sputum examination—For AFB and eosinophil count.

Other patho-biochemical investigations—For inflammatory cells, mediators, modulators, airway wall's smooth muscles and basement membrane studies through bronchoscopy biopsy and lavage are practically less of diagnostic value, are useful for research.

Diagnosis

Although a consensus on the exact definition and the diagnostic criteria of ACO remains elusive, the recent report of the GINA and the GOLD has highlighted a stepwise approach for the diagnosis of ACO[1] **(Table 2)**.

On the basis of detailed medical history, physical examination, and other investigations (as already described) asthma and COPD and possibility of extend of their overlap can be assessed **(Table 3)**.

Subsequently, diagnoses are confirmed through spirometric measures, including reversibility of airflow limitation. Post-bronchodilator (BD) increase in forced expiratory volume in 1 second (FEV1) ≥12% and ≥200 mL

TABLE 3 History and clinical evaluation of the patient suffering from asthma, COPD, and ACO

Parameters	***Obstructive Airway Diseases***		
	Asthma	***ACO***	***COPD***
History			
Symptoms—Dyspnea, cough, expectoration, wheezing, chest tightness			
Symptoms: • Variability • Triggers • Improvement	 • Vary over time & intensity • Allergen, seasonal, exercise, laughter • Spontaneous/quick with bronchodilator	 • Intermittent or episodic • Allergen, seasonal, exercise • Spontaneous with bronchodilator	 • Dyspnea persisted for most days. May have been preceded by cough/sputum • Nil • Limited response with bronchodilators
Age	<40 years	>40 years; 50–65 years	≥65 years if not younger
Sex	Adult women > Adult men	Slightly more amongst men	Men >women
Smoking habit and/or exposure to biomass	Nonsmoker or smokers (<5 pack years)	>10 pack-years and/or exposure to biomass or other toxic exposure	>10 pack-years and/or exposure to biomass or other toxic exposure
Obesity	More frequent	+/–	Usually not obese
Atopy/Rhinosinusitis/Asthma (Dr's. diagnosed)	Atopy/Rhinosinusitis present	Atopy/Rhinosinusitis/Asthma present	Usually no past or current diagnosis of asthma or atopy
Low birth weight	—	May have	May have
Respiratory illness specially infection, e.g., tuberculosis	Usually not	May have	May have
GERD	Present	Present	Present
Use of reliever drugs	Usually not frequent	Frequent	More frequent multiple daily doses
Limitation of exercise	Exercise not limited in between attacks	Limitation of exercise	Exercise significantly limited
Dependence	Patients with severe disease may frequently use Oral corticosteroid	Frequent use of oral corticosteroid	Oxygen
Hallmark problem	Frequent exacerbations	Very frequent exacerbations >COPD alone	Exacerbations and exercise intolerance

Based on clinical evaluation if suspected other alternative cardiorespiratory diagnosis such as heart failure, bronchiectasis and chronic bronchitis, and other forms of lung disease such as interstitial lung disease should be considered.

TABLE 4 Spirometric variables in asthma COPD overlap

Spirometric variable	***Asthma COPD overlap (ACO)***
Post-bronchodilator values	
Reduced FEV1/FVC (less than lower limit of normal, or less than 0.7 (GOLD))	Required for diagnosis of ACO
FEV1 80% predicted or more	Compatible with mild persistent airflow limitation if post-BD FEV1/FVC is reduced
Increase in FEV1 (12% or more) and 200 mL from baseline (reversible airflow limitation)	Common and more likely when FEV1 is low
Increase in FEV1 more than12% and 400 mL from baseline (marked reversibility)	Compatible with ACO

ACO: asthma COPD overlap; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: global initiative for obstructive lung disease

TABLE 5 Drug treatment of aqsthma, COPD and asthma—COPD overlap

Pharmacotherapy	
Bronchodilators	
A. Beta 2 agonists	***B. Anticholinergic or Anti-muscarinic agents (AMA)***
• **Short acting (SABA)**	• **Short acting (SAMA)**
– *Salbutamol*	– *Levosalbutamol* – *Ipratropium bromide*
– *Terbutaline*	– *Fenoterol* • **Long acting (LAMA)**
– *Metaproterenol*	– *Tiotropium Bromide* – *Oxitropium Bromide*
• **Long acting-(LABA)**	– *Glycopyrronium Bromide* – *Aclidinium*
– *Formoterol*	– *Formoterol inhalation sol.* – *Darotropium* – *Dexpirronium*
– *Salmetrol*	– *Indacaterol* – *Umeclidinium* – *QAT-370*
– *Vilanterol*	– *Olodaterol* – *TD-4208*
– *Carmoterol*	– *Milveterol* ***C. Phosphodiesterase inhibitors***
– *BI-1744-CL*	– *PF-00610355* • **Methylxanthines**
– *LAS-100977*	– *Theophylline* – *Doxofylline*
	– *Acebrophylline* – *Aminophylline*
Anti-inflammatory	
A. Corticosteroids	***E. Anti-IgE Antibody***
• **Inhaled (ICS)**	– *Omalizumab*
– *Beclomethasone*	– *Budesonide* ***F. Anti-cytokine asthma therapies***
– *Flunisolide*	– *Triamcinolone* – *Pascolizumab (anti IL4)*
– *Fluticasone*	– *Ciclesonide* – *Mepolizumab, & SCH55700 (anti IL5)*
– *Mometasone*	– *Infliximab, Adalimumab and Golimumab (anti TNF-a)*
• **Systemic-Oral (OS), IV/IM**	– *IMA-638, CAT-354, and AMG 317 (anti-IL-13)*
– *Prednisolone*	– *Hydrocortisone* – *MT203 (Anti-GM-CSF)*
– *Methyl prednisolone*	– *Deflazacort* – *Anti-IL-25 (IL-17E), IL-25, IL-33, and TSLP*
B. Anti-leukotrienes	– *Anti -IFN-g, -IL-9, -IL-17, and -IL-27*
– *Zafirlukast*	– *Montelukast* ***G. Toll-like receptors (TLRs) agonists***
– *Probilukast*	– *Pranlukast* – *CpG oligodeoxynucleotide of 1018 ISS (a TLR9 agonist)*
– *Tomelukast*	– *AZD8848 (a TLR7 agonist)* – *MPL® (a TLR4 agonist)*
• **5-lipoxygenase inhibitor**	– *VTX-1463 (a TLR8 agonist)* – *CRX-675 (a TLR4 agonist)*
– *Zileuton*	– *1018 ISS & QbG10 (TLR9 agonists)*
C. Mast cell stabilizers	***H. Immunomodulators & Antimetabolites***
– *Cromolyn sodium*	– *Ketotifen* – *Methotrexate* – *Gold salt (oral auranofin)*
– *Nedocromil*	– *Troleandomycin* – *Hydroxychloroquine*
D. Monoclonal antibodies against	– *Dapsone* – *Gamma globulin (IV)*
• **IL-4 & IL-13**	– *Cyclosporine*
– *Dupilumab*	– *Lebrikizumab* ***I. Phosphodiesterase-4 inhibitors***
	– *Roflumilast*
Other	
• **Drugs for smoking cession**	• **Vaccines**
– *Nicotine replacement treatments*	– *NTHi oral immunotherapeutic (HI-164OV) against*
– *Bupropion -Varenicline*	– *Haemophilus influenzae*
– *Nicotine vaccines*	– *Pneumococcal vaccine -Influenza vaccine*
• **Antimicrobial**	• **Mucoregulators**
– *Azithromycin*	–*Carbocisteine*
– *Azole antifungal agents, itraconazole*	• **Management of comorbidities**

Reliever drugs—SABAs, SAMA, *Non selective β_2 agonist*-Adrenaline & other Catecholamines, I.V. corticosteroids & theophylline & aminophylline.
Controller drugs—all other bronchodilators & anti-inflammatory drugs.

from baseline is a common feature in ACOS patients, particularly if they had lower FEV1. Post-BD increase in FEV1 of ≥12% and ≥400 mL from baseline is also considered as a compatible factor for the diagnosis of ACOS[41] **(Table 4)**.

Treatment

Pharmacological and non-pharmacological treatment options available for asthma and COPD are used to treat ACO also depending upon the dominating disease in the overlap; asthma or COPD. Till date definite specific management protocol for treating ACO has not been evolved. Despite this, there is a common opinion among specialists that patients with characteristics of overlapping asthma and COPD should be considered and treated differently from those with COPD.

Appropriate pharmacological and non-pharmacological treatment **(Table 5)** considering most effective doses, drug delivery, compliance, affordability, availability, as far as possible free from toxic side effects and patient-friendly therapy be started after due consideration for:

- There are broad spectrum drugs, for example, bronchodilators, corticosteroids, and antibiotics and narrow spectrum drugs, for example, leukotriene receptor antagonists (LTRAs) and monoclonal antibodies, such as omalizumab, to treat inflammatory obstructive airway diseases **(Table 4)**. Depending upon the predominating overlap of asthma or COPD, they can be used in different combinations.
- ACO patients need aggressive treatment with combination of appropriate bronchodilator and optimal dose of inhaled corticosteroids (ICS).
- Monotherapy with ICS or bronchodilators should be avoided.
- ICS is essential in treatment to prevent exacerbations in future.
- Triple therapy with long-acting beta agonist (LABA) + long-acting muscarinic antagonist (LAMA) + ICS may be considered for more severe patients or patients having recurrent exacerbation.
- Additional COPD treatment as per guidelines should be given according to patient's requirement.
- Some COPD patients continue to smoke or those who smoke and have asthma have poor response with ICS; in these patients theophylline, leukotriene modifier, roflumilast (used as per clinical status of the patient) are good add on drugs.
- Avoid maintenance oral corticosteroids.
- Non-pharmacological treatment should be considered as in asthma and COPD:
  - Avoidance/exposure of allergens, asthma triggers, tobacco smoke, biomass fuel and occupational and environmental toxins
  - Rehabilitation—physiotherapy and psychotherapy
- Bronchial thermoplasty may be considered in selected cases.

Future Research

There is need for better definition, recognition, safe and effective treatment through research on better understanding of pathophysiology, biomarkers, mechanism in larger population having respiratory manifestation of airflow limitation. Most clinical trials and research are focused on asthma and COPD excluding ACO and other airway diseases. There is need to diversify this trend.

Conclusion

Asthma and COPD both are basically inflammatory obstructive airway diseases dominantly involving upper or lower airways, of course with little difference in etiopathogenesis, type of inflammation and involvement of other parts of lungs and some systemic manifestation, may possibly part of same inflammation with different phenotype/endotype. Some patients of asthma and COPD (Chronic bronchitis + airway obstruction with or without emphysema) may have some overlapping manifestation of both the diseases; and are labeled as asthma-COPD overlap-ACO.

In coming time probably management of inflammatory obstructive airway diseases will be individualized for each patient depending upon the presence of quantum of chronic bronchitis, emphysema, asthma (atopy/allergy) and resultant inflammation leading to airway obstruction and manifestation of split over of airway inflammation.

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CHAPTER

111 Advanced Respiratory Failure

Arjun Khanna

Abstract

The etiology of advanced respiratory failure is varied and it is usually secondary to end stage respiratory diseases, which can stem from the lung parenchyma, chest wall, airways, and the pulmonary vasculature. Chronic respiratory failure (CRF) is defined as partial pressure of oxygen less than 60 mm Hg or partial pressure of carbon dioxide greater than 50 mm Hg, while breathing air at sea level. Respiratory failure in many respiratory diseases often starts during sleep. Thus, it is very important to evaluate the nocturnal saturation in patients with chronic respiratory diseases. Any features of SDB should raise an alarm in the physicians mind, and these patients should be subjected to nocturnal oximetry studies or full blown sleep studies. The management involves treating the underlying respiratory disease properly and offering rehabilitation and support in the form of oxygen, noninvasive ventilation, and pulmonary rehabilitation.

Introduction

Advanced or chronic respiratory failure (CRF) is a common and challenging problem faced by physicians. The etiology of advanced respiratory failure is varied and it is usually secondary to end stage respiratory diseases, which can stem from the lung parenchyma, chest wall, airways, and the pulmonary vasculature. Classically CRF is classified into hypoxemic and hypercapnic varieties. Often, patients have an overlap of both the varieties and it is not uncommon to see patients suffering from classical hypoxemic respiratory failure (e.g., interstitial lung disease—ILD), developing hypercapnia, during the course of their illness, owing to variable airway, and chest wall involvement, as the disease advances. Vice versa, also holds true as hypoxemia without hypercapnia, may be the dominant feature of chronic airways diseases such as chronic obstructive pulmonary disease (COPD) and bronchiectasis, where one usually expects to encounter hypercapnia.

Definition

The definition of this entity is based on arterial blood gas analysis. CRF is defined as partial pressure of oxygen (O_2) less than 60 mm Hg or partial pressure of carbon dioxide (CO_2) greater than 50 mm Hg while breathing air at sea level.[1] It is often, not prudent, to look for water tight compartments between hypoxemia and hypercapnia, as both often coexist in a single patient, and the erstwhile differentiation into type I and type II respiratory failure becomes more and more redundant.

Etiology

Advanced respiratory failure can arise from chronic malfunction of any of the compartments of the respiratory system. Common etiologies associated with CRF include:

- Chronic airways diseases—COPD, bronchial asthma, asthma-COPD overlap, bronchiectasis, cystic fibrosis.
- Pulmonary parenchymal disorders—Interstitial and diffuse parenchymal lung disorders, sequel

of respiratory infections such as acute respiratory distress syndrome (ARDS) and coronavirus disease (COVID-19).

- Chest wall disorders—Neuromuscular disorders including myopathies and dystrophies, kyphoscoliosis.
- Pulmonary vascular disorders—Chronic thromboembolic and other forms of pulmonary hypertension (PH), pulmonary vasculitis, pulmonary AV malformations.
- Sleep disordered breathing—SDB, which includes obstructive sleep apnea and its overlap with other chronic respiratory disorders.
- Disorders of respiratory control—Chronic hypoventilation syndromes, spinal cord and brainstem injury, some toxins and poisonings.

Clinical Features, Diagnosis, and Evaluation

The diagnosis of CRF is often delayed and patients with chronic lung disorders often present for the first time to the respiratory clinic, when they can only be offered condolences and palliation. A very important reason, why this happens is that patients with chronic respiratory diseases often decrease their activity due to increasing dyspnea. As the patient becomes more and more bed bound, the underlying disease condition often increases to an extent that the room air PO_2 falls below 60 mm Hg and pCO_2 rises above 50 mm Hg, without the patient or the caregivers realizing it.

Respiratory failure in patients with chronic respiratory disorders first sets in during sleep.[2] During sleep, there are multiple reasons of increase in hypoxia. The loss of sympathetic drive, pooling of secretions, nocturnal bronchoconstriction, and upper airway collapse, all add to nocturnal hypoxia. Patients with chronic hypoxia, function on the steep portion of their oxygen dissociation curve and tend to develop very severe hypoxia due to nocturnal changes, which take place during normal sleep. These changes have no effect on the saturation of normal people during sleep, but, in patients with long standing hypoxia, this sleep associated desaturation is often the first step in the development of CRF. These changes are often more pronounced in patients who have obstructive sleep apnea or other forms of sleep disordered breathing (SDB). The presence of SDB adds fuel to fire and pushes these patients toward frank respiratory failure.

Thus, it is very important to evaluate the nocturnal saturation in patients with chronic respiratory diseases. Any features of SDB should raise an alarm in the physicians mind, and these patients should be subjected to nocturnal oximetry studies or full blown sleep studies, as per situation. If respiratory failure is picked up during sleep and treated, the progression of these patients to frank respiratory failure can often be delayed.

Once a patient develops frank respiratory failure, he may develop frank cyanosis, fatigue, anxiety, confusion, and hypoxia. Rapid shallow breathing is often seen in patients with respiratory failure due to diseases such as ILD, wherein, patients are accustomed to breathing at very high respiratory rates. Tripod position, which implies, using limbs to support the chest wall is often seen in patients with advanced airways diseases. Cachexia and muscle wasting are ominous clinical signs in these patients, and signify advanced disease. Patients with hypercapnic predominant respiratory failure are often suffused and plethoric due to the vasodilatory effects of CO_2. Chronically elevated CO_2 levels can cause mental blunting and these patients develop subtle mental function decline, which is often overlooked.

Laboratory evaluation in these patients should be aimed at, finding the reason of CRF, if not already known. Basic evaluation should consist of a good quality HRCT Chest, 2D echo, arterial blood gas (ABG) analysis, complete pulmonary function testing including spirometry, lung volumes, and diffusion capacity. Six-minute walk test is a vital tool, which is often not done in clinical practice and provides important information regarding prognosis and response to drugs, oxygen, NIV, etc. in these patients. A very important clue in the ABG, which hints toward the development of CRF, is elevated bicarbonate levels. Bicarbonate levels more than 27 mmol/L represent a physiological response to persistently high CO_2 levels.[3] Any patient with chronic lung disease with high bicarbonate levels on ABG must be viewed with suspicion, and full CRF work-up protocol initiated.

Management

Treatment of underlying cause is not uncommon to see patients developing CRF due to suboptimal treatment of the underlying lung disease. The treatment modalities for many lungs are improving and providing hope to many such patients. A few path breaking treatment options

which are changing the face of many advanced lung diseases include:

Airway diseases: Airway diseases are among the most important and common causes of CRF in our country. One of the most important reasons why these patients reach the stage of CRF is avoidance of proper bronchodilator therapies. For COPD, excellent long acting bronchodiltaors are available. Newer anticholinergic agents such as glycopyrronium and umeclidinium, improve lung function, decrease exacerbations, and improve mortality in patients with COPD. Lung volume reduction surgery, bronchoscopic vapor ablation, etc. are newer modalities for treatment of advanced COPD, which can add years to a patient's life. For patients with advanced bronchial asthma, the key is to differentiate between Th1 and Th2 mediated inflammation. Th2 predominant patients respond to biological therapy, whereas, Th1 predominant patients may be offered bronchial thermoplasty, which is now readily available in India. For patients with advance bronchiectasis, the emphasis should be on airways hygiene and finding out the cause of bronchiectasis to personalize the therapy.

ILD: ILDs are being increasingly recognized as an important cause of CRF in our country. Owing to the more frequent usage of HRCT chest, we are picking up more ILD patients, than ever before. The first step of treating CRF in these patients is to first find out the reason of the ILD. Grossly, the ILDs may be divided into UIP (usual interstitial pneumonia) and NSIP (nonspecific interstitial pneumonia). UIP pattern on HRCT with any reason constitutes idiopathic pulmonary fibrosis. The diagnosis of IPF is associated poor outcomes. Currently approved therapies for IPF include Nintedanib and Pirfenidone, which modestly decrease lung function decline. For the NSIP, varieties of treatment would depend upon the underlying reason for ILD (sarcoidosis, hypersensitivity pneumonitis, connective tissue related), with most patients receiving a cocktail of oral steroid and immunosuppressant agents. Patients who present with frank CRF may be refractory to any kind of drug therapy and can only be offered oxygen therapy and pulmonary rehabilitation.

Pulmonary vascular disorders: PVDs are a group of challenging diseases to treat. Many of the advanced agents used to treat PH are still not available in the country, along with surgical options like pulmonary endarterectomy, which finds almost no takers in India. Riociguat is a newer agent, which is used to treat patients with chronic thromboembolic PH.[4] Most patients with group 3 PH are treated only with oxygen therapy and should not be offered any of the pharmacological agents for treatment of PH, as this might increase the VQ mismatch and worsen the respiratory failure. Like ILD, many patients with CRF due to advanced pulmonary vascular disorders, may only be candidates for pulmonary rehabilitation and lung transplantation (LT).

Oxygen therapy: Oxygen therapy may be the only treatment option left for many patients with advanced CRF. Oxygen relieves the hypoxic vasoconstriction and improves the VQ mismatch. Survival benefit in CRF has only been demonstrated in CRF in patients with advanced COPD. The indication of oxygen therapy in other reasons of CRF has been extrapolated from its use in COPD. Use of injudicious oxygen therapy in patient with underlying hypercapnia should be avoided. Uncontrolled oxygen therapy in such patients might actually be counterproductive and worsen hypercapnia. In many patients with hypercapnic respiratory failure, oxygen may have to be given with noninvasive ventilation (NIV). The classical indications for use of domiciliary oxygen therapy in patients with advanced COPD include:

- Arterial oxygen tension (PaO_2) less than or equal to 55 mm Hg, or a pulse oxygen saturation (SpO_2) less than or equal to 88%.
- PaO_2 less than or equal to 59 mm Hg, or SpO_2 less than or equal to 89%, if there is evidence of cor pulmonale, right heart failure, or erythrocytosis (hematocrit >55%).

For patients with normal awake oxygenation, oxygen may be prescribed during sleep if any of the following occurs during sleep: the PaO_2 is 55 mm Hg or less, the SpO_2 is 88% or less, the PaO_2 decreases more than 10 mm Hg, and/or the SpO_2 decreases more than 5% with signs or symptoms of nocturnal hypoxemia (e.g., impaired cognitive function, morning headaches, restlessness, or insomnia).[5]

NIV: NIV is an important tool used to treat various forms of CRF. NIV revolves around giving an inspiratory and an expiratory pressure support to the lung. The IPAP, takes care of the hypercapnia and the EPAP, opens the upper airways and recruits and opens the smaller airways and

the alveolar air sacs. NIV usage is vital in patients with CRF, due to chest wall disorders including myopathies and kyphoscoliosis. Any form of CRF, which has a component of hypercapnia, may be benefitted to some degree, by using NIV. NIV also unloads the respiratory muscles and improves oxygenation. Specific criteria are used for initiating NIV in patients with CRF due to various disorders.[6,7] However, the crux of the matter is to pick up nocturnal respiratory failure early in patients and offer them NIV early so that optimal benefits of NIV may be utilized.

Pulmonary rehabilitation (PR): PR is a broad therapeutic concept. It is defined by the American Thoracic Society and the European Respiratory Society as a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise, training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease, and to promote the long-term adherence to health-enhancing behaviors."[8]

PR can be utilized to help all kinds of patients with CRF. It is often overlooked, and we physicians tend to overlook this aspect of patient care, and focus most of our energies on pharmacotherapy only. PR programs include, exercise therapy, nutritional counseling, smoking cessation activities, psychosocial support, and an overall attempt to improve the patients quality of life. All patients with CRF should be offered the influenza and pneumococcal vaccines, as per the local guidelines and doses repeated when indicated. End of life care and advanced directives must always be taken well in time from these patients.

LT services are now available in India.[9] LT is often offered to patients with CRF, when all other options have been exhausted. The road to LT is a long drawn one, and requires considerable financial and psychosocial support. As of now, LT in India is limited primarily to the private sector. Apart from cost and logistic issues, a major problem with LT in India is the post LT care, which requires extensive immunosuppression and multiple interval lung biopsies.

Conclusion

Advanced respiratory failure can be the culmination of many respiratory disorders. It used to be classically distinguished into hypercapnic and hypoxemic varieties. However, these classifications are not watertight compartments. The aim of therapy of various chronic lung diseases should be to prevent the development of frank CRF, and treating these patients with the best possible treatment modalities available. Once frank CRF develops, the physician should look beyond pharmacotherapy and offer the patient NIV, domiciliary oxygen, pulmonary rehabilitation, vaccination, and periodically assess and counsel them regarding LT.

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CHAPTER

112 Current Treatment Guidelines—Pulmonary Embolism

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Abstract

Pulmonary embolism (PE) is a major cause of morbidity and mortality among hospitalized patients. It should be promptly diagnosed and treated. All PE patients require anticoagulation. Recent advances in thrombolytics have improved the present treatment options for high risk PE who are hemodynamically unstable. If used judiciously, direct oral anticoagulation therapies are safe and convenient.

Introduction

Pulmonary embolism (PE) is a common and potentially fatal disease with a highly variable clinical presentation. PE is regarded as an extension of a deep vein thrombosis (DVT) and not a separate entity. De novo PE forming in the pulmonary arteries is rare. It is essential that therapy be administered in a timely fashion specifically in critically ill patients so that recurrent thromboembolism, post-thrombotic syndrome and death can be prevented.

Classification

Pulmonary embolism patients are stratified into high risk, intermediate risk, and low risk after carefully considering clinical variables, hemodynamic stability, biochemical and radiological parameters. The treatment of PE depends upon the risk of death.

High Risk

- This accounts for 5–10% of cases.
- Nearly half of pulmonary vasculature is affected by extensive thrombosis in those groups.
- Patients in this category are hemodynamically unstable.

PE patients are defined as hemodynamic unstable in following situations:

- Cardiac arrest or
- Obstructive shock

In spite of adequately resuscitating with fluids patient had persistent hypotension, systolic BP < 90 mm Hg or required vasopressor to achieve a systolic BP > 90 mm Hg & end organ hypoperfusion, or

- 40 mm Hg drop in systolic BP lasting for more than 15 minutes, which is not caused by sepsis, hypovolemia or new onset arrhythmia.

Reperfusion Treatment

Thrombolytic: Thrombolytic agents activate plasminogen to form plasmin, which accelerates lysis of thromboemboli.

In acute PE thrombolytic therapy will rapidly dissolve the embolic burden and improve pulmonary artery pressure (PAP); pulmonary vascular resistance (PVR).[1-3]

Successful thrombolysis will also reduce right ventricular (RV) dilation on echocardiography.

Sooner is better for administration of thrombolytic. Thrombolytic therapy should be offered as early as possible, preferably within first 2 days of symptoms onset for greater benefits.[4]

Unlike in myocardial infarction and stroke; symptomatic PE patients can be thrombolyzed up to 2 weeks after onset of symptoms.

However, thrombolytic therapy is associated with bleeding, which can be fatal and catastrophic.[5]

The overall major bleeding rate is 10%, including a 2–3% risk of intracranial hemorrhage.

Reperfusion Medication (Fibrinolytic & Thrombolytic) and Dose

Recombinant tissue plasminogen activator (rtPA)	IV Total 100 mg infusion over period of 2 hours
Streptokinase (STK)	2,50,000 IU—loading dose over ½ an hour & 1,00,000 IU/hour for next 24 hours
Urokinase	4,400 IU/kg—loading over 10 minutes and then by 4,400 IU/kg/hour for next 24 hours

Extracorporeal Membrane Oxygenation (ECMO)[6-11]

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) may be helpful in patients with circulatory collapse or cardiac arrest and very high risk PE.

Specific attention needs to be given to bleeding complications particularly in patients receiving thrombolysis.

The outcome of ECMO depends upon number of factors including patient selection, expertise, and experience of center.

Till date no randomized clinical trial (RCT) done to prove statically significant improvement with ECMO in PE patients though case series showed survival in critically ill.

Intermediate Risk

Intermediate risk PE as acute PE that is associated with biochemical, echocardiographic, and/or imaging evidence of RV dilation or hypokinesis *without* systemic hypotension.

The intermediate risk group is the most heterogeneous and challenging.

In this group it is difficult to select patients who will benefit from thrombolytic treatment.

One needs to individualize the therapy and may require additional assessment.

While there is no agreed upon definition, some experts[12] distinguish between intermediate-high risk and intermediate-low risk patients using the following:

- Intermediate-low risk PE—Abnormal RV function *OR* elevated BNP or troponin.
- Intermediate-high risk PE—Abnormal RV function *AND* elevated BNP or troponin.

Intermediate high risk PE may get benefitted by thrombolytics, but there is no definitive evidence to support this.

Low Risk

Patients with low risk PE do not require thrombolytic therapy and should be treated with anticoagulation alone.

Low risk patients have excellent prognosis.

Parenteral Anticoagulation

Adequate and effective anticoagulation is the key for successful treatment of PE.

All patients with proven or suspected PE should receive anticoagulation as early as possible.

It can be done with subcutaneous, low-molecular weight heparin (LMWH) or IV unfractionated heparin (UFH) or Fondaparinux.

Fondaparinux is an anti Xa pentasaccharide synthesized in a laboratory.

LMWH has greater bioavailability and more predictable dose response and longer half-life.

Both LMWH and Fondaparinux require dose adjustments in renal failure and morbid obesity.

UFH anticoagulates by binding to and accelerating the activity of antithrombin, which prevents new thrombus formation.

Because lower risk of major bleeding and heparin-induced thrombocytopenia (HIT).

LMWH and fondaparinux are preferred over UFH for initial anticoagulation in PE.[13-16]

Oral Anticoagulant

Warfarin:

- This is Vit K antagonist.
- It requires 5 days to get full effect of warfarin.
- In acute thrombotic illness warfarin should be always overlap with UFH/LMWH/Fondaparinux for at minimum duration of 5 days.

A paradoxical exacerbation of hypercoagulability in acute thrombosis may be observed if warfarin is initiated as monotherapy.

Novel Oral Anticoagulant (NOAC)

- NOAC does not require laboratory monitoring.
- Rivaroxaban and Apixaban are direct factor X a inhibitor are approved for treatment of PE without parenteral bridging anticoagulant.
- Dabigatran is direct thrombin inhibitor, will require an initial 5 days course of parenteral anticoagulation.

Bleeding Risk

It is necessary to evaluate the risk of bleeding before starting anticoagulation.

Major risk factors for bleeding are:

- Advanced age (>75 years)
- Previous bleeding, or anemia
- Active malignancy
- Previous stroke
- Chronic kidney disease or liver disease
- Concomitant antiplatelet therapy or non-steroidal anti-inflammatory drugs
- Poor anticoagulation control

Meta-analyses done by *Kakkos SK* showed that there is 40% reduction in the risk for major bleeding with NOACs compared with VKAs.[17]

Duration of Anticoagulation

All PE patients should receive at least 3 months of anticoagulation.[18]

After 3 months of treatment, physician should plan the therapy on case-to-case basis considering benefit—risk ratio of VTE recurrence and that of bleeding.

In view of their ambiguous nature and not very clear cut defining criteria provoked or unprovoked terminologies are not taken into consideration while planning the treatment duration.

Terminology such as "provoked" versus "unprovoked" may be misleading and create confusion, hence these are no more supported by European Society of Cardiologist.[12]

Anticoagulation for Venous Thromboembolism

Unfractionated heparin	80 U/kg bolus, then infusion 18 U/kg, maintain ApTT 2–3 times the upper limit
Enoxaparin	1 mg/kg twice daily
Dalteparin	200 U/kg OD or 100 U/kg twice a day
Fondaparinux	7.5 mg once a day
Rivaroxaban	15 mg twice a day for 3 weeks and then 20 mg once a day
Apixaban	10 mg twice daily for 1 week and then 5 mg twice a day
Dabigatran	150 mg twice daily. Needs overlap with LMWH
Warfarin	Starting dose 5 mg, maintain INR 2–3 Needs overlap with UFH/LMWH

Pulmonary Embolism in Cancer[19-22]

In patients with cancer and PE, LMWH should be preferred over VKAs for first 6 months.

Edoxaban and Rivaroxaban are the two NOAC, which are tried in few cancer patients without gastrointestinal tumors.

Anticoagulation can be discontinued once cancer is cured but it is difficult to define the "cancer cure."

Pregnancy[23,24]

Pregnancy is a procoagulant state with increased risk of PE.

In pregnancy LMWH is the drug of choice to treat PE.

LMWH does not cross the placenta.

After delivery, anticoagulant treatment should be continued for more than 6 weeks and with a minimum duration of 3 months.

LMWH and warfarin can be safely administered to breastfeeding mothers.

In the event of life-threatening PE thrombolytic therapy can be attempted in pregnant patients.

VKAs and NOAC are not recommended in pregnancy possibly because of teratogenicity and fetal hemorrhagic risk.

In female patients of child bearing age, pregnancy, or breastfeeding should be excluded prior to commencing NOAC therapy.

Role of Inferior Vena Cava Filter[25-27]

The placement of inferior vena cava filter (IVC-filter) in the treatment of venous thromboembolism is controversial.

In the patients who are actively bleeding that precludes anticoagulation and who had recurrent venous thrombosis in spite of intensive anticoagulation, IVC-filter may be tried.

Early prophylactic IVC-filter after major trauma is not found to reduce symptomatic PE or death at 90 days than no placement of filter.

No convincing clinical outcome data is available to recommend prophylactic IVC filter use.

Percutaneous Catheter Directed Treatment

Pharmacomechanical catheter directed therapy involves physical fragmentation of thrombus with catheter directed low dose thrombolytic (24 mg of tPA).

As data is lacking from RCTs on clinical efficacy outcomes, this approach should be used with caution.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH)[28]

Chronic thromboembolic pulmonary hypertension develops in 2–4% of acute PE patients.

Pulmonary thromboendarterectomy, lifelong oral anticoagulation, and diuretics may give relief and reduce pulmonary hypertension.

Mobilization in DVT[29,30]

Mobilization may be beneficial in reducing pain and edemas from DVTs, but large scale randomized control trials are required to validate these outcomes.

Conclusion

- Pulmonary embolism is life threatening, but potentially treatable and preventable condition.
- High risks (hemodynamically unstable) are benefitted by thrombolysis.
- All patients with PE should receive therapeutic anti-coagulation for more than 3 months.
- LMWH is preferred drug for parenteral anticoagulation.
- NOAC are promising molecule to minimize bleeding risk.
- Role of IVC filter is controversial.

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Section 9

Section Editor: **Jyotirmoy Pal**

Clinical Medicine

CHAPTER

113 Approach to Ascites

Veerendra Singh

Abstract

Ascites, the collection of fluid in the peritoneal cavity, can originate from hepatic, malignant, cardiac, renal, and infectious diseases. Cirrhosis, tuberculosis, and malignancy are the most common causes in Indian patients. Ultrasonography and paracentesis with ascetic fluid examination are the modalities used to establish the etiology. Sodium restriction and diuretics are mainstay of treatment of ascites due to cirrhosis. Ascites due to other causes requires specific treatment. For refractory ascites large volume paracentesis along with infusion of albumin is used. Liver transplantation is the gold standard therapy. Despite the advances in modern medicine, development of ascites is associated with poor prognosis and high mortality.

Introduction

Commonly presenting with abdominal swelling, ascites is a pathological fluid collection in the peritoneal cavity. The common causes of ascites are cirrhosis, tuberculosis, malignancy, cardiac failure, pancreatitis, and nephrotic syndrome. The management depends on the etiology of ascites from hepatic to extrahepatic causes and on the stage of ascites from uncomplicated to refractory stage.

Causes of Ascites

Various causes of ascites are shown in **Table 1**. In India, cirrhosis of liver is most common cause of ascites followed by tuberculosis versus malignancy in developed countries. Sometimes more than one condition may coexist with significant management implications. Alcoholic patients can have cirrhosis with cardiomyopathy, tuberculosis, or malignancy. For management, perspective ascites is grouped under two heads: ascites due to cirrhosis or due to causes other than cirrhosis.

Ascites Due to Cirrhosis

Portal hypertension and renal salt and water retention are the key mechanisms of ascites in cirrhosis. Ascites denotes the transition from a compensated to a decompensated stage of cirrhosis. Initially ascites is uncomplicated, not infected, and responds well to diuretics.[1] As disease progresses, ascites ceases to respond to diuretics (refractory ascites) and renal dysfunction supervenes (hepatorenal syndrome).

Uncomplicated ascites is subdivided into three grades: mild, moderate, and massive ascites. Refractory ascites has two subtypes: diuretic-resistant and diuretic-intractable.[2]

Complications of Cirrhosis

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP), a lethal complication, results from ascitic fluid infection in absence of an intra-abdominal infective focus.

TABLE 1 Causes of ascites

Portal hypertension	Infections	Miscellaneous
• Cirrhosis liver • Alcoholic hepatitis • Hepatic congestion – Congestive cardiac failure – Constrictive pericarditis – Hepatic venous outflow obstruction • Portal vein thrombosis • Non-cirrhotic portal hypertension	• Bacterial peritonitits • Tubercular peritonitis • HIV associated periotonitis **Malignancies** • Peritoneal carcinomatosis • Primary mesothelioma • Hepatocellular carcinoma • Metastatic liver disease • Pseudomyxoma peritonei	• Pancreatitis • Hypoalbuminemia • Nephrotic syndrome • Lymphatic leakage • Myxoedema • SLE

Hepatic Hydrothorax

Pleural effusion develops in approximately 5–10% of patients with cirrhosis due to transdiaphragmatic movement of fluid from peritoneal cavity to pleural space.[3] Patients usually have minimal ascites. Pleural effusion is right sided in 85%, left sided in 13%, and bilateral in 2% cases.

Ascites due to Causes other than Cirrhosis

In malignancy and tuberculosis tumor cells and tubercles lining the peritoneum produce protein rich fluid. Pancreatitis, heart failure, nephrotic syndrome, and hypothyroidism may cause ascites.

Malignant Ascites

Malignant ascites occurs secondary to:

- Peritoneal carcinomatosis: malignant infiltration of peritoneum
- Massive hepatic metastasis
- Profound desmoplastic response to infiltrating breast cancer
- Chemotherapy induced nodular regenerative hyperplasia

Two-thirds cases of malignant ascites are caused by peritoneal carcinomatosis from adenocarcinomas of pancreas, stomach, colon, ovary, uterus, lungs, or breast. The remaining are caused by hapatocellular carcinoma or hepatic metastases.

Evaluation and Diagnosis

Clinical Assessment

Ascites may be asymptomatic or may just produce an increase in abdominal girth described as tightness of cloths or belt. Massive ascites produces abdominal discomfort, umbilical eversion, hernias, and breathlessness. Physical examination is not significant in mild ascites. In moderate ascites, flank dullness and shifting dullness are sensitive findings. Massive ascites produces marked distension of abdomen. Signs of liver disease and portal hypertension should be sought. Hepatic, renal, and cardiac status should be assessed.

Pathological Assessment

Routine urine examination, complete blood counts, blood sugar, liver function tests, viral markers (HBV, HCV, and HIV), serum screatinine, NT-Pro BNP, and thyroid function tests should be obtained.

Imaging

Ultrasound is the best modality to document the presence of ascites. It can provide information about cause of ascites (fibrosis in cirrhosis, nodules in HCC, or liver metastasis). Fibroscan is a new modality to document fibrosis of liver. Doppler sonography can detect portal or hepatic vein thrombosis. Contrast enhanced CT, echocardiography, upper GI endoscopy, and colonoscopy may be ordered in select conditions. MRI using gadolinium scan can demonstrate enhancement of peritoneal lining in peritoneal carcinomatosis.[4]

TABLE 2 Tests of ascitic fluid

Routine tests	*Additional tests*
• Appearance • Total protein • Serum ascites albumin gradient (SAAG) • Cell count	• Gram stain and culture • AFB smear, culture and adenosine deaminase activity • Glucose and lactate dehydrogenase • Amylase concentration • Cytology and carcinoembryonic antigen level • Triglyceride level

Abdominal Paracentesis

Once the presence of ascites has been confirmed, the etiology of ascites is best determined by paracentesis. Between 20–50 mL of ascitic fluid should be aspirated and examined **(Table 2)**.

Appearance

In ascites due to portal hypertension the fluid is clear and straw colored. Turbid fluid can result from infection or malignancy. Milky fluid, chylous ascites results from lymphatic disruption due to malignancy, trauma, and congenital abnormalities. Bloody ascites could be due to traumatic tap or malignant ascites. Blood in traumatic fluid clots but in malignant ascites does not clot.

Total Protein

Protein levels are useful in determining etiology of ascites. Traditionally ascitic fluid is grouped into:

- Exudate with protein concentration more than 2.5 g/dL.
- Transudate with protein concentration less than 2.5 g/dL.

Exudative ascites occurs secondary to peritoneal processes (malignancy, tuberculosis) or post-hepatic sinusoidal hypertension with normal sinusoids (heart failure, hepatic vein, or inferior venacava obstruction) whereas transudative ascites results from increased sinusoidal portal hypertension (cirrhosis). Total protein levels are also useful in determining susceptibility to infection. Patients with ascitic fluid protein less than 1.0 g/dL are prone to develop SBP.

TABLE 3 Diffrentiation of ascites based on hepatic venous pressure gradient measurement

Causes of ascites	*WHVP*	*FHVP*	*HVPG*
Cirrhosis	Increased	Normal	Increased
Cardiac ascites	Increased	Increased	Normal
Malignant ascites peritoneal tuberculosis	Normal	Normal	Normal

FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; WHVP, wedged hepatic venous pressure

Serum-ascites Albumin Gradient

Serum-ascites albumin gradient (SAAG) is the difference between albumin concentration in the ascitic fluid and that in the serum both collected at the same time. It is a very useful tool to establish the presence of portal hypertension. A SAAG value more than 1.1 g/dL reflects portal hypertension and indicates the ascites is due to increased pressure in the hepatic sinusoids. The SAAG has been found to be superior to the total protein concentration for the differential diagnosis of ascites.[5]

Hepatic Venous Pressure Gradient

Hepatic venous pressure gradient (HVPG) is direct measure of hepatic sinusoidal pressure measured via a catheter in right femoral or internal jugular vein. Portal hypertension is defined as HVPG value more than 6 mm Hg **(Table 3)**.

Laparoscopy

Laparoscopy offers the advantages of visual inspection of the peritoneal cavity and obtains targeted biopsies for histological studies. With the availability of new imaging techniques, the need for laparoscopy in determining the cause of ascites has decreased.

Diagnostic Developments

New novel diagnostic markers such as leukocyte esterase reagent strips for diagnosing SBP, viscosity measurement of ascitic fluid to discriminate between portal and non-portal hypertension, vascular endothelial growth factor (VEGF), bacterial DNA for documenting bacterial translocation, and markers of poor prognosis such as endotoxin and peptidoglycan/β-glucan have been proposed but still need validation.

Approach to a Patient of New Onset Ascites

See **Flowchart 1**.

Evaluation of Infection

Cell Counts

A predominance of neutrophils indicates an acute intra-abdominal inflammation. An ascites PMN count greater than 250/mm^3 establishes diagnosis of SBP.[6] Predominant mononuclear cells indicate tubercular ascites.

Smear and Bacterial Culture

Culture samples of ascetic fluid for both aerobic and anaerobic bacteria should be inoculated at the bedside into a blood culture bottle.

Ascitic Fluid Glucose and LDH Levels

Ascetic fluid LDH higher than serum LDH (ratio >1.00) and ascetic fluid glucose below 50 mg/dL suggests secondary bacterial peritonitis.

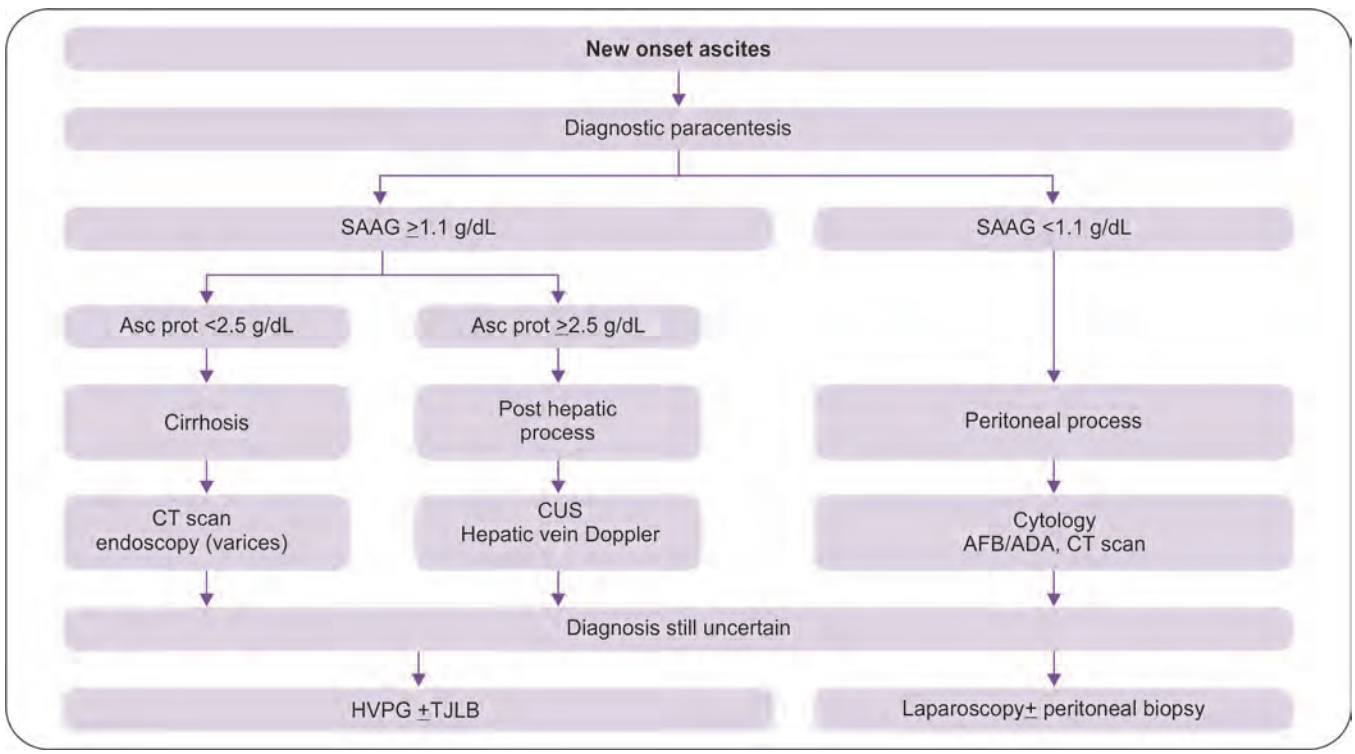
Evaluation of Tubercular Ascites

In tuberculous peritonitis, the smear for acid-fast bacilli is rarely positive and culture is positive only in about 50% of cases. Polymerase chain reaction for MTB has a high sensitivity (94%).[7] Adenosine deaminase activity (ADA) is a reliable marker of tuberculous ascites. Mononuclear cell predominant leucocytes >500/cc, total protein more than 3 g/dL, LDH >90 units/L, or ADA >36–40 IU/L has a sensitivity of 100% and a specificity of 97% for of peritoneal tuberculosis. Laparoscopy with peritoneal biopsy and histopathology is the gold standard for diagnosis of peritoneal tuberculosis.[8] Recommended stepwise approach for the diagnosis of peritoneal tuberculosis is detailed in **Flowchart 2**.

Evaluation of Malignant Ascites

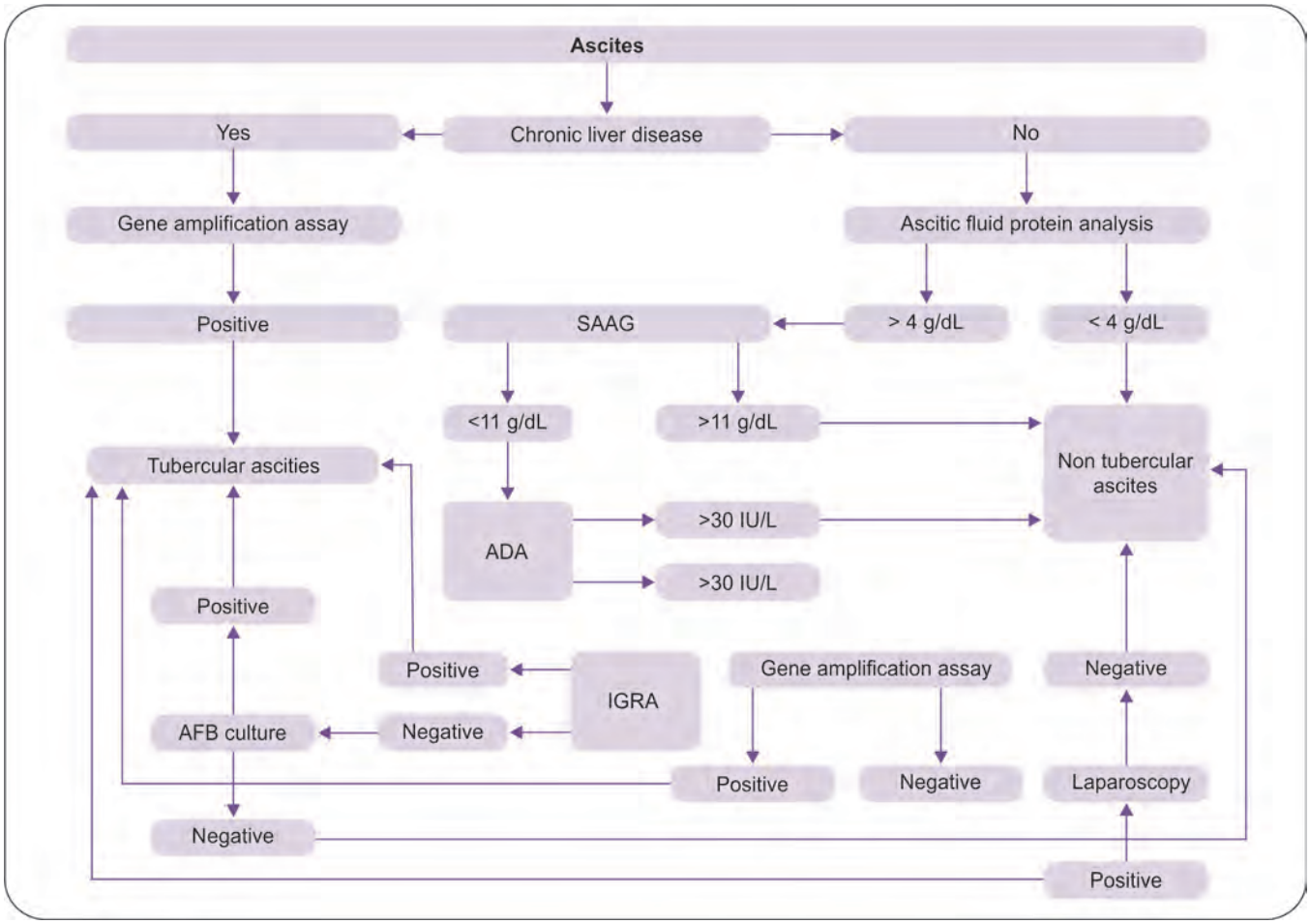
Abdominal ultrasound and CT may be useful to demonstrate the primary malignancy or hepatic metastases but seldom confirms the diagnosis of peritoneal carcinomatosis. Analysis of the ascetic fluid is the most important step in

Flowchart 1: Approach to a patient of new-onset ascites



Asc prot, ascites total protein level; CUS, cardiac echosonography, HVPG, hepatic vein pressure gradient

Flowchart 2: Algorithm for diagnostic strategies in tubercular ascites



ADA, adenosine deaminase; IGRA, interferon gamma release assays

TABLE 4 Ascitic fluid findings in malignant ascites

	SAAG	*Ascitic fluid protein*	*Cytology*
Peritoneal carcinomatosis	Low	High	High up to 97%
Liver metastasis	High	Low	Negative

the diagnostic work-up **(Table 4)**. Laparoscopy may be required to confirm the diagnosis.

Treatment of Ascites

Ascites due to Causes other than Cirrhosis

Treatment is to be directed at the underlying cause:

- *Infective ascites:* Appropriate antibacterial therapy
- *Tubercular ascites:* Anti-tubercular therapy along with large volume paracentesis for severe ascites
- *Pancreatic ascites:* Conservative measures like salt restriction and diuretics
- Malignant ascites: Does not respond to sodium restriction or diuretics. Large volume paracentesis (LVP), transcutaneous catheter placement, peritoneo-venous shunt, and autopumps are used

Treatment of Ascites due to Cirrhosis

Except for liver transplant, none of the therapies improves the survival. However, treatment of ascites not only improves the quality of life but prevents SBP, a lethal complication. The development of ascites in a patient of

cirrhosis denotes a poor prognosis with a median survival of 1.5 years so these patients should be considered for liver transplant.

Sodium Restriction and Diuretics

According to the European Association for the Study of the Liver, patients with cirrhosis and grade 1 ascites do not need diuretics and a low sodium diet.[9] In patients with grade 2 ascites, sodium consumption is restricted to 2 g sodium (5.2 g of dietary salt) per day along with diuretic therapy. The goal of diuretic treatment is a loss of weight up to 1.0 kg/day if both ascites and edema are present and up to 0.5 kg/day in patients with ascites alone.[10] Spironolactone, an aldosterone antagonist, is preferred as the initial diuretic. Recommended starting dose is 50–100 mg/day. Addition of a loop diuretic, furosemide or torsemide, potentiates effect of spironolactone. The maximum dose of diuretics recommended is a combination of spironolactone 400 mg/day with furosemide 160 mg/day.[11]

In patients with massive ascites, the method of choice is LVP followed by diuretic agents and a low sodium diet.[12] Approach to a patient of new ascites has been summarized in **Flowchart 3**.

Therapeutic Options for Refractory Ascites

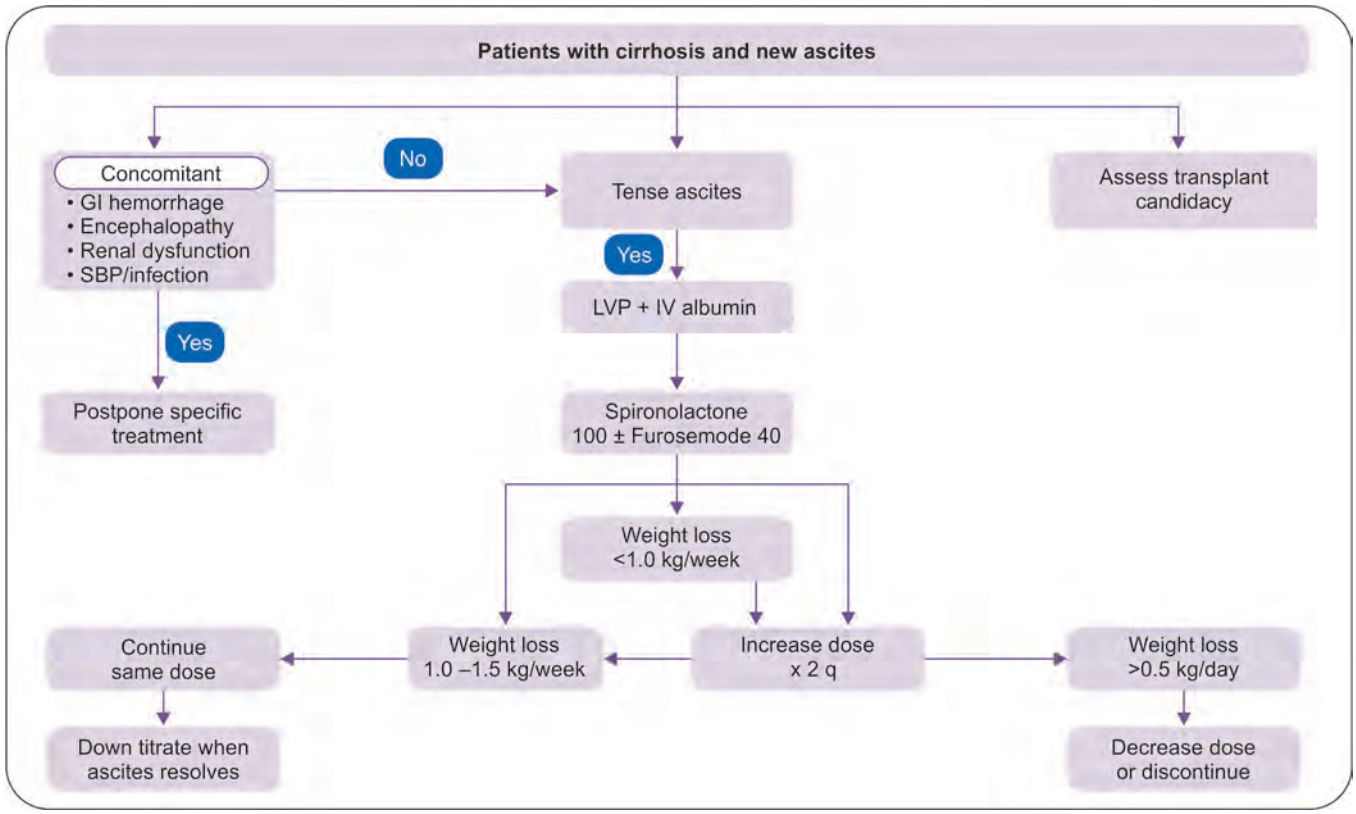
Large Volume Paracentesis

In normal clinical practice, the first-line therapeutic intervention is large volume paracentesis repeated every 2–3 week. Between 5–6 L of the ascitic fluid is removed in combination with I/V infusion of albumin (6–8 gm/L of fluid drained) to prevent paracentesis-induced circulatory dysfunction.

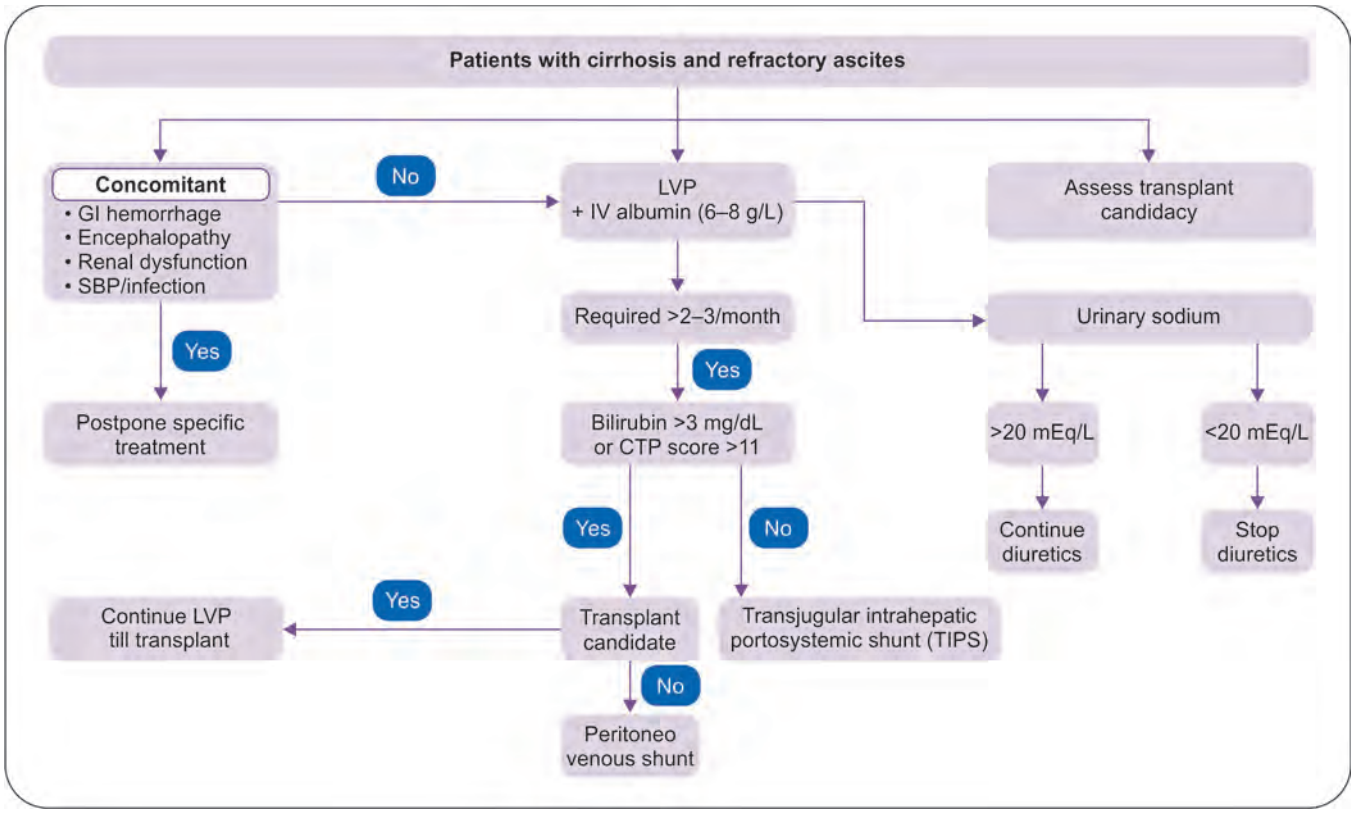
Peritoneovenous Shunt

Peritoneovenous shunt (PVS) drains ascitic fluid into the venous system. With laparascope a shunt is placed from peritoneal cavity to superior vena cava close to

Flowchart 3: Treatment strategies for patient of cirrhosis with new onset ascites



Flowchart 4: Treatment strategies for patient of cirrhosis with refractory ascites



the entrance of right atrium. A valve at the venous end prevents backflow of blood into the tubing. PVS has been reported to improve glomerular filtration rate in patients with renal insufficiency. However, long-term results were worse due to infection, shunt thrombosis, disseminated intravascular coagulation, and air embolism.

Surgical Portosystemic Shunt

In portosystemic shunt the portal vein is used as an outflow tract to relieve portal hypertension. However, because of high surgical mortality, they are seldom used nowadays.

Transjugular Intrahepatic Portosystemic Shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is a non-surgical portacaval anastomosis. In this procedure, a tract is created between branches of hepatic and portal veins. Portal pressure reduction improves renal blood flow and glomerular filtration rate. Current clinical guidelines recommend using TIPS only in patients who require frequent LVP.

A Patient with Contraindications to TIPS

- In malignant ascites implantation of a permanent Pleurx® tunneled peritoneal catheter allows drainage of small amount of ascitic fluid (<2 L/day) in small portions.[13]
- An automatic low-flow pump (Alfapump®) moves ascetic fluid to the bladder in small portions (5–10 mL) every 5–10 min. It may serve as a "bridge" to liver transplantation.

Liver Transplantation

Liver transplantation is the definitive treatment for ascites, as it eliminates portal hypertension and all other accompanying complications of liver cirrhosis. Overall, 1 year survival after liver transplantation exceeds 75%.

Approach to manage refractory ascites is shown in **Flowchart 4**.[14]

Novel Therapies in Refractory Ascites

V2 Receptor Antagonists

Satavaptan, a selective V2 vasopressin receptor antagonist, acts on the distal renal tubule to increase water excretion, making it an attractive novel drug for patients who do not respond to conventional diuretics.

Vasoconstrictors

Clonidine, a centrally acting α2-agonist, when used with spironolactone decreases the need for diuretics. Midodrine, an α1-adrenoreceptor agonist, increases sodium excretion in patients with cirrhosis and refractory ascites without azotemia. In an RCT by Hanafy et al., midodrine (15 mg/day) and rifaximin (1.1 g/day) added to diuretics, increased diuresis and improved short-term survival.[15] Terlipressin, a V1 receptor agonist, improved the glomerular filtration rate and induced natriuresis in patients with cirrhosis and ascites without HRS. Despite the positive results of the aforementioned studies, the addition of clonidine or midodrine to the diuretic treatment in refractory ascites is not recommended by current guidelines.

Conclusion

Ascites, commonly presenting as abdominal swelling, is accumulation of free fluid in peritoneal cavity. Cirrhosis, tuberculosis, and malignancy are the common causes of ascites. Mild ascites is asymptomatic but large ascites causes abdominal discomfort and breathlessness. Ultrasonography detects the presence of ascites. Paracentesis with fluid examination establishes etiology of disease. Sodium restriction and diuretic therapy is the mainstay of cirrhotic ascites treatment. Ascites due to causes other than cirrhosis requires specific treatment. In refractory ascites, LVP with albumin infusions, TIPS, PVS, and automatic pumps are helpful. Liver transplantation is the gold standard therapy. Despite the advances in modern medicine, development of ascites is associated with poor prognosis and high mortality.

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CHAPTER

114 Approach to Acute-on-Chronic Liver Failure

Anshuman Elhence, Abhinav Anand, Shalimar

Abstract

Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by hepatic and/or extra-hepatic organ dysfunction in a patient with chronic liver disease. Multiple definitions exist in the literature. Irrespective of the definition, ACLF is associated with high short-term mortality. The syndrome is dynamic, and daily estimation of prognostic scores and organ dysfunction can predict the prognosis. A multidisciplinary team involving hepatologists, liver transplant surgeons, intensive care specialists, radiologists and pathologists is essential for the comprehensive management of patients with ACLF. Early identification and treatment of the acute precipitant is as essential as intensive monitoring, nutrition, antibiotics, albumin, and supportive care for extra-hepatic organ dysfunction. Liver transplantation remains the definitive treatment, albeit with its limitations. Physicians need to recognize the entity early, refer to multidisciplinary care centers, explain the prognosis, and prime the family members for the need for liver transplantation.

Introduction

Acute-on-chronic liver failure (ACLF) syndrome is characterized by abrupt hepatic decompensation secondary to an acute insult in a patient with chronic liver disease, associated with high short-term mortality. Overall, there are more than 20 definitions of ACLF available in the literature. Different definitions of ACLF provided by the European association for the study of the liver-chronic liver failure (EASL-CLIF), Asian Pacific Association for the study of the liver (APASL), and North American Consortium for the Study of End-stage Liver Disease (NACSELD) in Asia, Europe, and the USA, respectively have led to more confusion, rather than unifying the recognition of this syndrome.[1-4]

Definition

The overall concept of defining ACLF is to identify high-risk patients with high short-term mortality. The possible reasons for the different definitions of ACLF syndrome include different etiologies (acute precipitants and chronic liver disease), and different clinical presentations of hepatic and extra-hepatic insults. Comparison of the major definitions—including EASL-CLIF, APASL, and NACSELD and World Gastroenterology Organisation (WGO)—is shown in **Table 1**. An important difference is the inclusion of patients with chronic liver disease (all stages of fibrosis) in the APASL definition **(Flowchart 1)**; in contrast, the EASL-CLIF and NACSELD definitions include patients with cirrhosis only. Patients with prior decompensation are excluded in the APASL definition, while they are included in the EASL-CLIF and NACSELD definitions.

Acute Decompensation vs. ACLF

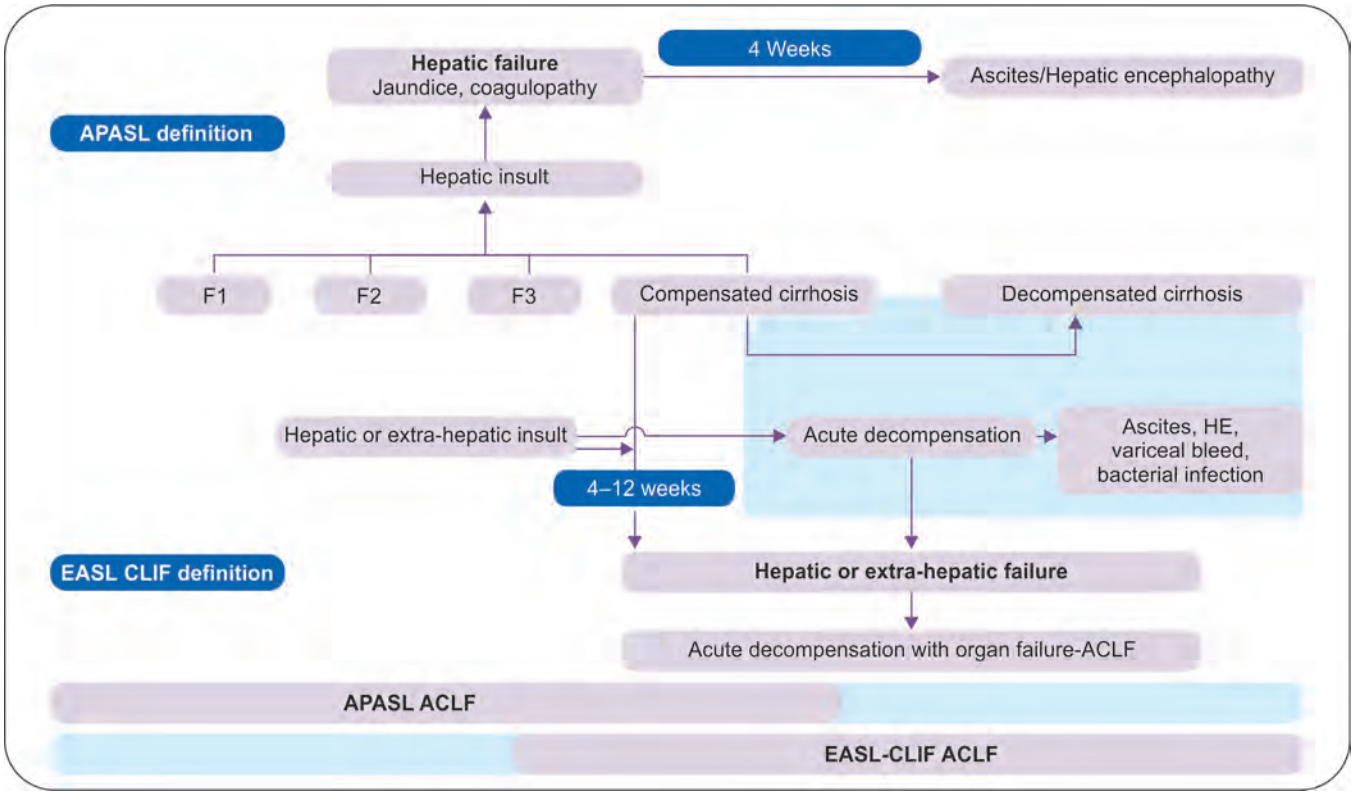
Acute decompensation (AD) refers to an event in the natural history of cirrhosis characterized by the development of jaundice, ascites, variceal bleed, or encephalopathy. AD when associated with organ failure is defined as ACLF.

TABLE 1 Comparison of various definitions of acute-on-chronic liver failure

	EASL-CLIF	*APASL*	*NACSELD*	*WGO*
Definition	Based on the presence of the three major characteristics: • Acute decompensation • Organ failure (as per SOFA-CLIF score) • High 28-day mortality rate (predefined threshold of 15%)	ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL and coagulopathy) (INR ≥ 1.5) complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis, and a high 28-day mortality	Infection-related ACLF—defined as the presence of two or more organ failures—shock, grade III/IV HE, need for ventilation or renal replacement therapy	ACLF is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extra-hepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset
Basis of definition	CANONIC study—1343 prospectively included AD patients	Initial arbitrary cut-off of bilirubin and INR. 2019 consensus updated based on AARC data (>3,300 cases)	Prospective, multicenter study—507 patients with infection	Expert group
Clinical presentation	OF essential Isolated renal failure or any combination (2 or more) of any 6 OFs	Liver failure essential—jaundice	Infection ≥2 OF	
Time interval since acute insult and development of ACLF	3 months	Less than 4 weeks	? 30 days	Less than 3 months
Patient inclusion	Cirrhosis only Both compensated and decompensated	Chronic liver disease (any stage of fibrosis) Compensated cirrhosis	Cirrhosis only Both compensated and decompensated	Chronic liver disease (any stage of fibrosis)
Patient exclusion	HIV HCC beyond Milan criteria	HCC Prior decompensated cirrhosis	HIV Prior organ transplant Disseminated malignancy	-
Acute precipitants	Hepatic and extrahepatic both	Hepatic	Infection	Both hepatic and extra-hepatic
Prognostic models	CLIF-C ACLF	AARC Score	MELD, CLIF-C ACLF	Not defined

AARC, APASL ACLF research consortium; ACLF, acute-on-chronic liver failure; AD, acute decompensation; APASL, Asia Pacific Association for the study of liver diseases; CLIF-C, chronic liver failure-consortium; EASL, European Association for the study of liver; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; INR, international normalized ratio; MELD, model for end stage liver disease; NACSELD, North American Consortium for the study of end stage liver disease; OF, organ failure; SOFA, Sequential Organ Failure Assessment; WGO, World Gastroenterology Organisation.

Flowchart 1: APASL and EASL-CLIF definition of acute-on-chronic liver failure



Approach to ACLF

The definition of ACLF embodies the basic constituents of the syndrome—an acute precipitant on a background of underlying chronic liver disease leading to organ failure and high short-term mortality. Each of the constituents must be addressed separately **(Flowchart 2)**.

Prognosis and Scoring Systems

The Child-Turcotte-Pugh (CTP) score and model for end-stage liver disease (MELD) do not accurately assess the risk of patients with ACLF. The EASL-CLIF and APASL divide ACLF into three grades of severity based on short-term mortality. As per the EASL-CLIF, the 28-day mortality in grade 1 ACLF [defined as single renal failure (creatinine >2.0 mg/dL) or any other single organ failure with renal dysfunction (creatinine 1.5–2 mg/dL)] is around 20–25%, grade 2 ACLF (2 organ failures) is 35–40%, and grade 3 ACLF (3 or more organ failures) is 70–80%. A linear score has been proposed CLIF-C ACLF (based on 6 organ failure scores, age, and total leukocyte count), which correlates with outcomes.

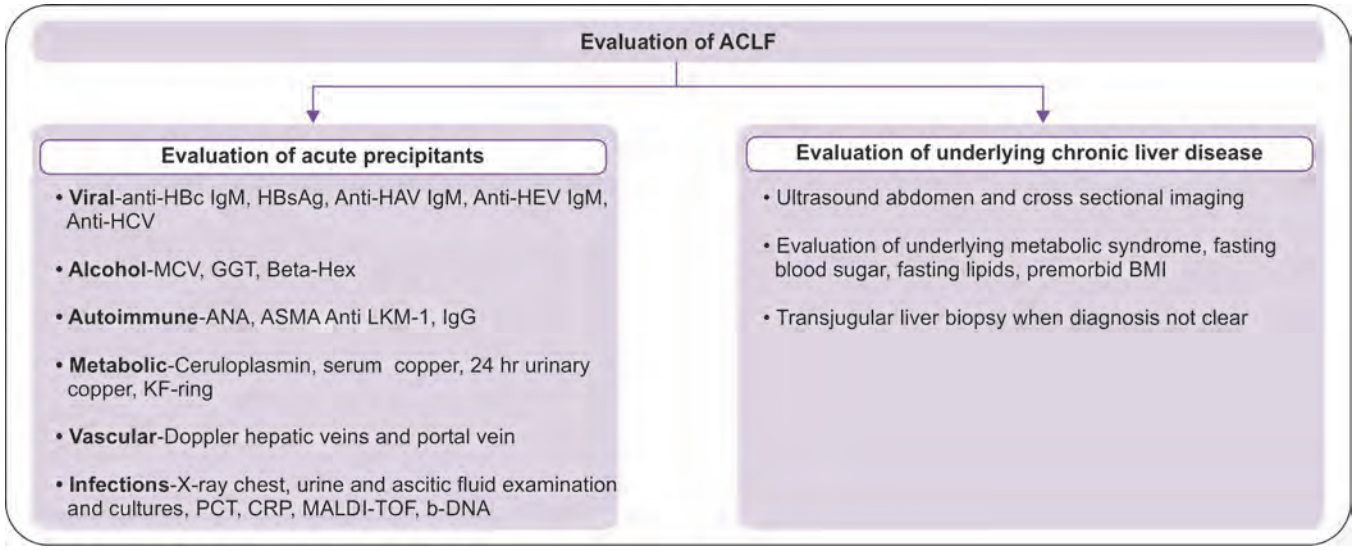
The APASL-ACLF-AARC score includes bilirubin, INR, hepatic encephalopathy (HE), lactate, and creatinine with an overall score ranging from 5 to 15. Based on the AARC score, ACLF is graded into grade 1 ACLF (score 5–7), grade 2 ACLF (8–10), and grade 3 ACLF (>10) with predicted 28-day mortality of 13%, 45%, and 86%, respectively.[1]

While assessing prognosis in patients with ACLF, it is important to use the scores as defined by definition, that is, use AARC score, if ACLF is defined by APASL definition and EASL-CLIF C ACLF in patients defined by EASL-CLIF definition.

Dynamic Assessment of the Prognostic Score

ACLF is a dynamic syndrome; therefore, it is important to assess patients daily for changes in organ failures and scores. A change in the score helps in early detection of deterioration and warrants change in the management plan. Patients showing an improvement in the grade of ACLF over the first 3 days are associated with a better outcome. The grade of ACLF between day 3 and 7 predicts outcome better than the grade at presentation.

Flowchart 2: Evaluation of patients with acute-on-chronic liver failure



ACLF, acute-on-chronic liver failure; ANA, anti-nuclear antibody; Anti-HBc, antibody to hepatitis B core antigen; ASMA, anti-smooth muscle antibody; bDNA, bacterial deoxyribonucleic acid; Beta hex, beta-hexosaminidase; BMI, body mass index; CDT, carbohydrate deficient transferrin; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; IgM, immunoglobulin M; KF, Kayser-Fleischer; LKM-1, liver-kidney microsomal-1; MALDI-TOF, matrix assisted laser desorption ionization-time of flight; MCV, mean corpuscular volume; PCT, procalcitonin.

Role of Liver Biopsy

A liver biopsy is not routinely recommended in the management of patients with ACLF. It may be indicated when the diagnosis is unclear, clinical suspicion of autoimmune hepatitis, or Wilson disease. The presence of neutrophilic infiltration, bilirubinostasis, mega-mitochondria are markers of poor prognosis in alcoholic hepatitis. Since patients with ACLF often have concomitant ascites and coagulopathy, if indicated, a transjugular route is recommended over a percutaneous one.

Management

Management of Acute Precipitants

Withdrawal of the acute insult is essential to stall the inflammatory cascade **(Fig. 1)**. Etiology specific interventions are effective. Patients with active alcoholism benefit from abstinence. It is unclear whether use of corticosteroids is associated with mortality benefit in patients with alcohol-related ACLF. Steroids are associated with increased risk of infections; their use needs to be individualized and justified in each case depending on the risk-benefit ratio. In patients with reactivation of hepatitis B presenting as ACLF, use of antiviral drugs such as tenofovir disoproxil fumarate (TDF) is associated with a better outcome. For hepatitis E virus infection, no specific therapy is recommended. Patients with autoimmune hepatitis (AIH)-ACLF without hepatorenal syndrome and sepsis can be considered for a trial of steroids.[1] In patients with Wilson disease, chelation therapy is recommended. Also, consideration should be given to early liver transplantation (LT) in those categorized as likely to have poor prognosis, as documented by new Wilson Index of more than 11. Plasmapheresis can be tried as a bridge to LT in patients with fulminant presentation of Wilson disease.

Drugs are another important precipitant of ACLF. The common drugs include anti-tuberculosis therapy and complementary and alternative medicines. A detailed history of drugs should be elicited at presentations and all drugs should be stopped.

Patients with acute variceal bleed (AVB) need to be managed with resuscitation, splanchnic vasoconstrictors and endoscopic therapy. In select cases, placement of preemptive (<72 hours of presentation) transjugular intrahepatic portosystemic shunt (TIPS) can be considered. Among patients with uncontrolled bleeding

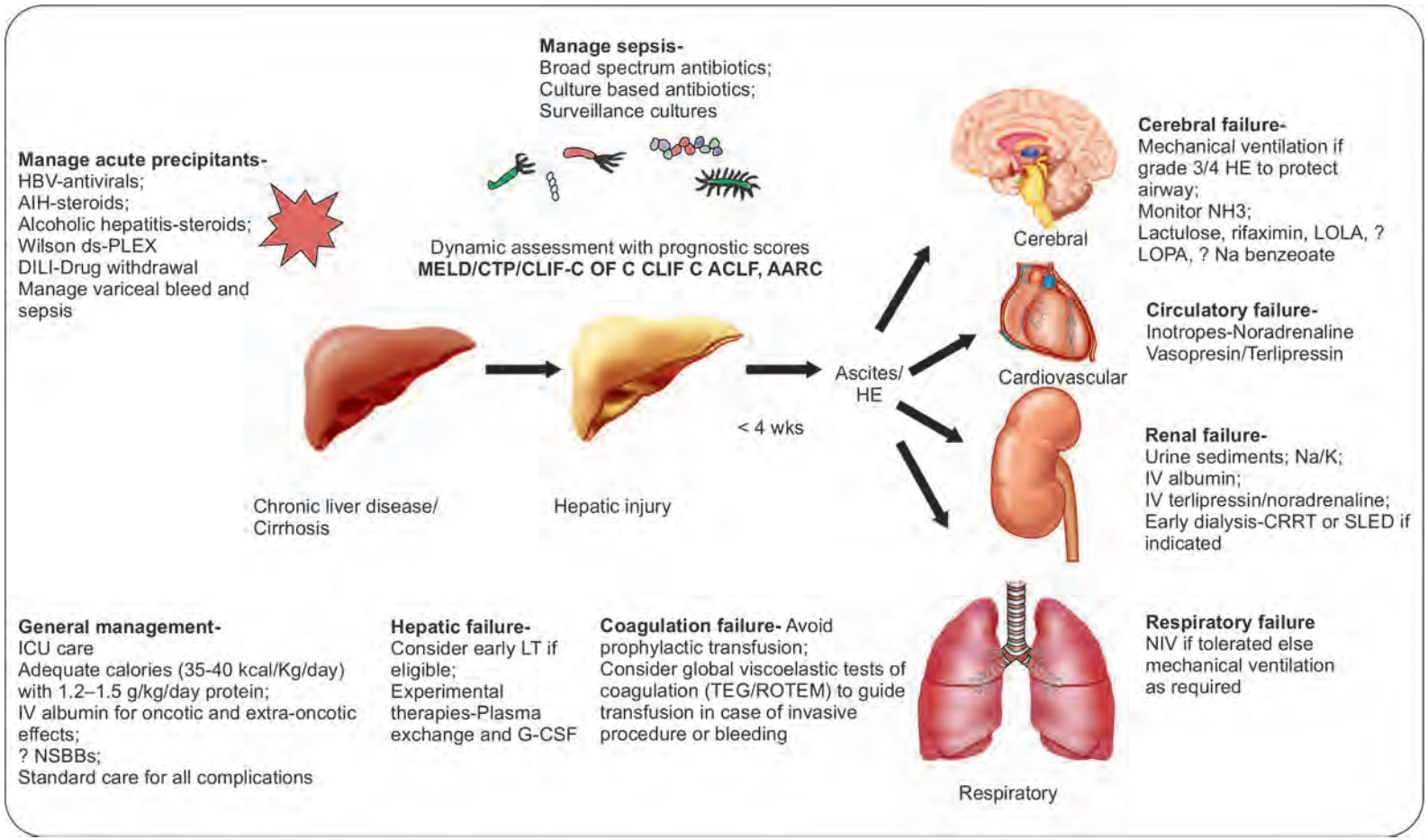


Fig. 1: The management approach to acute-on-chronic liver failure

rescue TIPS is an option, such patients usually have a poor outcome.

Bacterial infections are present in 10–30% of ACLF patients at admission, and another 30–50% may develop an infection during the hospital stay. Choice of empirical antibiotics depends on the setting. For community acquired infections a 3rd generation cephalosporin is a good choice. For nosocomial infections, piperacillin/tazobactam is preferred for areas with low-prevalence of multidrug resistance organisms (MDROs), while carbapenems are preferred in areas of high MDRO, with or without a gram positive glycopeptide for areas of high methicillin resistant *Staphylococcus aureus* (MRSA). Appropriate antibiotics according to local sensitivity patterns need to be administered at the earliest once culture reports are available.[5]

Management of Extrahepatic Organ Failures

Renal

Acute kidney injury (AKI) in ACLF can arise due to structural as well as functional causes. The withdrawal of diuretics and volume expansion with albumin is the first step. Terlipressin and noradrenaline can be considered with data suggesting that the former is more effective in the management of the hepatorenal syndrome. Renal replacement therapy (RRT) indications include symptoms of uremia, volume overload, hyperkalemia, and metabolic acidosis. Continuous RRT involves very slow blood and dialysate infusion and is preferred in patients with hemodynamic instability. Alternatively, a shorter hybrid procedure called slow-low efficiency dialysis (SLED) can offer shorter procedure times of 6–12 hours, maintaining hemodynamic stability as well.

Cerebral

Management of HE includes evaluation and management of precipitants **(Fig. 1)**. Hyperammonemia is associated with HE. Baseline hyperammonemia and persistent hyperammonemia are associated with poor outcomes in patients with ACLF. Lactulose and rifaximin are useful first-line drugs that help in reducing ammonia. The role of L-ornithine L-aspartate (LOLA), L-ornithine phenylacetate (LOPA), and sodium benzoate have not been studied in ACLF patients. Elective intubation to prevent aspiration may be considered in patients with advanced (grade 3 and 4) HE.

Coagulation

Prophylactic transfusion of plasma, based on the international normalized ratio (INR), is not recommended. Similarly, prophylactic transfusion of platelet may not be of use in the absence of active bleeding. Viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) should be used to guide transfusion in cases, which require an invasive procedure or develop bleeding complications.

Circulatory

In patients with circulatory failure, noradrenaline should be considered as a first-line agent. Vasopressin or terlipressin can be an alternative second line agent.

Respiratory

Respiratory failure should be managed with ventilatory support using either noninvasive ventilation or invasive ventilation, as tolerated, if the PaO_2/FiO_2 is less than 200. Low tidal volume lung protective ventilation should be considered, and therapeutic paracentesis done to aid in decreasing work of breathing.

General Management

ACLF patients should be managed in an intensive care unit (ICU). The higher mortality rate in ACLF should not deter physicians from providing ICU care. The overall outcomes in ACLF patients are similar to patients with other diseases, matched for the severity of the illness.

Nutrition is essential in patients with ACLF and a diet comprising of 35–40 kcal/kg/day and protein intake of 1.5 g/kg/day is recommended. Supplementation with trace elements and vitamins should be considered **(Fig. 1)**.

The use of albumin is recommended for its oncotic effects in presence of renal failure, spontaneous bacterial peritonitis, prevention of post-paracentesis circulatory dysfunction, as well as for its anti-inflammatory and antioxidant pleiotropic effects. The uses of non-selective beta-blockers and carvedilol have been shown to be safe and their discontinuation is not recommended.

Definite Management

Liver Transplantation

LT is the definite management of ACLF. There are no validated criteria for appropriate selection of candidates

for early LT. Early LT within the first week should be offered to those having poor prognosis at presentation (MELD >30 or AARC >10) without multiple organ failures and sepsis.[1] Dynamic monitoring with prognostic scores may help in early identification of patients who are at risk for poor outcome. Recent data suggests that LT is feasible, even in ACLF-3 cases who have 5–6 organ failures and is associated with a 1-year survival rate of more than 80% as compared to less than 10% among those not transplanted. Optimal timing of LT is crucial to have the best outcomes.

There are no established delisting criteria for LT in ACLF; however, transplant is not recommended in the presence of active sepsis.

Emerging Therapies

Artificial Liver Support Systems

Molecular adsorption and recirculating system (MARS) and fractionated plasma separation and adsorption (FPSA-Prometheus) have not shown any survival benefit in ACLF. Bioartificial liver support systems that substitute detoxification, biotransformation, and synthetic function as well by utilizing either human hepatoblastoma cell lines or porcine hepatocytes are promising. The recent creation of 3D liver organoids using hepatic progenitor cells or induced pluripotent stem cells might evolve as options for therapeutic use in future.

Plasma Exchange

Plasma exchange appears to be promising in small series. RCTs are needed to evaluate its role in management of ACLF.

Liver Regeneration

Since human liver has a huge regenerative potential due to the presence of progenitor cells, as evidenced by rapid regeneration after donor hepatectomy, it can also recover following acute insults. Contrasting results have been reported with granulocyte-colony stimulating factor (G-CSF), RCTs are needed before routine recommendation. Both bone marrow and umbilical cord derived mesenchymal stem cells have shown improvement in liver function when transfused via a peripheral vein.

Fecal Microbiota Transplantation

Evolving data suggests a potential role in alcohol-related ACLF not eligible for steroids or LT. Presently FMT remains an experimental therapy and should not be used outside of clinical trials.

Futility of Care

If LT is not available or contraindicated, presence of four or more organ failure and a CLIF-C ACLF score more than 64 is associated with a high mortality approaching 100%. In such situations, relatives should be explained about the poor outcomes.

Prevention of ACLF

Prevention of ACLF is of paramount importance. This can be achieved by preventing the acute triggers such as viral hepatitis—by universal vaccination (hepatitis B) and secondary prophylaxis with antivirals, abstinence from alcohol, and careful consideration before prescription of hepatotoxic drugs. However, despite active search, the trigger may not be detectable in up to 40% cases and is often attributed to pathological bacterial translocation occurring due to a combination of increased gut permeability and dysbiosis. Potential therapies targeting this aspect of pathogenesis are being evaluated.

The Role of a Physician

It is important for physicians to identify patients with poor prognostic factors early, so that they can be referred to higher centers for further treatment. Patients with ACLF should ideally be managed at a center with a multidisciplinary team comprising of hepatologists, gastroenterologists, LT surgeons, and critical care specialists. About one-third of patients reaching a referral hospital have an evidence of bacterial infection, making them poor candidates for LT. Hence, it is important to refer patients early, when they can still undergo LT. It is also the responsibility of the referring physician to explain the prognosis and prime the relatives to the need of LT.

Conclusion

It is essential to recognize ACLF as a distinct entity with high short-term mortality and potential reversibility. Prompt recognition and treatment strategy can result in a transplant-free survival of close to 50%.

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CHAPTER

115 Approach to a Patient with Chronic Dyspnea of Undetermined Etiology

Manish Kumar, Krishna Kumar, DP Singh

Abstract

Dyspnea is a very common complaint encountered by medical professionals working both in general medical outpatient practice and also in emergency setup. Pulmonary and cardiac etiology are most commonly encountered; however, other causes like hematological or psychogenic causes are not very uncommon. A prompt and accurate diagnosis requires meticulous examination followed by proper use of investigative tools as per protocol.

Introduction

Dyspnea is a common presenting symptom that is encountered by clinician in everyday practice. It is said to be chronic if it is present for more than 4 weeks.[1] Dyspnea is a debilitating symptom that affects the overall quality of life, exercise tolerance, morbidity, and mortality in various disease states. It is a better predictor of mortality than angina in patients with cardiac disease and forced expiratory volume in 1 second (FEV1) in patients with chronic pulmonary disease.[2] In patients with chronic obstructive pulmonary disease (COPD) and sedentary adults, chronic dyspnea leads to low adherence to exercise training programs, decreased functional status, and poor psychological health.

The exact mechanisms of dyspnea are still not very well understood. Several recent studies have emphasized on the multidimensional nature of dyspnea. The perception of dyspnea depends on varying cortical integration of several afferent and efferent signals that involves a complex chain of events.

Chronic dyspnea is most frequently either due to respiratory or cardiac cause. However, in about one third of cases, the etiology is multifactorial.[1] COPD, cardiac failure, asthma, ischemic heart disease, interstitial lung disease (ILD), and impaired psychological condition are some of the most common causes of chronic dyspnea.

Definition

The American Thoracic Society (ATS) defines dyspnea as "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses." The ATS statement also reiterates the importance of self-reporting by patients, as dyspnea can be perceived only by the person experiencing it.[3]

Epidemiology

It is difficult to ascertain the exact prevalence of chronic dyspnea in general population as different studies incorporate both acute and chronic dyspnea. Individuals above age of 70 years have higher prevalence of chronic dyspnea. Studies have shown that almost half of the patients admitted to acute tertiary care hospitals and

one-fourth of patients in ambulatory settings present with dyspnea.[4] The prevalence of mild to moderate dyspnea ranges from 9% to 13% in adults according to some population-based studies. This figure is around 25–27% in persons older than 70 years.[5]

Clinical Assessment

A proper history and clinical examination is of utmost importance. More than two-thirds of the patients need diagnostic testing beyond clinical examination. The initial clinical assessment of a patient with chronic dyspnea is directed toward determining the underlying cause, which is fundamental for management and subsequent referral to a specialist if needed. According to a study amongst patients with chronic dyspnea who were referred to a specialist cardiologist or respiratory clinic at a tertiary center, only 51% were appropriately referred as per their final diagnosis.[1] This improper initial referral leads to significant delays in final diagnosis.

The history and findings from physical examination have low positive predictive value (PPV) individually and are more useful as negative predictive factors. However, usually the clinical findings are considered in combination, hence they are more likely to provide greater diagnostic accuracy.

History

The history given by the patient in his own words is of utmost importance. The effect of position, environmental stimuli, timing, aggravating, and relieving factors are helpful in arriving at a provisional diagnosis. For example, orthopnea indicates congestive heart failure (CHF), and nocturnal dyspnea is suggestive of CHF or Asthma. Chronic persistent dyspnea is suggestive of COPD, ILD, and chronic thromboembolic disease. A previous history of drug induced or occupational lung disease, ischemic heart disease is very vital. If the patient complains of dyspnea in the upright position with relief in supine position, that is, platypnea, it could be suggestive of left atrial myxoma or hepatopulmonary syndrome.[3]

Physical Examination

A thorough physical examination is imperative for assessment of cause, severity and proper management. It starts during history taking itself when the patient's ability to complete full sentence while talking is observed. Clinical signs of pallor, cyanosis, clubbing, and pedal edema are important. The symmetry of chest wall movements with respiration should be observed.

The hemodynamic stability of patient is confirmed by measuring the vital signs. Pulsus paradoxus (i.e., decrease in systolic blood pressure of more than 10 mm Hg during inspiration) could be due to cardiac causes such as pericardial disease, restrictive heart disease, or cardiac tamponade. Pulmonary disease such as COPD, asthma, large bilateral pleural effusion, tension pneumothorax, and pulmonary embolism may also be present with pulsus paradoxus. Increased work of breathing is evident by supraclavicular retraction, use of accessory muscles of respiration and sitting with the hands braced on knees, that is, tripod position. These signs are indicative of increased airway resistance or stiffness of lungs and chest wall.

Dullness on percussion of chest wall is indicative of pleural effusion. Likewise hyperresonance is a sign of emphysema or pneumothorax. On auscultation, wheeze, crepitations, and diminished breath sounds are vital clues to the etiological diagnosis.

On examination of cardiovascular system, signs of right heart failure like elevated jugular venous pressure (JVP), peripheral edema, accentuated pulmonary component of second heart sound, S3 gallop rhythm, and presence of murmur are important.

In a study done by Pratter et al., an algorithmic approach to diagnosis of chronic dyspnea was found to be helpful in correct diagnosis in 99% of the cases.[6] At the initial visit, the patient underwent Tier 1 testing and subsequently the clinician made a diagnosis. Patient was subjected to Tier 2 and 3 testing if needed **(Flowchart 1, Table 1)**.

There are various scales to measure dyspnea, but the two most commonly used are Medical Research Council Scale for pulmonary disease and New York Heart Association functional classification for cardiac diseases **(Table 2 and Box 1)**.

Investigations

A number of diagnostic tools may be helpful in the initial the workup of a patient with chronic dyspnea.

Flowchart 1: Algorithm for evaluation of a patient presenting with dyspnea[6]

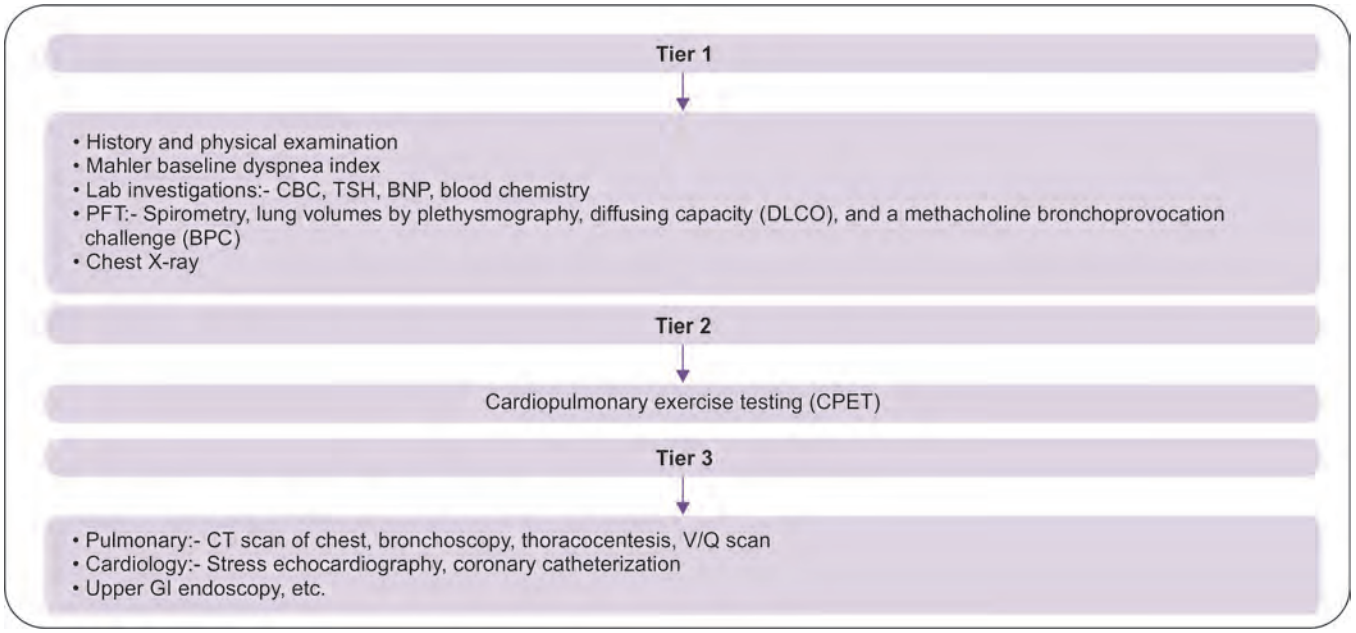

TABLE 1 Causes of dyspnea[7]

Type	*Subtype*	*Probable diagnosis*
Pulmonary	Airways	COPD, asthma, bronchiectasis, airway mass, vocal cord dysfunction
	Interstitial	ILD, passive congestion, malignancy, radiation exposure
	Alveolar	Chronic pneumonia, malignancy, emphysema
	Vascular	Pulmonary emboli, PAH
	Extrinsic	Pleural effusion, obesity, kyphoscoliosis
Cardiac	Myocardial	Ischemic heart disease, cardiomyopathy, HFrEF, HFpEF
	Arrhythmia	Atrial fibrillation, tachycardia, bradycardia
	Pericardial	Restrictive/Constrictive pericarditis, pericardial effusion
	Valvular	Aortic stenosis/Aortic regurgitation/Mitral stenosis/Mitral regurgitation
	Congenital heart disease	Intracardiac shunt, Eisenmenger syndrome
Neuromuscular	Neurogenic	Diaphragmatic paralysis, GB syndrome, myasthenia gravis, ALS
	Muscular	Muscular dystrophy, myositis, metabolic abnormalities, thyroid disease
Other causes	Anemia	Iron deficiency
	Pain	Pleural disease, postoperative period
	Psychological	Anxiety, depression, hyperventilation

ALS, amyotrophic lateral sclerosis; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension.

TABLE 2 Medical Research Council Dyspnea Scale[8]

MRC Dyspnea Scale
• Breathless only with strenuous exercise
• Short of breath when hurrying on the level or up a slight hill
• Slower than most people of the same age on a level surface or have to stop when walking at my own pace on the level
• Stop for breath walking 100 meters or after a walking few minutes at my own pace on the level
• Too breathless to leave the house or breathlessness while dressing or undressing

BOX 1 NYHA Classification[9]

A. Class I: Symptoms with more than ordinary activity
B. Class II: Symptoms with ordinary activity
C. Class III: Symptoms with minimal activity
   1. Class IIIa: No dyspnea at rest
   2. Class IIIb: Recent dyspnea at rest
D. Class IV: Symptoms at rest

Chest Radiography

After initial clinical assessment, chest X-ray is the most valuable tool for diagnosis. Hyperinflated lung fields are suggestive of chronic obstructive lung disease. Low lung volumes are seen in interstitial edema or fibrosis, diaphragmatic dysfunction or impaired wall motion. The evidence of interstitial disease, pulmonary infiltrates should be looked in pulmonary parenchyma. Pulmonary venous hypertension is suggested by prominent pulmonary vasculature in upper zones. Enlarged central pulmonary arteries suggest pulmonary arterial hypertension (PAH). Enlarged cardiac shadow could be due to dilated cardiomyopathy or valvular heart disease. CHF may present as bilateral pleural effusion on X-ray. Unilateral effusion may be due to carcinoma, pulmonary embolism, parapneumonic effusion, or even heart failure.[1,3]

Laboratory Investigations

A complete blood count is essential to assess the hemoglobin levels for anemia, which may cause dyspnea or polycythemia, which may indicate chronic hypoxemia. B-type natriuretic peptide detects cardiomyocyte strain. Hence, this can be used to differentiate between cardiac and respiratory causes of dyspnea. Chronic respiratory failure may cause carbon dioxide retention resulting in elevated bicarbonate levels. Here arterial blood gas (ABG) analysis may prove to be useful.[3,7]

Electrocardiography

An electrocardiogram (ECG) is a relatively cheap and readily available investigation that may suggest any underlying cardiac problem, which may be the cause for dyspnea. It may show evidence of ischemic heart disease, prior myocardial infarction resulting in systolic dysfunction, or valvular heart disease. In a study done amongst patients with chronic dyspnea, 8% were found to have atrial fibrillation on ECG. Among these patients 80% were later diagnosed as having dyspnea due to an underlying cardiac disease.[1]

Spirometry

Spirometry is a useful test for detecting obstructive and restrictive ventilatory defects. It is especially useful when airway diseases such as bronchial asthma or COPD are suspected. However, it is underused in clinical practice due to lack of time and resources. In a study of patients with chronic dyspnea in primary care setting, the diagnostic accuracy after clinical assessment was 55%, which increased to 72% after spirometry test.[1,2]

Echocardiography

Echocardiography is a vital tool to assess cardiac structure and function. In patients with chronic dyspnea, echocardiography can identify conditions such as heart failure (HFrEF), ischemic heart disease, valvular heart disease, pulmonary hypertension, and pericardial pathology. According to recommendations from International Heart Failure guidelines, echocardiography should be done at the earliest during the diagnostic workup of high-risk patients with chronic dyspnea. It is

noninvasive, can be easily performed even at the bedside in ICU or ER and has no side effects like radiation in CT scan.

Ultrasound

Chest ultrasound provides a wealth of information and it can be performed quickly and easily in critically ill patients. It has a higher diagnostic accuracy than a combination of physical examination and chest X-ray. Various patterns such as in acute interstitial syndrome, pneumothorax, pleural effusion, consolidation, etc. can be identified. It avoids ionizing radiation, and hence is quite safe. Lung ultrasound can also be used to guide fluid management and perform therapeutic procedures such as thoracocentesis.[10]

Chest Computed Tomography (CT)

CT scan of chest is most commonly used after an abnormal chest X-ray. It has a high sensitivity for diffuse parenchymal lung disease. It is also helpful in early detection of ILD or pulmonary emphysema. Although it is not the recommended modality, but still cardiomegaly and pulmonary edema can also be detected on CT chest. The only disadvantage of CT scan is the risk of radiation exposure. Hence, careful patient selection with assessment of risk and benefits should be done by the clinician prior to the CT scan. CT pulmonary angiography (CTPA) can be used to detect acute pulmonary embolism or chronic thromboembolic pulmonary hypertension (CTEPH).

Advanced Respiratory Function Tests

The advanced respiratory function tests are also valuable in detecting chronic dyspnea of respiratory etiology. The diffusing capacity of lung for carbon monoxide (DLCO) assesses the ability of lungs to transfer oxygen to blood. DLCO can be reduced both in PAH and ILD. DLCO in isolation is not sufficient to confirm or differentiate between the above two conditions. DLCO may predict mortality in a number of lung diseases, severe PAH, cancer, and various ILDs.[1]

Test for bronchial hyperresponsiveness by broncho-provocation helps in diagnosis of patients with suspected asthma having normal spirometry. A study showed hyperresponsiveness to challenge testing in 34% of patients with chronic dyspnea. Among these 69% were diagnosed with asthma or COPD.[1,3]

Tertiary Investigations

Depending upon the results of initial investigations, more specialized investigations are done if needed to determine the cause of chronic dyspnea. Imaging modalities such as cardiac MRI, CT, coronary angiography, stress echocardiography, lung ventilation/perfusion (V/Q) scan are done if required. Coronary angiography may also be done for assessment of coronary artery disease or pulmonary pressure. Bronchoscopy, muscle biopsy, or surgical lung biopsy are other tools. A FeNO test, or exhaled nitric oxide test, determines the lung inflammation and its suppression with steroids in patients with allergic or eosinophilic asthma.[11]

Cardiopulmonary Exercise Test (CPET)

In patients having dyspnea, which is out of proportion to known cardiorespiratory disease, CPET can provide valuable information. It involves incremental testing of exercise capacity while the patient is seated and continuously monitored on a stationary bicycle. CPET measures intake of oxygen, elimination of carbon dioxide, and minute ventilation, while exercising on the bicycle. It is helpful in confirming the diagnosis of psychogenic dyspnea. In a study among patients with chronic dyspnea, 90% with normal CPET results were diagnosed to be having a non-cardiorespiratory cause for dyspnea.[12]

Treatment

The optimal approach in the treatment of chronic dyspnea involves interventions that reduce the ventilatory demand, improve ventilatory capacity and respiratory mechanics and take care of the psychogenic aspect as well. Supplemental O_2 is usually given if resting O_2 saturation level is below 88% or if the saturation falls to this level with work or sleep. Supplementary oxygen has shown to improve mortality, especially in patients with COPD.[2,3]

Multiple interventions are often required and they may have additive or synergistic effects. Some of these interventions include oxygen therapy, bronchodilators, noninvasive ventilation, exercise training, lung volume reduction surgery, etc.

Opiates alter affective component of dyspnea and reduce the respiratory drive. Psychological counseling, behavioral therapy, and anxiolytics have favorable effects on affective dimension of chronic dyspnea. An important

component of dyspnea management is cardiac and pulmonary exercise training.

Conclusion

The diagnosis of patients presenting with chronic dyspnea in primary or tertiary care is challenging. Chronic dyspnea is most common due to a cardiorespiratory cause. However, one third of patients have multifactorial etiology. Common comorbidities such as obesity and deconditioning often contribute to symptomatology. This increases diagnostic difficulty and problems in management. Evidence-based algorithms are helpful to improve the diagnosis and subsequent management of patients presenting with chronic dyspnea.

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CHAPTER

116 "Choice versus Chance": Mathematics behind Clinical Decision-making

Alladi Mohan, Alladi Vikramchandra

Abstract

In their everyday clinical practice, doctors are faced with decisions related to investigations, interventions, or therapeutic options. These decisions are sometimes routine and simple, but may be complicated on other occasions. Clinical decision-making is challenging because, these decisions are not only unavoidable but also must be made under uncertain conditions. Mathematics underlying decision-making includes basic mathematical language of probability and Bayes' theorem. Understanding these mathematical principles and judicious application of diagnostic reasoning can help clinicians in arriving at the appropriate course of action in a rational, scientific, and objective way.

Introduction

Clinicians have to make decisions in daily practice either regarding the choice of diagnostic testing or regarding therapeutic options or interventions. These decisions are unavoidable, and are often made intuitively under uncertain conditions and, therefore, constitute a significant challenge. In this chapter we have attempted to provide an overview regarding the mathematics behind decision-making.

Basic Mathematics

To understand the science of clinical decision-making, an understanding of the basic mathematical language of probability and Bayes' theorem is essential. Bayes' theorem is a mathematical rule that defines how existing beliefs should be revised or modified when new evidence becomes available.[1-3]

Probability

In the context of clinical decision-making, probability is defined as a measure of the belief regarding the occurrence of an event. Mathematically, probability of an event A occurring is denoted as P[A] and is read as "P of A"; this value ranges from 0.0 to 1.0.[4]

Summation Principle

If in a given clinical situation, let us assume that four possible outcomes A, B, C, and D can occur by chance. The summation principle states that the "sum of probabilities" of all these four possible chance events (outcomes) equals 1.0.[4] This is mathematically written as:

$$P[A] + P[B] + P[C] + P[D] = 1$$

Joint Probability

The concomitant occurrence of a number of events is termed as "joint probability" of occurrence of those events.[4] The joint probability of occurrence of two events A and B is expressed as P[A,B].

Conditional Probability

The probability that an event A occurs, given that the event B is known to occur is termed "conditional probability" of

event A given occurrence of event B. This is expressed in statistical notation as (P[A | B]).[4]

We can also express the relationship between joint and conditional probabilities by the following formula:

$$P[A \text{ and } B] = P[A \mid B] \times P[B]$$

Independence

In a clinical situation, if the "conditional probability" of event A, given that event B occurs, is identical to the "unconditional probability" of event A occurring, then, the events A and B are probabilistically considered to be independent.[4]

This relationship is expressed as:

$$P[A \mid B] = P[A]$$

The "joint probability" of occurrence of independent events is governed by the "product rule" which states:

$$P[A,B] = P[A] \times P[B]$$

Summation Principle for Joint Probabilities

The summation principle for joint probabilities states that if B1, B2, B3, and B4 are mutually exclusive events (i.e., only one of these can occur), and A is another event, then, probability of occurrence of event A is given by the formula:

$$P[A] = P[A,B1] + P[A,B2] + P[A,B3] + P[A,B4]$$

For computing the probability of an event from several conditional probabilities, the "averaging out" method is used.

Bayes' Theorem

In clinical practice, diagnostic tests are performed to ascertain the definitive diagnosis. The possible results that are obtained on performing such a diagnostic test are listed in **Figure 1 and Table 1**. The performance of the diagnostic test is evaluated using a "gold standard" for categorization of the subjects as "having disease" or "no disease." In this situation, Bayes' theorem can be applied to estimate the probability of the disease given a positive or a negative test result. Generally, the possibilities of two disease states (disease is present/absent) are considered. However, several disease states D1, D2, and so on (up to Dn) can also be considered. Then, by applying Bayes' theorem, the revised probability of any one disease (Di)

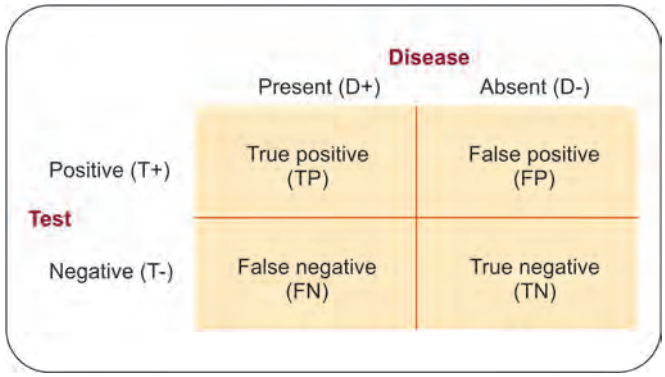

Fig. 1: Important conditional probabilities used in clinical practice

occurring given the test result R can be calculated using the formula:

$$\frac{P[R \mid Di] \times P[Di]}{P[R \mid D1] \times P[D1] + \ldots\ldots + P[R \mid Di] \times P[Di] + \ldots\ldots + P[R \mid Dn] \times P[Dn]}$$

Odds

Odds of an event are defined by the number of occurrences divided by the number of non-occurrences. For example, odds of a disease = No. of persons who develop disease during follow-up/No. of persons who do not develop disease.

If p is the probability of an event occurring, then, the probability that the event will not be occurring is denoted as (1–p). Then, the odds favoring the occurrence of the event are calculated as p/(1–p); and the odds against the event occurring are calculated as (1–p)/p.

Bayes' theorem can also be expressed in terms of odds as:

$$\underbrace{\frac{P[D+ \mid R]}{P[D- \mid R]}}_{\text{Posterior odds}} \quad \underbrace{\frac{P[D+]}{P[D-]}}_{\text{Prior odds}} \quad \underbrace{\frac{P[R \mid D+]}{P[R \mid D-]}}_{\text{Likelihood ratio}}$$

Here, D+ = disease present; D– = disease absent; R = test result; P[D+ | R] denotes the probability of the disease being present given the test result.

Likelihood Ratio

The likelihood ratio (LR) of a positive test result is the ratio of the probability of occurrence of the test result in persons with or without the disease.

LR for a positive test result = sensitivity/(1–specificity)

TABLE 1 Probabilities associated with the test results shown in **Figure 1**

Variable	*Probability notation*	*Estimate of probability*
Sensitivity True-positive rate; frequency of positive test results in persons with disease	P[T+ | D+]	TP/(TP+FN)
Specificity True-negative rate; frequency of negative test results in persons with disease	P[T- | D-]	TN/(TN+FP)
False-negative rate Frequency of negative test results in persons with disease	P[T- | D+]	FN/(TP+FN)
False-positive rate Frequency of positive test results in persons without disease	P[T+ | D-]	FP(TN+FP)
Predictive value of positive test Frequency of disease in persons with a positive test result	P[D+ | T+]	TP/(TP+FP)
Predictive value of negative test Frequency of non-disease in persons with a negative test result	P[D- | T-]	TN/(TN+FN)

FN, false negative; FP, false positive; TN, true negative; TP, true positive

Similarly, LR for a negative test result = (1–sensitivity)/specificity

Post-test odds can be computed from the "pre-test odds" and LR, using the formula:

Post-test odds = pre-test odds × LR

Some Applications of Bayes' Theorem in Clinical Medicine

Some of the applications of the aforementioned mathematical principles that are used in clinical medicine for decision-making[3,5,6] are briefly described below.

Receiver-operator Characteristic Curve

The receiver-operator characteristic (ROC) curve is plotted with 1-specificity (false positive rate) on the X-axis against sensitivity on the Y-axis. The ROC curve graphically portrays the trade-off between sensitivity and specificity for different chosen criteria (cut-off values) of positivity for the test result[4,7,8] and facilitates the identification of the optimum threshold or cut-off value **(Fig. 2, thick arrow)**. Some examples for the use of ROC curve analysis in decision-making include, defining the cut-off value of carotid intima media thickness as a surrogate marker for subclinical atherosclerosis,[9] glycosylated hemoglobin (HbA_{1c}) for the diagnosis of diabetes mellitus,[10] among others.

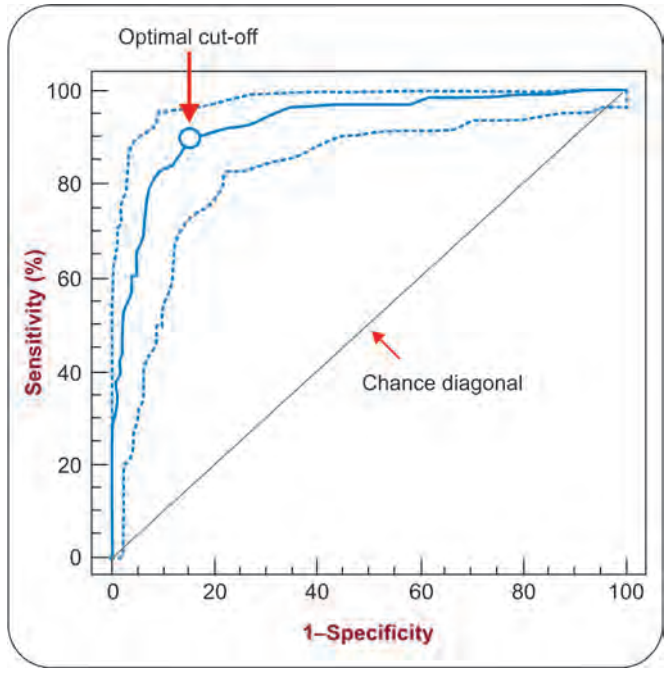

Fig. 2: Receiver-operator characteristic (ROC) curve along with 95% confidence bands (dotted lines). The ROC curve represents a graphical description of the "dynamic trade-off" between more accurate identification of subjects with disease versus those without disease. Each point on the ROC curve represents a potential cut-off value with an associated sensitivity. Area under the ROC curve (AUC) is a measure of the overall performance and ranges between 0 and 1. The line segment drawn from (0,0) to (1,1) represents the *chance diagonal* and this has an AUC = 0.5. Therefore, a diagnostic test with an AUC greater than 0.5 is better than "pure chance" in correctly categorizing a cut-off

Decision Analysis

While evaluating patients in everyday practice, a clinician takes into consideration the data obtained from the history and physical examination findings. On the basis of information thus gathered, clinicians, based on their previous experience and intuitive thinking, formulate a diagnostic work-up plan. Even though this intuitive approach has the advantage of being flexible, it is subjective and varies between various clinicians.

"Clinical decision analysis" approach has remarkably influenced decision-making in a rational way under conditions of uncertainity[4,11-14] and has facilitated choosing the best possible course of action.[4,11-14] It is an explicit, quantitative and prescriptive approach to clinical decision-making. In this approach, probabilities of arriving at a choice or chance decision, utility of the outcome from each of the options are considered and logical structure of the problem called "decision tree" is constructed. The decision tree is analyzed by considering the probability of each outcome along with its associated utility and the path with the highest expected value is chosen to arrive at a clinical decision. Clinical decision analysis has been applied in various commonly encountered clinical situations to arrive at a decision.[14-17]

Conclusion

Clear understanding of the mathematics underlying decision making and judicious application of diagnostic reasoning can help clinicians in arriving at the appropriate course of action in a rational, scientific and objective way.

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CHAPTER

117 Approach to Syncope in Emergency Room

Prasanta Kumar Bhattacharya

Abstract

Syncope, characterized by transient loss of consciousness due to cerebral hypoperfusion, is a common clinical condition requiring emergency medical attention. Emergency room approach to syncope entails its diagnosis and differentiation from other causes of transient loss of consciousness such as epilepsy, vertebrobasilar insufficiency, hypoglycaemia and psychiatric illnesses; risk stratification into high- and low-risk etiologies; and management. Vasovagal syncope and syncope due to orthostatic hypotension, which carry low-risk, usually have uneventful outcomes. Syncope due to underlying cardiac causes is usually difficult to diagnose and carry a poorer prognosis, and commonly requires hospitalization for further evaluation and management. In developed countries having well-equipped syncope units, most cases of syncope can be managed and discharged from the emergency room. However, in developing countries like India, lacking such facilities, high-risk cases of syncope should ideally be hospitalized for further evaluation and management.

Introduction

Syncope is the loss of consciousness (LOC) occurring transiently due to cerebral hypoperfusion. It is characterized by a rapid onset of the LOC, which occurs for a short duration, with a spontaneous complete recovery.[1] Syncope is a common presenting problem, accounting for 1–3% of all emergency department visits with up to 50% being hospitalized.[2-5] The LOC is associated with a brief period of actual or apparent LOC, along with loss of awareness during this period of unconsciousness, associated with abnormal motor control and loss of responsiveness.[1] Transiently occurring LOC (T-LOC) can be due to either head trauma, or can be due to non-traumatic causes. Syncope falls under the latter group, but has to be differentiated from other conditions within this sub-group of non-traumatic causes, important among these are various forms of generalized seizures; psychogenic causes like psychogenic pseudosyncope, and non-epileptic seizure; vertebrobasilar insufficiency, hypoxemia, narcolepsy with cataplexy; and hypoglycemia.[4] The term presyncope is commonly used to describe a condition resembling the prodrome of syncope, but which is not followed by actual LOC,[1] probably because the hypoperfusion of the brain in presyncope does not result in LOC. Most of the times syncope presents as a medical emergency necessitating prompt management in the emergency ward. However, differentiating it from the other common causes of T-LOC, as well as identifying patients with syncope with potentially life threatening etiologies poses as a challenge in management especially in the emergency room (ER) settings. Therefore, the main focus should be in diagnosing syncope, differentiating it from other common causes of T-LOC and its risk stratification for hospitalization and optimum management.

TABLE 1 Types of syncope with underlying mechanism and causes

Type	*Mechanism*	*Causes*
Neurally mediated (*reflex* or *vasovagal*) syncope	• Transient alteration in reflexes maintaining cardiovascular homeostasis • Transient vasodilatation/loss of vasoconstrictor tone plus bradycardia with resultant loss of blood pressure control	• Vasovagal syncope • Reflex syncope, e.g.: – Post-micturition syncope – Gastrointestinal – Carotid sinus syndrome – Ocular
Syncope due to orthostatic hypotension	Sympathetic vasoconstrictor failure ± failure of compensatory tachycardia with resultant hypotension on standing	• Primary autonomic failure • Peripheral neuropathy with secondary autonomic failure, e.g.: – Diabetes mellitus • Drug-induced • Volume depletion
Cardiac syncope	Arrhythmia and/or structural heart disease leading to decreased cardiac output	• Arrhythmia: – Bradyarrhythmias (sinus node dysfunction), high grade type II AV block, complete heart block – Tachycardia-bradycardia syndrome – Ventricular tachyarrhythmias • Structural heart disease: – Valvular heart disease – Hypertrophic cardiomyopathy – Atrial myxoma

Approach to Syncope in the Emergency Room

Classification and Etiology of Syncope[1,3]

Syncope can be classified into three broad groups:

- Reflex (neurally mediated), or vasovagal syncope
- Syncope due to orthostatic hypotension
- Cardiac syncope

In about one-third of cases the etiology of syncope is unexplained,[6] while in 10–15% of patients the etiological diagnosis of syncope remains unclear even after thorough evaluation using current diagnostic guidelines.[7,8] The different types of syncope, their underlying mechanism of development and common causes are outlined in **Table 1**.

Step-by-Step Approach in the Management of Syncope in the Emergency Room[9,10]

Step-by-step approach in the management of syncope in the ER settings can be broadly sub-divided under the following headings **(Box 1)**:

BOX 1 Step-by-step approach in management of syncope in the emergency room

- Confirmation of diagnosis of syncope by differentiating from other common causes
- Determination of the cause of syncope
- Risk assessment of syncope
- Management strategy based on risk profile

Confirmation of Diagnosis of Syncope by Differentiating from Other Common Causes

Syncope occurs due to a transiently occurring global cerebral hypoperfusion. Since cerebral hypoperfusion cannot be clinically determined one has to depend on the clinical parameter of T-LOC for a diagnosis of syncope. But T-LOC can occur due to various causes other than syncope as already mentioned. Setting aside the traumatic causes of T-LOC from our current discussion, the various common non-traumatic causes of T-LOC **(Table 2)** should be brought into the differential diagnosis of syncope

TABLE 2 Common causes of transient loss of consciousness

Causes of transient loss of consciousness	*Types/Causes*
Syncope	• Reflex/vasovagal • Orthostatic hypotension • Cardiac
Epileptic seizures	• Generalized seizures • Partial seizures
Metabolic	• Hypoglycemia
Psychogenic	• Psychogenic pseudosyncope • Psychogenic non-epileptic seizures
Uncommon	• Transient ischemic attack • Sub-arachnoid hemorrhage • Subclavian steal syndrome

in any patient brought to the ER with T-LOC without any apparent cause.[1] Some of the common causes from which syncope has to be frequently differentiated include seizures, hypoglycemia, narcolepsy with cataplexy, and certain psychiatric disorders.

Syncope versus Seizures

Syncope and seizure are the two most common causes of T-LOC and differentiation between the two is not always as easy.[1,2] Both generalized and partial seizures may be confused with syncope, although there are several differentiating points between the two. Similar to the tonic-clonic movements of generalized seizures involuntary movements like myoclonus may occur in up to 90% cases of syncope, along with mild flexor and extensor posturing. Likewise, partial or partial-complex seizures with secondary generalization are commonly preceded by an aura, which should be differentiated from the premonitory features of syncope. Further, autonomic manifestations of seizures like cardiovascular, urogenital, pupillary, and cutaneous manifestations may mimic the premonitory features of syncope; the arrhythmias associated with the cardiovascular manifestations may even lead to LOC. Nevertheless, the presence of accompanying non-autonomic auras may help differentiate these episodes in seizures from syncope. Among the points of differentiation between seizures and syncope, the LOC in seizures is usually more than 5 minutes duration with prolonged postictal drowsiness and disorientation, whereas in syncope the patient regains orientation almost immediately after the event. Muscle aches may occur after both syncope and seizures, but are more severe and long lasting after a seizure. Unlike syncope, seizures are rarely provoked by emotions or pain. Further, while incontinence of urine may occur with both seizures and syncope, fecal incontinence very rarely occurs with syncope.[4]

Syncope versus Hypoglycemia

Insulin induced hypoglycemia in diabetes mellitus may cause T-LOC, which is usually preceded by features of sympathetic overactivity like tremor, palpitations, anxiety, sweating, hunger, and paresthesia. Hunger is particularly not a typical premonitory feature of syncope. Additional neuroglycopenic features in hypoglycemia include fatigue, weakness, dizziness, and cognitive and behavioral symptoms, which are not found in syncope. Diagnostic difficulties of hypoglycemia may occur in those with strict glycemic control and repeated hypoglycemic episodes leading to blunting of the characteristic warning symptoms of hypoglycemia, or hypoglycemia unawareness.

Syncope versus Cataplexy

Patients with cataplexy, which occurs in about two-thirds of patients with narcolepsy, experience an abrupt onset of partial or complete loss of muscular tone lasting for short durations of 30 seconds to 2 minutes; usually triggered by strong emotions like anger or laughter. Unlike syncope, consciousness is maintained throughout the attacks, and there are no premonitory symptoms.

Syncope versus Common Psychiatric Ailments

Various psychiatric disorders like generalized anxiety, panic disorders, major depression, and somatization disorders are associated with an apparent LOC. These should be considered in individuals who faint frequently without prodromal symptoms. In such patients there is rarely any injury in spite of repeated falls; and there are no clinically significant hemodynamic changes like hypotension and bradycardia associated with these episodes which is found typically in vasovagal syncope.

Determination of the Cause of Syncope

Once a diagnosis of syncope has been made in the ER and other likely causes of T-LOC have been clinically excluded, one should look for any serious underlying cause for the

syncope. In about 50% of cases the cause can be identified in the ER; the serious among them are usually some non-cardiovascular causes like a ruptured abdominal aortic aneurysm, an upper gastrointestinal bleeding or a subarachnoid hemorrhage.[2] Underlying cardiovascular conditions especially arrhythmias are less frequently recognized in the ER unless it is present in the ECG on admission.[11]

Risk Assessment of Syncope

When the cause of syncope cannot be ascertained in the ER, subsequent management should be guided by assessing the risk of a serious outcome in the future, especially a major cardiovascular event or sudden cardiac death. Such risk stratification includes determining the type of syncope and the patient's risk factors for a cardiac event.[1,2,9]

There are three major types of syncope as described earlier **(Table 1)**. Syncope, which is thought to be due to either reflex or postural cause, is likely to be at low risk of serious outcome. Patients with syncope of cardiac origin are usually at a higher risk of serious coucomes.[1] The 2018 European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope provide a list of high-risk and low-risk features for risk stratification of syncope in the ER.[1] These are based on certain clinical features of the syncopal attack, past history of the patient, and findings in the ECG.

Management Strategy Based on Risk Profile

Patients who have low-risk features are usually due to reflex or postural syncope. These patients usually have either some prodromal features or typical precipitating event(s). There may be a history of recurrent syncope, and the physical examination and ECG are usually normal. The outcome in patients with reflex syncope is usually very good. Syncope due to postural hypotension also has a low risk, but the prognosis is poorer than in reflex syncope due to their comorbidities.[12] These patients can be usually discharged from the ER without hospitalization. Some patients with frequent episodes of syncope or syncope-related injuries are usually referred to special clinics for further evaluation.[2]

Patients who have high-risk features usually do not have associated prodromal symptoms or typical precipitating events like in those with low-risk features. These patients also usually have history of structural heart diseases, and their physical examination and ECG findings are usually abnormal. Structural heart disease[13] and primary arrhythmias[14] are major risk factors for sudden cardiac death and overall mortality. These patients are candidates for further investigations such as echocardiography, ECG monitoring, and other sophisticated tests and referral to specialists. These patients should not be discharged from the ER and preferably hospitalized for specialist consultations and special tests mentioned.

Clinical Evaluation in the Emergency Room Setup

Some specific baseline investigations should be carried out in the ER setup. An ECG is important because a normal ECG practically rules out any cardiological cause of syncope, except for transient arrhythmia. First-degree heart block is neither associated with a cardiac nor reflex cause of syncope. An estimation of the random blood glucose should be done to exclude hypoglycemia, which may present as collapse or seizure. Estimation of hemoglobin and the hematocrit will exclude anemia, and blood loss as a cause of syncope. Blood tests for troponin and D-dimer should be done when myocardial ischemia-related syncope or pulmonary embolism is suspected.[1] A chest X-ray or a CT brain is routinely not required.[2]

Special Tests and Investigations

Carotid Sinus Massage

Carotid sinus massage (CSM) should be considered in patients over the age of 40 years with reflex syncope of unknown origin.[1] In patients with history or clinical features of reflex syncope, if CSM causes symptomatic bradycardia and/or hypotension one can diagnose carotid sinus syndrome.[2,15]

Active Standing to Measure Postural Blood Pressure

Postural hypotension is a progressive and sustained fall of more than 20 mm Hg of systolic or more than 10 mm Hg of diastolic blood pressure (BP) from baseline or a decrease in systolic BP to less than 90 mm Hg. In classic orthostatic hypotension the time from upright position to abnormal BP response is less than 3 minutes and in delayed orthostatic hypotension it is more than 3 minutes. It is important that the procedure should be done by the clinician and not delegated to other ER staff.[2,16]

ECG Recording

In addition to the standard 12-lead ECG, the patient should be put on continuous ECG monitoring if cardiac arrhythmia is suspected to be the cause of the syncope. It has been found that ambulatory ECG monitoring in unexplained syncope can identify arrhythmia to be the cause for the syncope in about 10% patients with a diagnostic yield in about 75% of such cases.[17]

Echocardiography

Patients with a heart murmur or history of structural heart disease requires an echocardiographic examination. One has to differentiate a benign flow murmur from a murmur of aortic stenosis and hypertrophic cardiomyopathy.[18]

Troponin to Rule Out Acute Coronary Syndrome

Where ECG changes are consistent with acute myocardial ischemia high sensitivity troponin test should be done to rule out acute coronary syndrome.[19]

Decision Regarding Hospitalization

Across the world the hospitalization rate of patients with syncope attending the emergency department is quite high. About one half of these patients attending the emergency department are usually hospitalized; and approximately half of the admitted patients would be discharged with no clear diagnosis, even after extensive investigations.[20] Many of the hospitalizations for syncope are unnecessary;[2] two-thirds of serious outcomes occur while the patient is in the ER and the rate of serious outcomes after the patient is shifted out of the ER is actually quite low, being as low as 3.6% at one-month follow-up.[1] Hospitalization is indicated mainly for patients requiring syncope-related treatment and those with severe comorbidities or syncope-related injury caused by the primary event. In developed countries where there are specialized syncope clinics with facilities for investigations and treatment in the ER setups patients with higher risk profiles can be managed in the ER settings and so hospitalization can be rationalized.[21,22] However, since such advanced syncope units are not commonly available in developing countries patients with high-risk should be ideally hospitalized for further evaluation and appropriate management.

Conclusion

Syncope is a common medical emergency. In the ER setting it is very important to first differentiate it from other serious causes of transient LOC like seizure or hypoglycemia. Thereafter, one should try to find out the underlying cause of syncope. A thorough history and clinical examination, and an ECG can most of the time distinguish the high-risk group of syncope due to heart diseases from those with lower risks due to orthostatic hypotension or reflex syncope. Additional tests like carotid sinus massage, echocardiography, cardiac troponin, or ECG monitoring may be required in the ER setting. Those with a high risk require urgent investigation and hospitalization.

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CHAPTER

118 Nailing the Diagnosis through Nail Changes

Bidita Khandelwal, Pradeep Balasubramanian

Abstract

Nail, a cutaneous appendage, serves as an invaluable tool in unveiling the underlying systemic diseases. The nail changes can precede or coexist with the underlying systemic diseases. The presence of a particular nail change in several or all the nails is the feature of systemic disease or associated dermatologic disorder. The nail changes can involve various components of the nail such as nail matrix, nail plate, nail bed, or periungual tissue. In this chapter, we have discussed about various nail changes, specific features to identify them and its usefulness in delineating the associated systemic diseases comprehensively.

Introduction

Nail changes serves as window for diagnosis of several systemic diseases. Hippocrates in 5th century described clubbing to be associated with several systemic diseases.[1] Since then several nail changes were found to be associated with systemic diseases. The nail changes in isolation or as a complement help to diagnose underlying disease. Nail changes can precede or can occur coexist with systemic disorders. Fingernail changes are more reliable than toenail changes since toenail changes can be altered by trauma. The components of nail unit is illustrated in **Figure 1**.

In this chapter, comprehensive facts regarding identification of nail changes and the systemic diseases associated with them are discussed. An important fact that needs to be emphasized upon is that trauma to the nail matrix or nail can result in several nail changes which will be confined to the trauma inflicted nail only. Whereas the nail changes due to the systemic diseases will be seen uniformly involving all the nails. The nail disorders that will be discussed are briefed in **Table 1**.

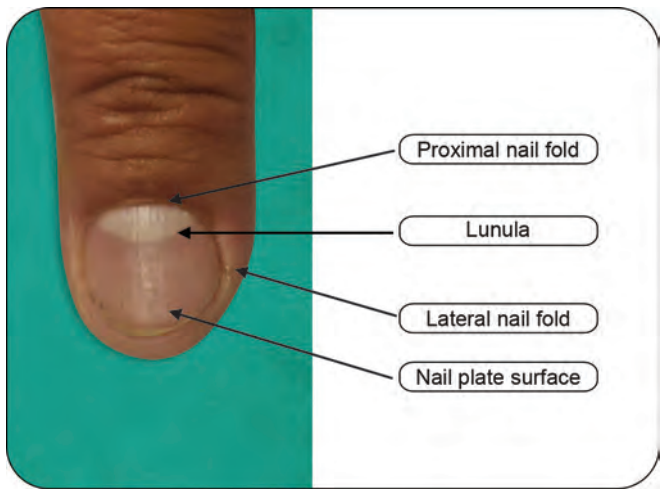

Fig. 1: Components of nail unit

Koilonychia (Spoon-shaped Nails)

It is characterized by concave dorsal surface of the nail **(Fig. 2)**. It is due to fragility of nails coupled with increased pressure exerted at the lateral and distal edges of the nails that make these edges to get reverted. The

TABLE 1 Classification of nail changes pertaining to systemic diseases

Abnormalities of nail surface	*Abnormalities of nail color*
• Koilonychia • Beau's lines • Clubbing • Pitting • Longitudinal ridging • Pterygium	• Leukonychia (total, striate, & punctate) • Terry nails • Muehrcke's lines (Apparent leukonychia*) • Lindsay nail • Splinter hemorrhages • Melanonychia • Cyanosis • Icterus • Yellow nail syndrome • Nicotine staining
Abnormalities in nail attachment	***Abnormalities in periungual region***
• Onycholysis • Pterygium	• Periungual telangiectasia • Paronychia

*Apparent leukonychia is due to the changes in the nail bed, which makes the nail look white

central aspect is depressed since it's tightly attached to nail bed.[2] Koilonychia can be congenital, acquired, or idiopathic. Iron deficiency anemia is the most common systemic cause followed by hemochromatosis, Raynaud's phenomenon, or systemic lupus erythematosus and among high altitude inhabitants.[3,4] It can also develop due to trauma to the nail matrix area, occupational exposure to petroleum-based solvents.[5]

Beau's Lines

These are transverse lines or ridges, which are parallel to lunula of the nails **(Fig. 3)**. They develop due to acute febrile illnesses, acute myocardial infarction, malnutrition, chemotherapeutic drugs, or trauma to nail matrix area. It occurs due to temporary cessation of nail growth. Nail grows at a rate of 3.5 mm per month approximately.[6] Considering this fact, the distance of these lines from the cuticle tells about the time period before when the systemic disease had resulted. The width of the line tells about the duration of illness.

Clubbing

Clubbing refers to the nail change featured by increased longitudinal and transverse curvature of nail plate combined with soft tissue hypertrophy of the digital pulp

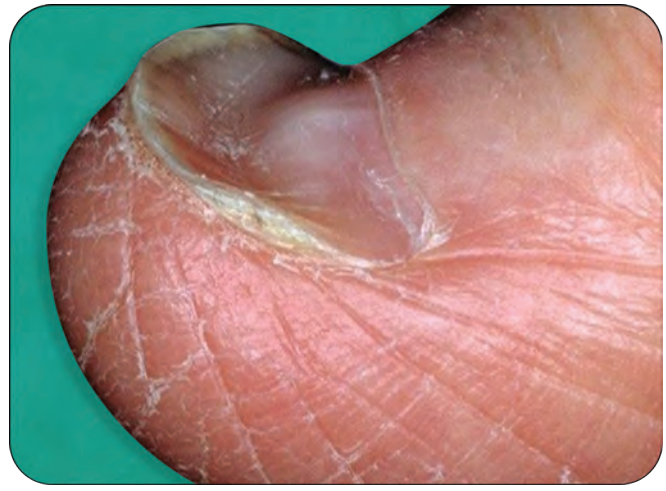

Fig. 2: Koilonychia

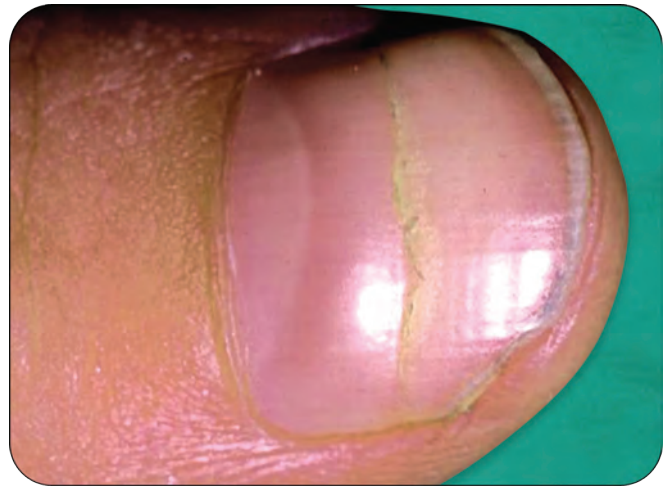

Fig. 3: Beau's lines

usually seen involving all the nails **(Fig. 4)**. Clubbing is extensively studied and it forms an integral component of general physical examination. Clubbing can be hereditary, acquired, or idiopathic.

The causes for clubbing can be remembered by the mnemonic CLUBBING which include:

- Cardiac diseases: congenital cyanotic heart diseases, acyanotic congenital heart diseases with reversal of shunt, infective endocarditis, atrial myxoma
- Lung diseases: lung abscess, bronchiectasis, emphysema, mesothelioma, cystic fibrosis, tuberculosis, pulmonary AV malformation, tuberculosis with cavitation

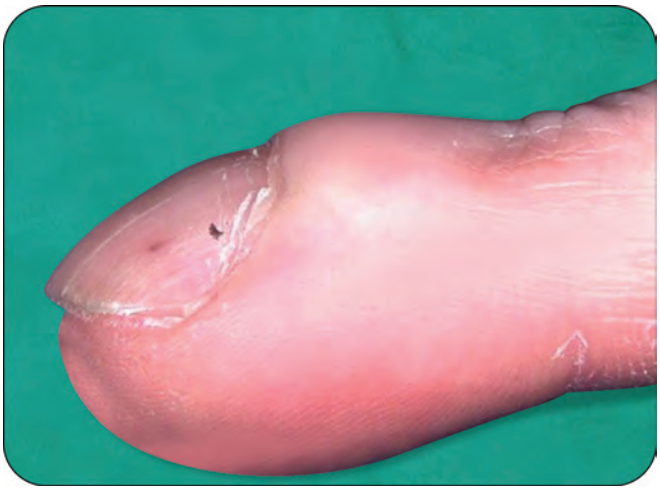

Fig. 4: Clubbing

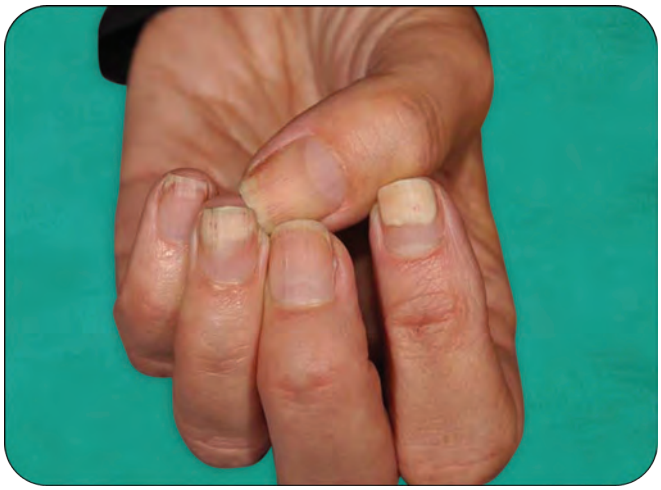

Fig. 5: Onycholysis

- *U*lcerative colitis & Chron's disease (inflammatory bowel disease)
- *B*iliary cirrhosis (primary), cirrhosis due to other causes
- *B*ronchogenic carcinoma (most commonly small cell)
- *I*diopathic
- Co*n*genital
- *G*astrointestinal: malabsorption (celiac disease)

Miscellaneous causes: HIV, sarcoidosis, Hodgkin's disease, thyroid disorders, thymus tumor, and acromegaly.

Clubbing is caused by proliferation of connective tissue (fibroblasts, blood vessels, and bone tissue) and edema under the influence of VEGF (Vascular Endothelial Growth Factor) or PDGF (Platelet Derived Growth Factor) the levels of which get increased due to hypoxia or malignancies.[7]

Unilateral and unidigital clubbing can be caused by several factors as mentioned in the **Table 2**.

There are three famous geometric forms associated with clubbing namely:

- *Lovibond angle:* It is the angle between the nail plate and the proximal nail fold. It is usually less than 160° but increases beyond 180° in clubbing.
- *Curths angle:* It is the angle at the distal interphalangeal joint. Normally it is 180°. But in clubbing, it is reduced to less than 160°.
- *Schamroth sign:* It is featured by the obliteration of the diamond shaped space which is formed by approximation of the distal interphalangeal joint and the nail plate of the right and left identical digits.

TABLE 2 Causes of unilateral and unidigital clubbing

Causes of unilateral clubbing	*Causes of unidigital clubbing*
• Aortic or subclavian artery aneurysm • Axillary artery aneurysm • Brachial AV fistula • Recurrent dislocation of shoulder • Pancoast tumor • Erythromelalgia • Lymphangitis • Hemiplegic stroke	• Median nerve injury • Tophaceous gout • Sarcoidosis • Trauma

Following are the grades of clubbing:

- *Grade 1:* Fluctuation of nail bed
- *Grade 2:* Increased anteroposterior and transverse diameter of nails
- *Grade 3:* Increase in pulp tissue resulting in drumstick appearance of the fingers
- *Grade 4:* Hypertrophic osteoarthropathy (HOA) characterized by deep pain in the distal extremities more during night and on dependency[7]

Onycholysis

It is characterized by detachment of nail plate from nail bed resulting in whitish or yellowish coloration **(Fig. 5)**. This color change is due to the presence of air column beneath the detached portion of the nail plate. It can result due to numerous factors namely local causes (trauma, working in wet environment), cutaneous disorders (psoriasis,

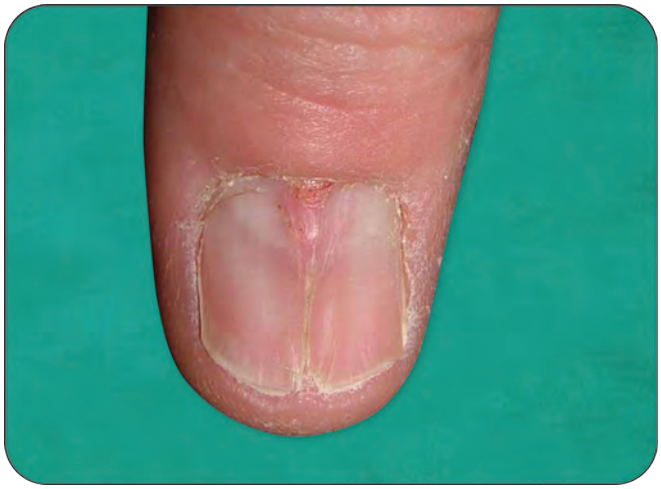

Fig. 6: Pterygium of the nail

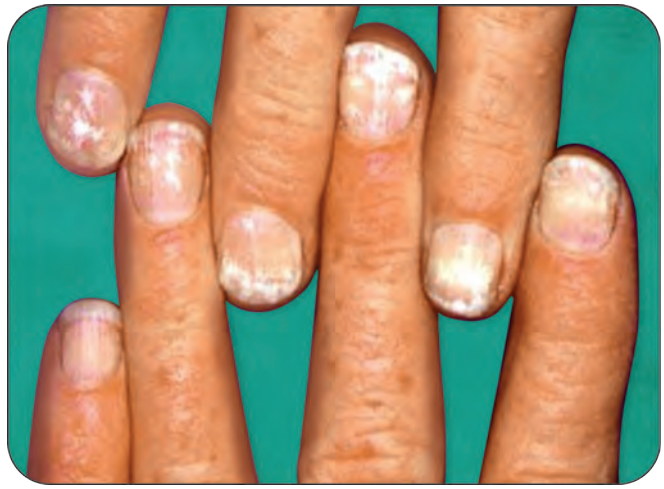

Fig. 7: Leukonychia

onychomycosis), and systemic causes (hyperthyroidism). Onycholysis in hyperthyroidism is called "Plummer's nails."[8]

Pterygium

It is the extension of the proximal nail fold over the surface of nail plate commonly seen in lichen planus **(Fig. 6)**. Pterygium inversum is a condition in which the nail bed tissue is attached to the distal under surface (ventral surface) of the nail associated with obliteration of distal groove. It is commonly seen in scleroderma.

Leukonychia

It denotes the white coloration of the nails **(Fig. 7)**. If the white color is due to abnormal keratinization it causes true leukonychia whereas the changes in nail bed lead to apparent leukonychia. Apparent leukonychia fades on application of pressure to the surface of the nails whereas true leukonychia remains unaltered. True leukonychia grows out along with the growth of the nail plate whereas apparent leukonychia persists since it is due to the changes in the nail bed.

Total Leukonychia

It is most commonly congenital or can develop secondary to renal failure, liver disorders, protein losing enteropathies, following acute illnesses.[9]

Punctate Leukonychia

It is characterized by white dot or streak seen involving nail(s). It is caused by trauma to the nail plate or nail matrix, commonly due to nail biting or habitually picking the proximal nail fold.

Mees' Lines

It is a classic example of striate true leukonychia, which is seen involving the whole width of the nails. They do not fade on application of pressure and they grow out with time.[10] Though it is characteristically known to occur in Arsenic toxicity, it is also reported in carbon monoxide poisoning, congestive cardiac failure, renal failure, due to chemotherapeutic medications, Hodgkin's disease, and pneumonia.[11]

Terry Nails

It is featured by whitish (pale) proximal portion and normal vascular band distally. It is seen associated with congestive cardiac failure, adult-onset diabetes mellitus, peripheral vascular disease, hemodialysis, and HIV.[12] Altered nail bed vascularity is a probable pathogenesis.

Muehrcke's Lines

These are apparent leukonychia featured by paired white lines, which run parallel to the lunule most commonly seen on the 2nd, 3rd, and 4th fingernails. They fade on

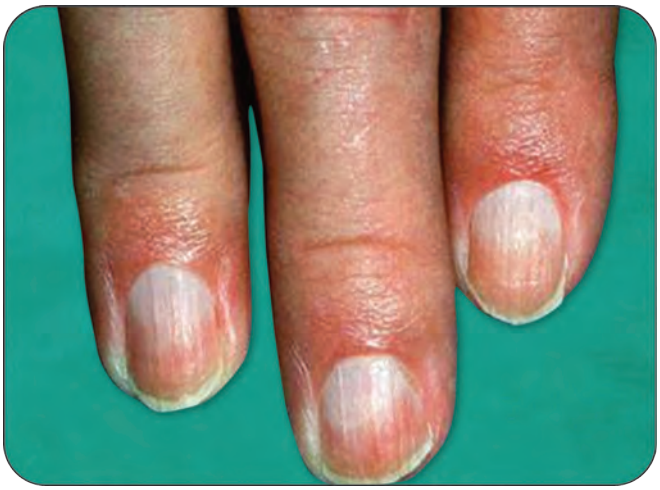

Fig. 8: Lindsay nails

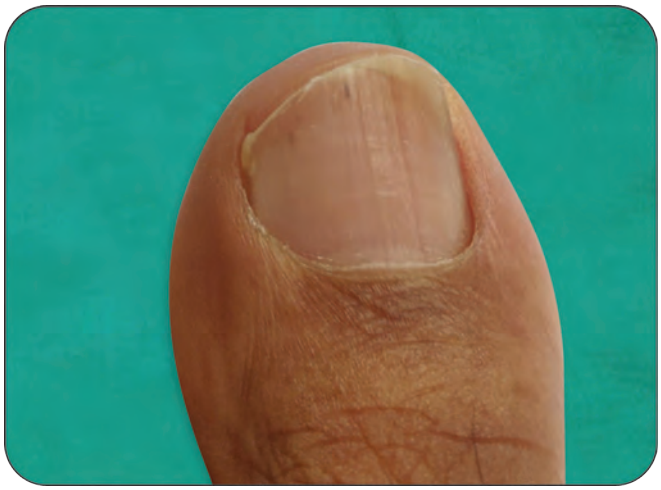

Fig. 9: Splinter hemorrhages

application of pressure and they do not grow out with time. It is commonly caused by chronic hypoalbuminemia and chemotherapeutic medications (commonly by doxorubicin and cyclophosphamide).[13] The localized edema of nail bed that compresses the vasculature is hypothesized as the pathogenesis.

Half and Half Nail (Lindsay Nail)

It is characterized by normal proximal half and brownish discoloration of distal half of the nail **(Fig. 8)** and is seen in patients with chronic renal failure.[14] It is due to increased vascular proliferation in the distal nail bed.

Splinter Hemorrhages

These are tiny linear red or brown streak oriented linearly and longitudinally **(Fig. 9)**. It occurs due to extravasation from subungual blood vessels. Its occurrence in many or all the nails indicates systemic cause. Subacute bacterial endocarditis is the most common systemic cause followed by SLE, antiphospholipid antibody syndrome, Raynaud's disease, rheumatic heart disease, rheumatoid arthritis, internal malignancies, and medications (aspirin, warfarin, chemotherapeutic medications, tetracycline, and ganciclovir).[3,15-17] Certain dermatologic diseases like psoriasis and lichen planus can also be associated with splinter hemorrhages.

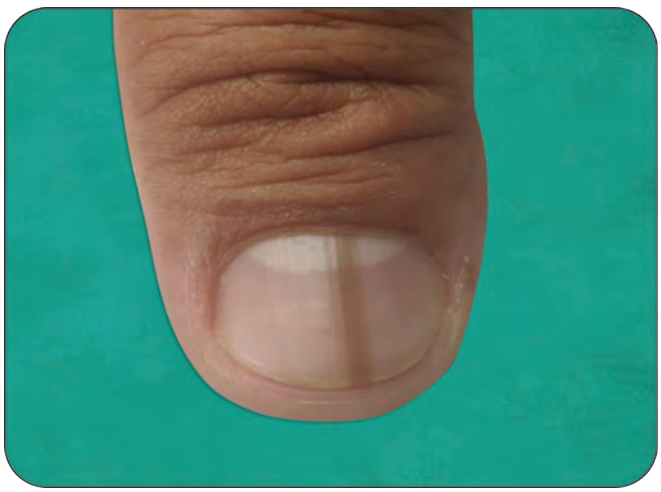

Fig. 10: Longitudinal melanonychia

Melanonychia

It is featured by black discoloration of the nail most commonly in the form of longitudinal black line (longitudinal melanonychia) **(Fig. 10)**. It occurs due to trauma, racial factors, smoking, iron deficiency anemia, hemochromatosis, thyroid disease, Addison's disease, HIV infection, and medications (antimalarials, minocycline, phenytoin, psoralens, sulfonamides, zidovudine, doxorubicin, methotrexate, and azathioprine).[18] It can be due to melanoma, which is characterized by pigmentation

of the proximal nail fold (Hutchinson sign), irregular black pigmentation of nail plate and wider band size.

Nicotine Staining of Nails

It is characterized by yellowish discoloration of the nails seen in chronic smokers.

Cyanosis

The bluish discoloration is due to the change in the color of the nail bed, which is seen through the nail plate. It is seen in the conditions causing peripheral cyanosis such as cold exposure, congestive cardiac failure, peripheral vascular disease. Transient cyanosis preceded by pallor and followed by erythema is the sequence of color change in Raynaud's phenomenon.

Icterus

In hyperbilirubinemia, the nails appear yellowish.

Yellow Nail Syndrome

It refers to the triad of yellowish color change of the nails, lymphedema and pleural effusion. It usually develops in the adults but can occasionally occur during childhood also.[19]

Red Lunula

It is seen in collagen vascular disorders, psoriasis, cardiac failure, cirrhosis, chronic obstructive pulmonary disease (COPD), and carbon monoxide poisoning.[19]

Periungual Telangiectasia

It serves as an important marker in the diagnosis of SLE, scleroderma, and dermatomyositis. It is also seen in diabetes mellitus, COPD, and rheumatoid arthritis.

Paronychia

It is the inflammation of the nail fold(s) **(Fig. 11)**. Acute paronychia is commonly caused by staphylococcus, the presence of which needs ruling out diabetes. Chronic paronychia is seen commonly among those who use detergents over a long span of time.

Psoriatic Nail Changes

Psoriasis is considered as systemic disease nowadays due to its association with metabolic disorder. Coarse pitting, longitudinal ridging, salmon patch, oil drop sign, and subungual hyperkeratosis are some of the classical nail changes in psoriasis **(Fig. 12)**. The presence of nail changes in a patient with psoriasis predicts increased chances of development of psoriatic arthritis, especially distal interphalangeal arthritis type.[20]

Onychomycosis

It is the fungal infection of the nail unit caused by dermatophytes or non-dermatophyte molds **(Fig. 13)**. It can be of various colors such as white, yellow, gray, or black. Onychomycosis is of four types based on the portion of nail it affects namely:

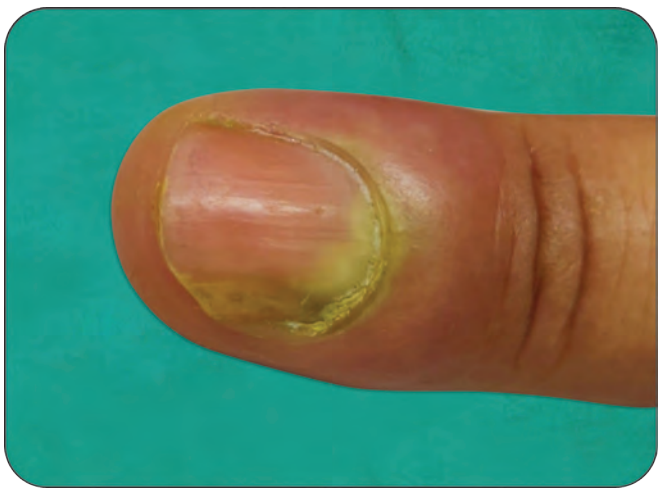

Fig. 11: Acute paronychia

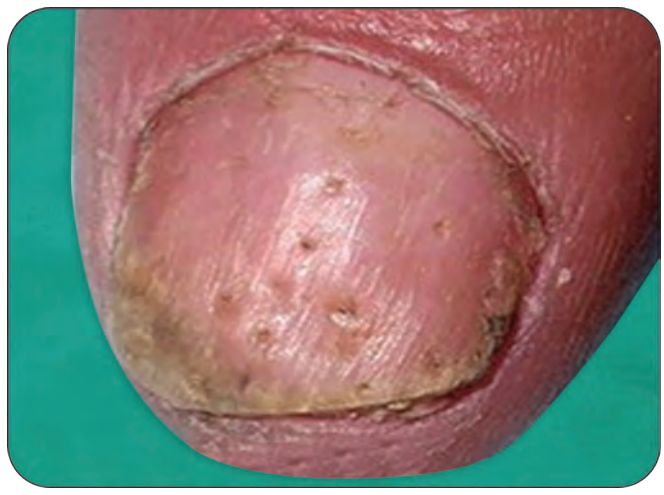

Fig. 12: Coarse nail pits in psoriasis

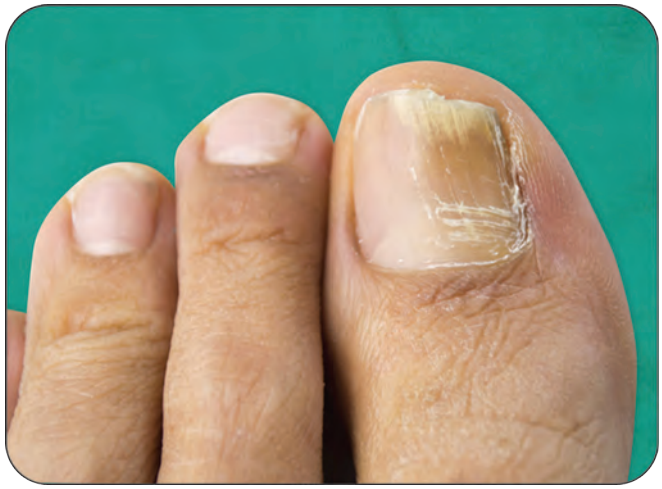

Fig. 13: Onychomycosis

- Distal subungual onychomycosis (common type) is often seen in those whose feet or hands remain moist for prolonged duration. In diabetics and immunocompromised individuals, it is thicker and resistant to therapy,
- Proximal subungual onychomycosis is usually seen in immunocompromised individuals,
- Superficial white, and
- Total dystrophic type.

Pseudomonas Nail Infection

It causes greenish discoloration of the nails. It is seen commonly in whom the hands or feet remain wet for prolonged duration.

Acknowledgement: Journal of the American Academy of Dermatology for the figures.

Conclusion

Nails serve as an invaluable tool to diagnose the underlying systemic diseases and thus it is important to identify the nail changes. Nails can be easily examined and is a convenient diagnostic tool and thus the importance of including the nail changes as a part of general physical examination should always be emphasized.

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CHAPTER

119 Anatomic Localization of Classical Neurological Symptoms

Uddalak Chakraborty, Avik Mukherjee, Jyotirmoy Pal

Abstract

Anatomical localization means the site of lesion responsible for a patient's symptoms and signs. Neurological localization requires a comprehensive understanding of anatomy and physiology of the nervous system. The process of localization shall begin during history taking, may be refined during clinical examination, and shall be reassessed after relevant diagnostic studies. Despite the advent and use of modern neuroimaging, nothing can replace a clinician's acumen to localize based on history and examination.

Introduction

"I believe a neurologist who can happily spend 3 days examining a patient for challenging anatomical localization will also be able to make a correct diagnosis within 3 minutes in acute stroke. The most important outcome of a neurological examination is anatomical localization."[1] Localization is derived from the Latin word locus which means site. The diagnostic exercise of determination of the site of nervous system affected by a disease process, from the signs and symptoms, is termed as localization in neurology.

Some authors argue that emphasis on anatomical localization over years has hindered the development of therapies in neurological diseases including epilepsy, migraine, Guillain-Barré syndrome, Parkinson's disease, multiple sclerosis and ischemic stroke, etc. However, the diagnosis of idiopathic epilepsy, migraine, and Parkinson's disease still remains clinical. Specialized neuroimaging may have complemented the clinical diagnosis, but can hardly replace it; there lies the importance of localization.

Common neurological symptoms can be localized by meticulous history taking and appropriate clinical examination, but sometimes one should be aware of false localizing signs or symptoms, which may misguide the clinician. In this chapter, we will try to localize lesions based on a few common neurological symptoms.

Weakness

Weakness is a characteristic and common motor neurodeficit, which may or may not be accompanied by other symptoms per se. First of all, true weakness should be differentiated from apparent weakness, either a vague feeling of tiredness or even malingering which may present like organic weakness. Proper clinical examination noting especially the distribution of weakness, any distractibility and a properly conducted Hoover's test may differentiate between these. After identification of true weakness, it should be categorized into an upper motor neuron type (UMN) or lower motor neuron type (LMN) weakness, differentiating features of which are given in **Table 1**.

UMN weakness predominantly affects extensors of upper limbs and flexors of lower limbs.

Hemiparesis

Weakness of upper limb, trunk, and lower limb of one side of body is usually the commonest presentation of stroke.

TABLE 1 Differentiation of UMN and LMN weakness based on symptoms

	UMN lesion	*LMN lesion*
Tone	Spastic	Flaccid
Wasting	Nil/Minimal	Significant Wasting
Fasciculation	Absent	May be present

TABLE 2 Possible localization of hemiparesis

Site of lesion	*Features*
Cerebral lesion ***Complete hemiparesis:*** Involvement of same side of face (predominantly lower half) with ipsilateral hemiparesis can be commonly localized in the internal capsule.	• **Contralateral cortex:** Distal predominant distribution of mild to moderate weakness with seizures, loss of cortical sensations, agnosia, aphasia, etc. • **Contralateral subcortical (corona radiata):** Faciobrachial weakness with aphasia, homonymous visual field defects. • **Internal capsule:** Dense hemiplegia, hemianopia, hemianesthesia.[2]
Brainstem	• Cranial nerve palsy LMN type with contralateral hemiparesis—crossed hemiparesis • Ipsilateral Horner's syndrome due to involvement of sympathetic trunk. May also be seen in ipsilateral thalamic lesions. • Ipsilateral hemiataxia due to involvement of cerebellum and its connections.
Cervical cord	• Ipsilateral hemiparesis sparing face • Ipsilateral loss of vibration and joint position sense with contralateral pain and temperature loss, usually one to two segments below the lesion (Brown-Sequard syndrome) • LMN findings at the level of lesion.

Hemiplegia means complete loss of motor function on that side.

Hemiparesis is usually due to involvement of contralateral corticospinal tract (CST) from cerebral cortex to lower medulla or ipsilateral CST in case of a high-cervical cord lesion. Localization of hemiparesis is demonstrated in **Table 2**. CST with possible sites of lesion in hemiparesis has been shown in **Figure 1**.

Cruciate hemiparesis: Weakness of ipsilateral upper limb with contralateral lower limb weakness is termed as cruciate hemiparesis. The neuroanatomical explanation involves the complex somatotopic and anatomical segregation of the CSTs in the decussation at the lower medulla oblongata or cervicomedullary junction. At this level, the ventromedially located arm fibers decussate rostral to the leg fibers, and a lesion at this specific point can lead to this entity.[3]

False Localization in Hemiparesis

Kernohan's Notch Syndrome **(Fig. 2)***:* A supratentorial lesion may lead to transtentorial herniation of the temporal lobe, with compression of the ipsilateral cerebral peduncle against the tentorial edge; since this is above the pyramidal decussation, this may lead to a contralateral hemiparesis. Occasionally, the hemiparesis may be ipsilateral to the side of lesion, and hence false-localizing; this occurs when the contralateral cerebral peduncle is compressed by the free edge of the tentorium.[4]

Monoparesis may be localized to cerebral cortex or subcortex due to selective involvement representing that particular limb.

Paraparesis

Weakness of both lower limbs may also be a common presenting symptom. We have to differentiate UMN and LMN type of lesions from history and clinical examination **(Table 3)**.

Features suggestive of myelopathy include a definite level below which sensory modalities may be impaired/absent; LMN weakness at the level of lesion and UMN weakness below the level of lesion and bladder/bowel disturbance.

Patient may complain a girdle-like sensation suggestive of the sensory level of cord involvement. *False localization:* Compressive lower cervical or upper thoracic myelopathy may produce spastic paraparesis with a mid-thoracic girdle sensation.[5]

Cerebral cause of paraparesis may be accompanied by seizure, headache, etc. Cauda equina and conus medullaris may be differentiated based on symptoms as in **Table 4**.

Quadriparesis

Weakness of all four limbs; may be again categorized into UMN and LMN **(Table 5)**.

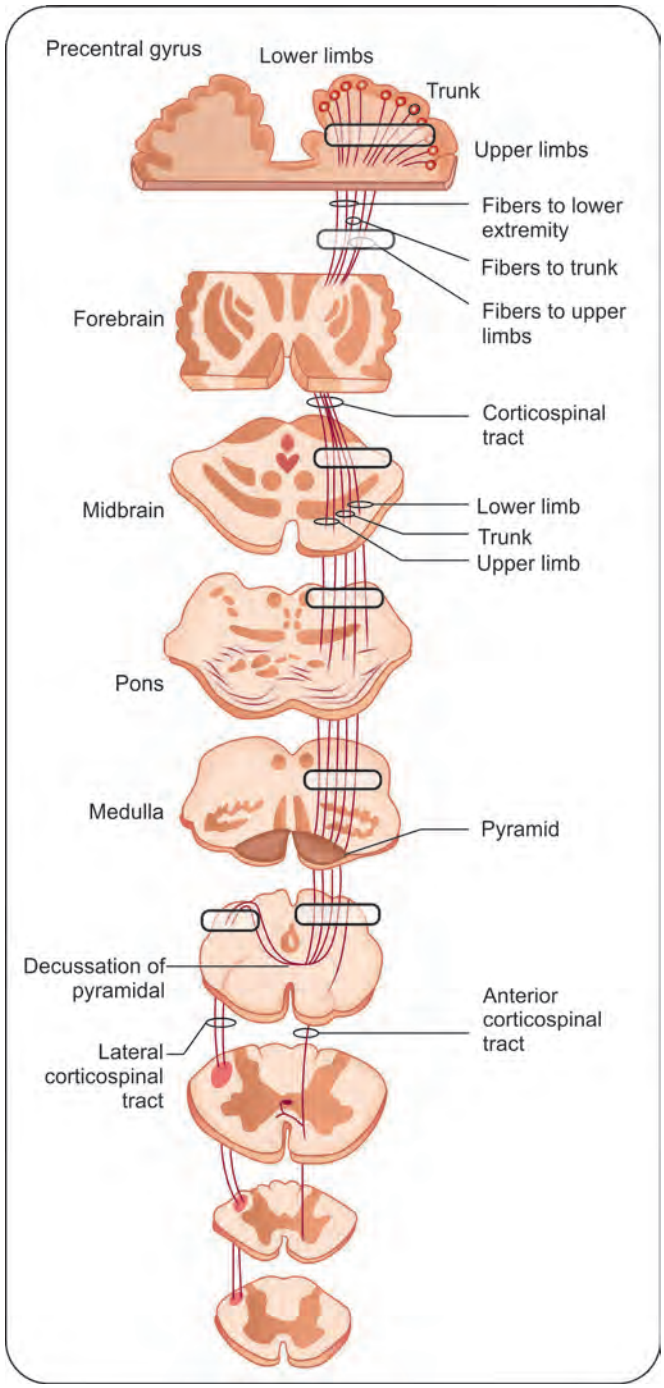

Fig. 1: Corticospinal tracts with possible levels of lesion in hemiparesis

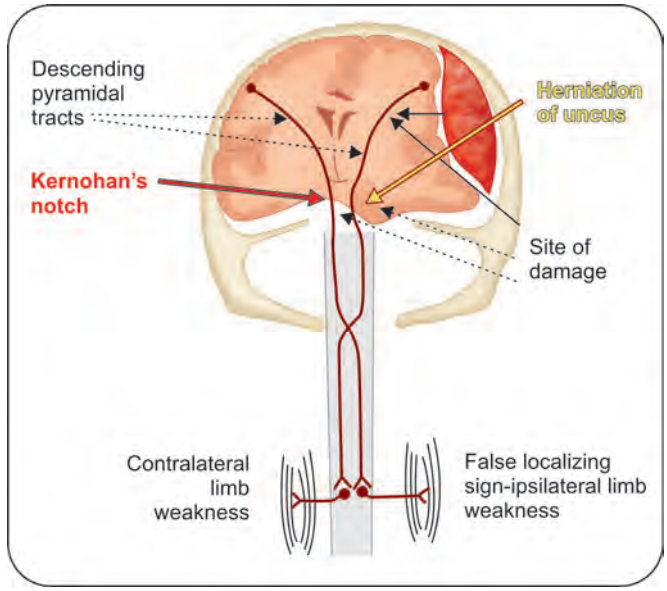

Fig. 2: Kernohan's notch syndrome

TABLE 3 Possible localization of paraparesis

Type of lesion	*Localization*
UMN	• Central nervous system above lumbosacral cord. • Commonly in thoracic cord • Rarely in cervical cord • Occasionally, midline cerebral lesion like parasagittal meningioma
LMN	• Conus medullaris • Cauda equina • Anterior horn cells in lumbar cord • Motor root of nerves of lower limb • Motor nerves of lower limb • Neuromuscular junction • Muscle

Sensory Abnormalities

Positive symptoms: Tingling (pins and needles), burning, band like, itch, aching.

Negative symptoms: Numbness, difficulty in coordination of limbs in dark places or closure of eyes **(Table 6)**.

Pattern of sensory abnormalities have been shown in **Figure 3**. Localization of sensory abnormalities are given in **Table 7**.

Incoordination

In a patient with gait imbalance, we have to rule out any nerve and muscle disorder, spinal cord or basal ganglia disorder.

Localization of ataxia has been discussed in **Table 8**.

TABLE 4 Cauda versus conus medullaris

	Cauda equina	*Conus medullaris*
Pain	Severe, asymmetric, radicular	Less common
Sensory loss	Asymmetric lower limbs, patchy	Symmetric saddle anesthesia
Motor loss	Asymmetric	Symmetric
Sphincter involvement	Less common and late	Common and early

TABLE 5 Possible localization of quadriparesis

Type of lesion	*Localization*	*Features*
UMN	**Cervical cord** **False localization**: Thoracic sensory level, paresthesia, clumsiness, and atrophy of hands.	**Cervical myelopathy**: • Weakness of all muscles below a particular level. • Sensory loss below a circumferential level. • Sphincter disturbance **High cervical cord/foramen magnum:** • Neck stiffness, suboccipital pain in C2 distribution. • Electric shock like sensation on flexion of neck. • Sequential weakness (Ehrlich's phenomenon) • Downbeat nystagmus, cerebellar ataxia (foramen magnum) • Onion skin pattern of sensory loss of face
	Brainstem	Cranial neve palsies, Horner's syndrome, Internuclear ophthalmoplegia
	Brain (bihemispheric lesion)	Pseudobulbar palsy (emotional lability/incontinence, spastic dysarthria)
LMN	**Anterior horn cells**	Pure motor weakness, prominent wasting, distal>proximal
	Polyradiculopathy **False-localizing radiculopathy** may occur in Idiopathic Intracranial Hypertension and cerebral venous sinus thrombosis and may manifest as acral paresthesias, backache and radicular pain, and less often with motor deficits	Predominant proximal weakness with sensory symptoms.
	Polyneuropathy	Distal symmetric weakness with sensory impairment in glove and stocking distribution.
	Neuromuscular junction	Predominant proximal pure motor weakness with diurnal variation, fatiguability.
	Muscle	Pure motor weakness without diurnal variation, fatiguability.

Speech Disorders

A communication disorder in the form of slurred speech, strained/effortful speech, monotonous low volume speech, word finding difficulty, comprehension difficulty, and naming problems should be recognized at first.[7,8]

Dysarthria as difficulty of articulation should be segregated from aphasia; if dysarthria present, it may be localized depending on the following types:

- *Spastic dysarthria:* Pseudobulbar/UMN involvement
- *Flaccid dysarthria:* LMN involvement

TABLE 6 Distribution of symptoms in reference to sensory and autonomic fibers

Fibers	*Symptoms*
Small fibers	Burning, painful dysesthesia, autonomic dysfunction
Large fibers	Sense of imbalance, limb incoordination, tingling
Autonomic	Postural dizziness, fainting, heat or cold intolerance, sphincter dysfunction

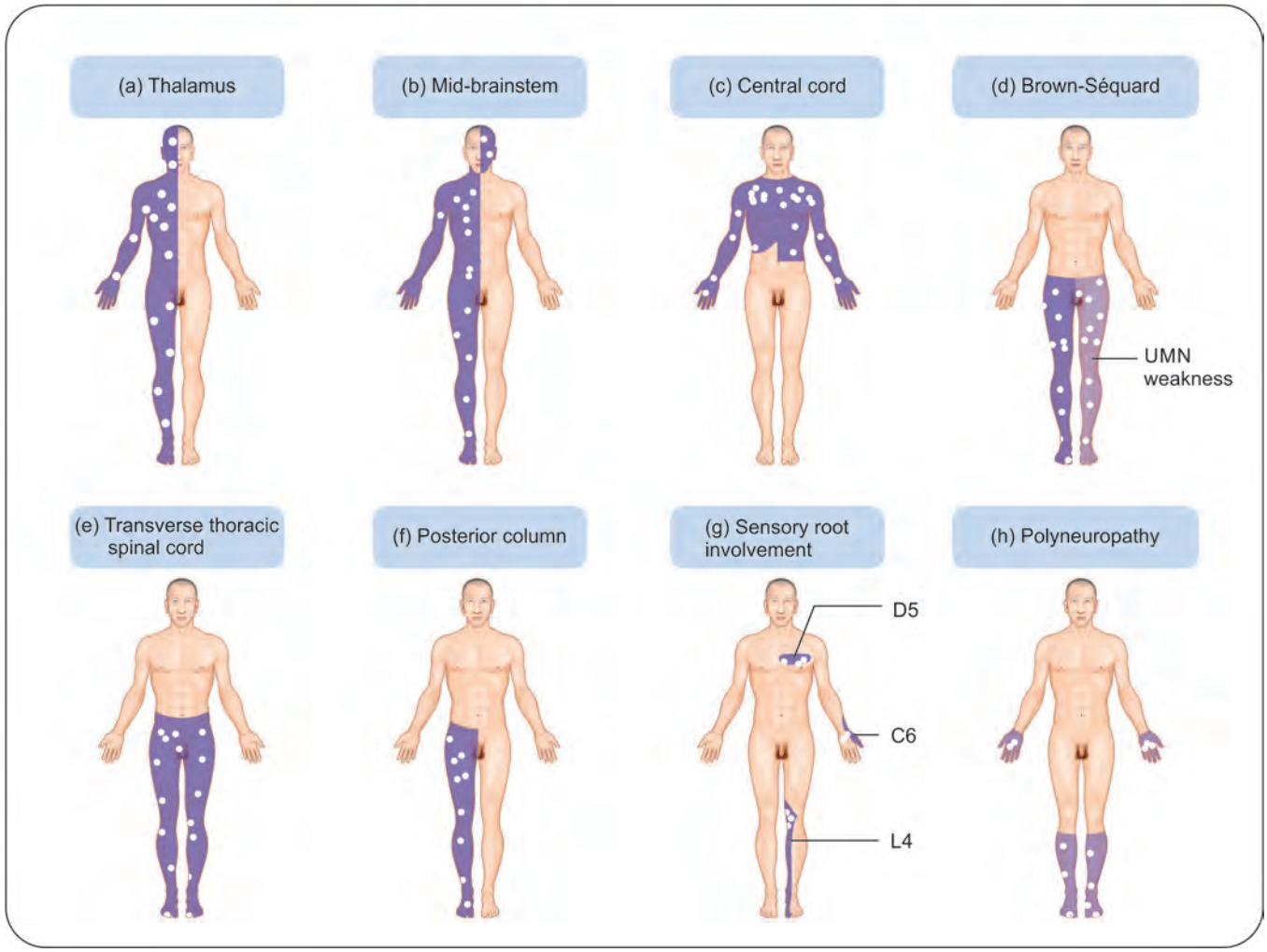

Fig. 3: Pattern of sensory abnormalities. **Principal patterns of loss of sensation. (a) Thalamic lesion:** sensory loss throughout opposite side (rare). **(b) Brainstem lesion:** contralateral sensory loss below face and ipsilateral loss on face. **(c) Central cord lesion,** e.g., syrinx: 'suspended' areas of loss, often asymmetrical and 'dissociated', i.e., pain and temperature loss but light touch intact. **(d) Hemisection of cord/unilateral cord lesion** = Brown-Séquard syndrome: contralateral spinothalamic (pain and temperature) loss with ipsilateral weakness and dorsal column loss below lesion. **(e) Transverse cord lesion:** loss of all modalitiesm, including motor, below lesion. **(f) Dorsal column lesion,** e.g., MS: loss of proprioception, vibration, and light touch. **(g) Individual sensory root lesions,** e.g., C6, D5, L4. (h) Polyneuropathy: distal sensory loss

- *Monotonous, hypophonic speech:* Extrapyramidal involvement
- *Clumping of syllables with undue separation:* Cerebellar involvement

Localization of aphasia may be done as follows:

- Reduced fluency with difficulty in word finding and impaired repetition: Broca's aphasia
- Comprehension difficulty in terms of word and sentences with impaired repetition: Wernicke's aphasia
- Expressive and comprehension difficulty: Global aphasia
- Isolated repetition difficulty: Conduction aphasia
- Preserved repetition with execution/comprehension difficulty: Isolation/transcortical aphasia.

Visual Loss

First of all, one shall be able to differentiate between decreased ability to see things, double vision or loss of pieces of visual field.

TABLE 7 Possible localization of sensory symptoms

Site of lesion	*Features*
Cerebral lesion	• **Cortex:** Cortical sensation impaired. May affect only a portion of contralateral part represented by the affected homunculus.[6] • **Internal capsule:** Uniform involvement of contralateral side with or without weakness. • **Thalamus:** Contralateral hemisensory loss; contralateral hyperalgesia and allodynia (Dejerine-Roussy syndrome).
Brainstem	• Contralateral side sensory involvement. • Ipsilateral sensory loss in face with contralateral hemisensory loss in body—usually in lateral medullary lesion.
Spinal cord	• **Complete transection**: Sensory loss below a level. • **Spinal hemisection**: Brown Sequard syndrome (ipsilateral vibration loss and proprioception loss with contralateral pain, temperature loss) • Selective dorsal (posterior column) or lateral cord (spinothalamic tract) involvement. • **Central cord:** Suspended sensory loss with sacral sparing; dissociative anesthesia.
Nerve root	Focal symptoms depending on root of involvement in a dermatomal pattern. Sensory symptoms may be minimal in case of single root involvement, due to considerable overlap by adjacent root territories.
Sensory ganglion	Pure sensory involvement in non-length dependent asymmetric fashion with sensory ataxia.[6]
Plexus	Diffuse symptoms corresponding to two or more adjacent roots usually associated with motor deficits.
Peripheral nerve	Sensory impairment in the distribution of the affected peripheral nerve; symmetric in case of polyneuropathies or asymmetric in case of mononeuropathy/mononeuritis multiplex.

TABLE 8 Possible localization of ataxia

Type of ataxia	*Features*
Frontal	Magnetic gait with out of proportion ataxia, spasticity.
Sensory	• Paresthesia, numbness with aggravation of symptoms in the dark, high steppage gait. • **Peripheral nerve (Large fiber):** Sensory symptoms in glove and stocking distribution. • **Dorsal root ganglion**: Non length dependent profound pure sensory symptoms. • **Posterior column:** Definite spinal level • **Medial lemniscus:** Brainstem symptoms
Peripheral Vestibular	Prominent vertigo with vomiting, nausea, and relative sparing of speech.
Cerebellar **False localization** Frontocerebellar pathway damage, may result in incoordination of the contralateral limbs, mimicking cerebellar dysfunction.[7]	• Dysmetria, cerebellar speech, and other symptoms, with or without brainstem symptoms may localize the lesion in cerebellum and its connections. • Usually ipsilateral lesion leads to ipsilateral symptoms. • Appendicular involvement suggestive of cerebellar hemisphere involvement, while truncal involvement may be localized to vermis; cerebellar speech due to paravermal involvement; and a combination of all may be seen in pancerebellar disease.

Monocular visual loss is suggestive of lesion in the eye itself or optic nerve anterior to the optic chiasma.

Binocular visual loss is suggestive of bilateral optic nerve lesion or a chiasmal/retrochiasmal lesion.[9]

Visual loss correctable by pin hole/glasses: Refractive error.

Visual loss not correctable by pin hole: Opacity in ocular media/neurological illness.

Color Vision

Acquired disturbance of color vision is suggestive of optic neuropathy and maculopathy; color desaturation being one of the earliest manifestations of optic neuropathy.

Localization of visual loss has been shown in **Table 9**.

Pattern of involvement of visual field and their respective localization has been shown in **Figure 4**.

Headache

Headache is one of the most common symptoms we come across in our day-to-day practice. The pain sensitive structures in the cranium which may give rise to headache are as follows:

- Scalp and aponeurosis
- Middle meningeal artery
- Dura mater and dural sinuses
- Falx cerebri

TABLE 9 Possible localization of visual loss

Site of lesion	*Features*
Ocular media	Eye pain, lacrimation, redness, no improvement in vision with pin hole
Anterior visual pathway	• Monocular vision loss • Central scotoma/altitudinal field defect in one eye • Impaired color vision • Orbit: Isolated optic neuropathy • Optic canal/intracranial site: Other cranial nerves may be involved (III, IV, VI) • Lesions close to optic chiasma: Junctional scotoma
Posterior visual pathway	• Binocular visual loss • Homonymous/heteronymous hemianopia • Color vision may be impaired
Cortical defect	• Ventral occipitotemporal defect: – Visual agnosia, prosopagnosia, topographognosia • Dorsal occipito-temporal defect: – Akinetopsia, Simultagnosia, optic ataxia, ocular motor apraxia

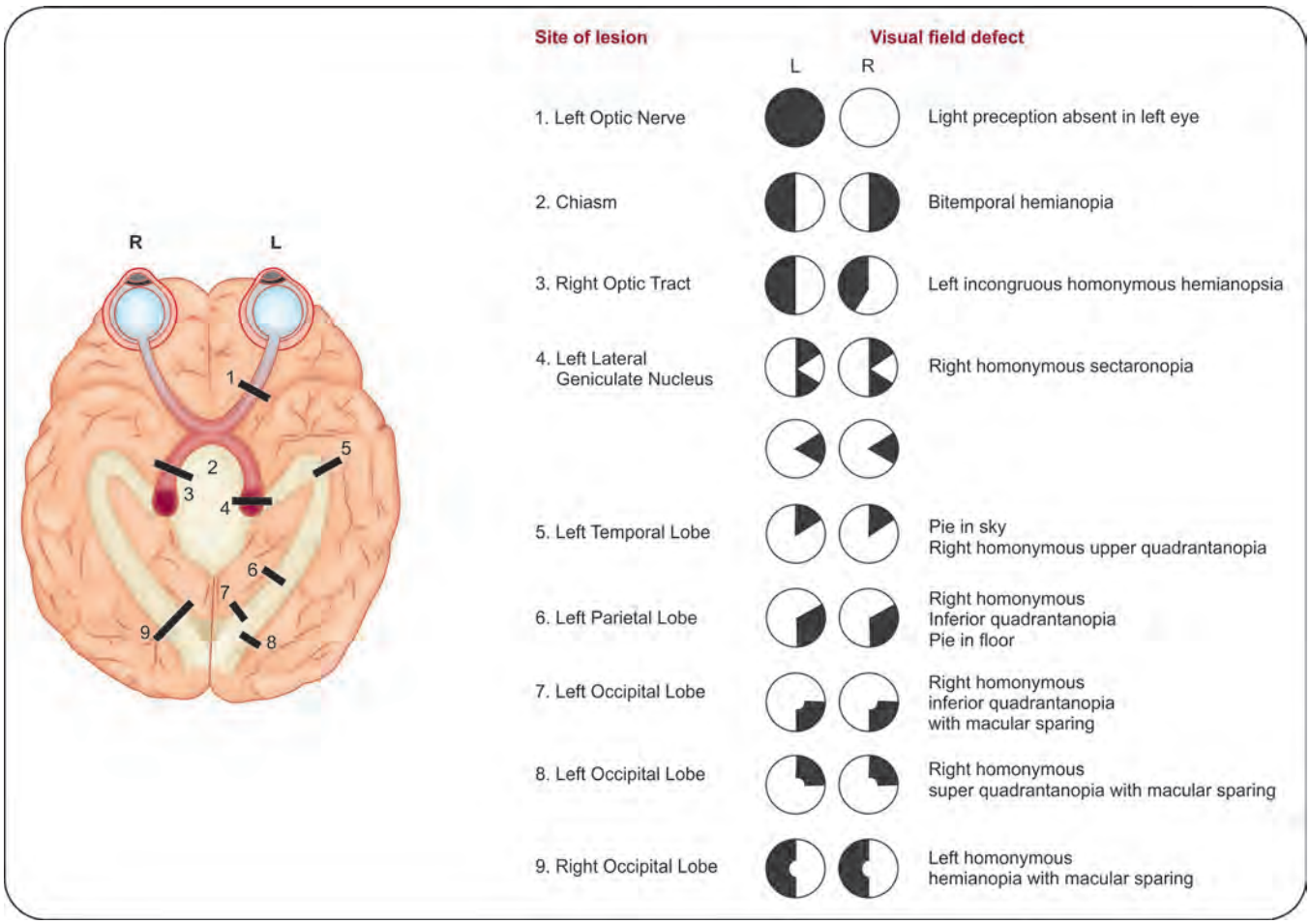

Fig. 4: Localization of visual field loss

- Proximal segments of the large pial arteries
- Cranial nerves V, VII, IX, and X
- Cervical nerves C1, C2, and C3

Headache may result due to inflammation, traction, compression, or malignant infiltration of these structures.

Primary involvement of these structures may give rise to primary headaches, which have little localizing value, while secondary involvement, for example, trauma, raised intracranial tension may give rise to secondary headaches.

In case of an extracranial structure as the source of headache, the site of pain is precise, for example, inflammation of extracranial artery in giant cell arteritis can be localized to the tender vessel.

Lesions of paranasal sinuses, teeth, eyes, upper cervical vertebrae have less sharp localization, but pain is referred in a regional distribution.

Infratentorial lesions tend to produce an occipitonuchal distribution of headache, while supratentorial lesions produce a frontotemporal headache.[10]

Among the primary headaches, cluster headache and trigeminal cephalgias have a periorbital location while migraine is usually unilateral and tension type headache is bilateral in distribution.

Conclusion

In this chapter, the authors have tried to give an overview of anatomical localization of a few classical neurological symptoms. Despite the recent advances in neuroimaging and electrodiagnostics, the importance and significance of anatomical localization is still indispensable, as it can guide the clinician to focus on a particular neuroanatomical substrate and even cut the need of unnecessary extensive investigations. We hope that this overview serves as a useful guide to the clinicians in day-to-day practice.

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CHAPTER

120 Clinical Signs of Diaphragm Dysfunction

Atanu Chandra, Aritra Kumar Ray, Arkapravo Hati

Abstract

Diaphragm is a musculofibrous structure separating thorax and abdomen. While unilateral diaphragmatic weakness is mainly secondary to inflammatory, infiltrative or traumatic etiologies; bilateral weakness mainly happens in systemic neurological or myopathic disorders. Unilateral weakness is usually asymptomatic. Abdominal paradox is a characteristic clinical sign of diaphragm weakness. Sniff test is a very important diagnostic test for assessment of unilateral weakness. Thorough history, meticulous examination, and appropriate investigations are of paramount importance to evaluate and plan for management.

Introduction

The term "Diaphragmatic dysfunction" is used to describe mainly three conditions—diaphragmatic eventration, weakness, and paralysis of diaphragm.[1] Eventration can be defined as a persistent and permanent elevation of a part or all of the hemidiaphragm due to thinning.[1] Diaphragmatic weakness may be described as a partial impairment of the strength of the muscles of diaphragm to produce and maintain adequate pressure required for ventilation. On the other hand, paralysis of the diaphragm is used to denote complete impairment of this capacity.[2] Based on the etiology, this disorder can be unilateral or bilateral; permanent or temporary. Diaphragmatic flutter is another rare variety of diaphragm dysfunction which is characterized by repeated and variable cycles of regular and involuntary contractions of diaphragm. Features of diaphragmatic flutter are dyspnea, epigastric pulsations, and pain in the thoracoabdominal region.

Anatomical Considerations

Diaphragm is the musculofibrous structure, which separates the abdominal cavities from thoracic cavities. It is formed of a peripherally located muscular part and a non-contractile central fibrous portion, which is again divided into costal, sternal, and lumbar muscular groups. The muscular component of the diaphragm is composed of Type 1 (slow, fatigue resistant) and Type 2 (fast) fibers.

Phrenic nerve, which originates from the 3rd, 4th, and 5th cervical nerves (C3, C4, and C5) almost exclusively provide the afferent neurological supply to diaphragm. Both the phrenic nerves descend anterior to the scalene muscles and then travel between the subclavian arteries and veins in the neck to enter into the thorax. The right phrenic nerve travels caudally anterior to the brachiocephalic trunk along the right atrium and finally enters the abdominal cavity. The left phrenic nerve travels along the left ventricle caudally and supplies the diaphragm.

Diaphragmatic thickness is variable with gradual tapering from anterior to posterior costal areas and from the costal insertions toward central tendon. Under normal situation, the diaphragm functions as a piston to generate flow as it descends in the thoracic cavity and displaces the contents of abdominal cavity caudally thereby causing elevation of the lower portion of thorax. The negative

intrathoracic pressure thus created results in an inflow of air from mouth to lung, thereby creating tidal volume.

Etiology

Causes of unilateral diaphragm weakness:

- *Infiltrative or compressive processes:* Goiter, pathological lymph nodes, mediastinal or pulmonary malignancy, cervical arthrosis, and spondylosis.
- *Inflammatory disease:* Shingles, post-viral, mononeuritis, chronic inflammatory demyelinating polyneuropathy, parsonage—Turner syndrome.
- *Traumatic lesions:* Central venous cannulation, nerve blockade', heart/lung/liver transplant, neck/heart surgery, chiropractic manipulation.
- *Central neurological disease:* Multiple sclerosis, stroke, rhizotomy.
- *Idiopathic.*

The etiologies of diaphragmatic dysfunction are described in **Table 1**.

Causes of bilateral diaphragm weakness:

- *Neurological disease:* Multiple sclerosis, amyotrophic lateral sclerosis, medullary transection, Guillain-Barré syndrome, severe cervical spondylosis, poliomyelitis, chronic inflammatory demyelinating polyneuropathy.
- *Myopathy:* Malnutrition, dysthyroidism, muscular dystrophies, amyloidosis, corticosteroid use, post-viral critical illness/ventilator induced diaphragm dysfunction, disuse atrophy/inactivity.

TABLE 1 Etiology of diaphragmatic dysfunction

Anatomical location of the lesion	*Disease*
Cerebral cortex	• Cerebrovascular accident (CVA)
Internal capsule	• Arnold-Chiari disease • Vascular accident
Spinal cord	• Traumatic injury to the cord • Degenerative (severe spondylosis)
Central nervous system (CNS)	• Multiple sclerosis (MS)
Motor neurons	• Amyotrophic lateral sclerosis (ALS) • Post polio syndrome • Paraneoplastic neuropathy • Syringomyelia • Spinal muscular atrophy (SMA)
Brachial plexus	• Traumatic injury to the plexus • Idiopathic • Iatrogenic (Obstetric procedures, anesthetic blockade, radiotherapy)
Phrenic	• Compression/infiltration (mediastinal neoplasms) • Trauma[3] • Guillain Barre syndrome[4] infection—Pneumonias,[5] Lyme disease,[6] Herpes zoster, HIV infection[7] • Amyotrophic neuralgia (Parsonage-turner syndrome)[8] • Thoracic surgeries[9] • Others (Hypothyroidism,[10] Malnutrition,[11] Diabetes,[12] Benign thyroid hypertrophy,[13] vasculitis, porphyria, Charcot-Marie-Toot[14] disease) • Idiopathic[15]
Lung	• Obstructive airway diseases (Asthma and COPD)
Neuromuscular junction	• Lambert-Eaton syndrome[16] • Myasthenia gravis • Botulism[17]
Muscular	• Steroid myopathy[18] • Pompe disease[19] • Myositis • Muscular dystrophies • Mechanical ventilation[20]

- *Connective tissue disease:* Dermatomyositis, mixed connective tissue disease, systemic lupus erythematosus/shrinking lung syndrome.
- *Idiopathic.*
- *Sepsis.*

Clinical Features

Unilateral diaphragmatic paralysis: Patients are usually asymptomatic but may have limited ability to exercise.[21] They may also have dyspnea on exertion and in supine position. Symptoms are more severe in persons with obesity or with other comorbidities including cardiac and pulmonary pathology.[22] They may also have symptoms of gastroesophageal reflux and nocturnal hypoventilation.[23] It is often diagnosed as an incidental finding on chest skiagram as an isolated elevation of hemidiaphragm.

Clinical examination is rather nonspecific. On auscultation, decreased breath sounds are heard at the base of affected hemithorax. Reduced diaphragmatic excursion may be clinically detected by percussion of the lower rib cage at the end of expiration and inspiration respectively. Occasionally, paradoxical thoracoabdominal movement occurs during sleep.

Bilateral diaphragmatic paralysis: Patients may show dyspnea on lying down (orthopnea). Respiratory distress, which occurs sometimes during rest, may be exacerbated at the time of immersion in water.[24] Most of the patients with this disorder present with sleep disorders and features of significant hypoventilation.

On clinical examination, cyanosis, superficial, and rapid respiration, bilaterally diminished breath sounds or abdominal paradox may be noted. In bilateral diaphragmatic paralysis, inspiration occurs due to contraction of the accessory muscles of respiration such as scalene and sternocleidomastoid along with external intercostals.

Abdominal paradox: The characteristic clinical sign of diaphragmatic dysfunction is abdominal paradox.[25] During inspiration, when there is rib cage expansion, paradoxical inward motion of abdomen does occur. When accessory inspiratory muscles of the rib cage and neck contract as compensatory mechanism and lower pleural pressure, the flaccid diaphragm moves in a cephalad direction with inward movement of the abdomen. This abnormal breathing pattern is mainly seen in supine position. It is mostly seen in bilateral diaphragmatic paralysis and rarely occurs in unilateral cases. When abdominal paradox is seen in unilateral diaphragmatic paralysis, it indicates generalized respiratory muscles weakness. The mechanism of abdominal paradox has been described in **Figures 1A to D**.

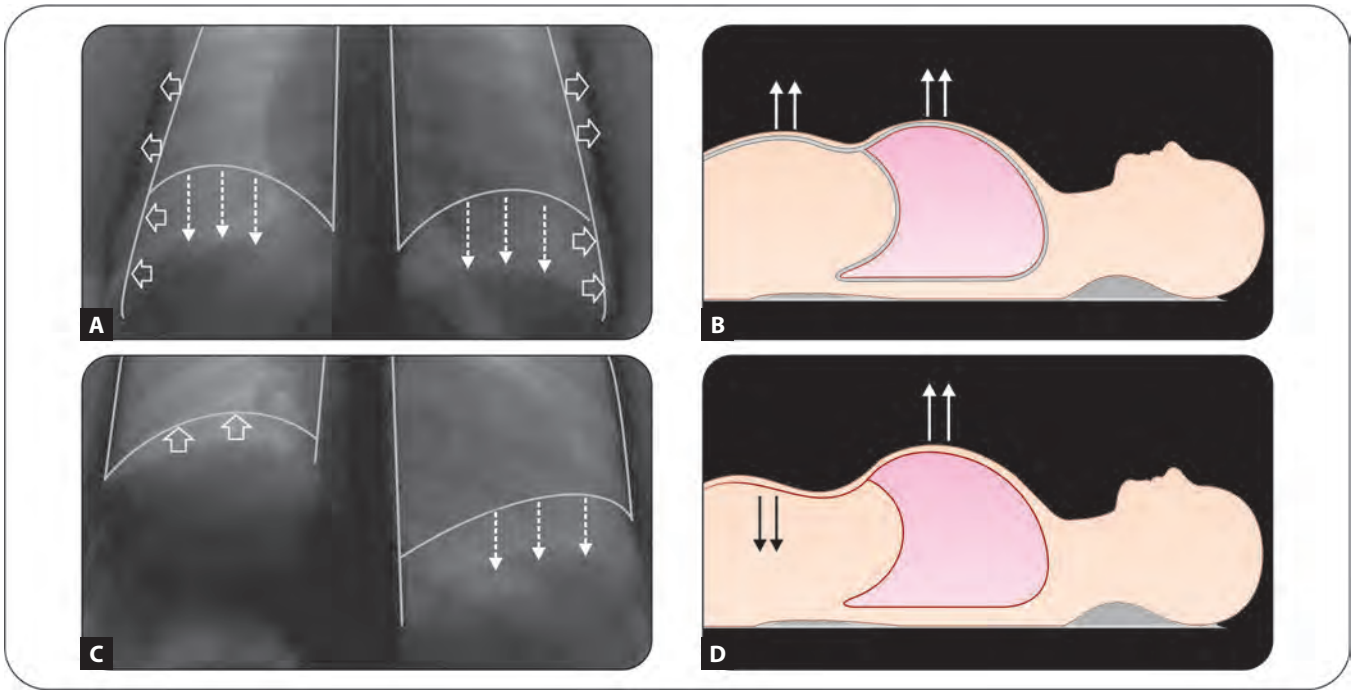
Sniff Test

Fluoroscopy of diaphragm is very important to evaluate diaphragmatic function.[25] The motion of the diaphragm is assessed by doing a rapid and short inspiratory effort through nostrils (also known as "Sniff test"). In normal persons, diaphragm will move caudally. In unilateral diaphragmatic paralysis, paradoxical (cephalad) movement is seen on the side of paralysis. There is no diagnostic value of this test in case of bilateral diaphragmatic paralysis. False negative results may be obtained due to sudden caudal motion of the paralyzed diaphragm at the onset of inspiration, which is misinterpreted as contraction. This phenomenon happens due to abrupt relaxation of abdominal muscles at the beginning of inspiration following active contraction at expiration. False positive results may be seen in about 6% cases.

Diagnosis

Diaphragmatic dysfunction is most often suspected after the incidental finding of an isolated elevation of hemidiaphragm on chest skiagram or during evaluation of unexplained dyspnea. Diagnosis is mainly based on imaging modalities including radiography, chest ultrasound, and fluoroscopy. Tests include:

- *Lung function test* is often performed as a first-line investigation to quantify and assess the physiological impact of diaphragm weakness.
  - *In unilateral diaphragmatic weakness*, functional residual volume (RV) and total lung capacity (TLC) are normally preserved. Vital capacity (VC) is mildly decreased to approximately 75% of predicted value[26] and 10–20% further decrease is noted in supine position.[27]
  - *In bilateral diaphragmatic weakness*, VC usually reaches 50% of predicted values and 30–50% further decrease is noted in supine position. RV remains elevated and TLC can even get reduced.
- *Radiologic fluoroscopy* (real time view) with sniff maneuver to depict paradoxical motion.[25,28]



Figs. 1A to D: (A) Normal contraction of the diaphragm during quiet inspiration. (B) In supine position, both the rib cage and abdomen move outward. (C) When the diaphragm is paralyzed, the negative intrathoracic pressure pulls the diaphragm and the abdominal viscera toward the thoracic cavity, thereby generating a negative abdominal pressure. (D) In supine position, it is noted how the negative abdominal pressure creates a paradoxical movement during inspiration and the abdomen moves inward

- *Ultrasound* to look at the movement of the diaphragm and changes in the muscle thickness. It is noninvasive, simple, readily available, and widely used both in the research and clinical setting. It is used to assess to assess Tdi (static measurement of diaphragm thickness) and TFdi (inspiratory diaphragm thickening fraction).
- *Sleep studies:* Polysomnography with concomitant noninvasive ventilation may be considered routinely as this approach has both a therapeutic and diagnostic value. Sleep disordered breathing (SDB) can be seen both in unilateral and bilateral diaphragmatic weakness and it becomes more prominent with the progression of the disease. Early consideration of polysomnography is very important in such patients.
- Cardiopulmonary exercise testing.
- Chest X-ray: The common alternative causes of an elevated hemidiaphragm on imaging have been depicted in **Table 2**.
- Maximum inspiratory mouth pressures.

TABLE 2 Common alternative causes of an elevated hemidiaphragm on imaging

'False' hemidiaphragm paralysis	*Extra-diaphragmatic disease*
• Morgagni hernia	• Subphrenic abscess
• Bochdalek hernia	• Pulmonary or mediastinal mass
• Hiatal hernia	• Pulmonary embolism
• Traumatic rupture	• Ascites
• Lung resection	• Asymmetrical emphysema
• Lipomas	• Atelectasis

- *Stimulation of phrenic nerve* in the neck by magnetic or electrical stimulation.
- *Transdiaphragmatic pressure measurement* (measure of strength of diaphragm).
- *Electromyography (EMG)*, a test which records and evaluates electrical activity produced by skeletal muscles.

TABLE 3 Comparison between unilateral and bilateral diaphragmatic paralysis

Diagnostic tools and treatment	***Unilateral diaphragmatic paralysis***	***Bilateral diaphragmatic paralysis***
History	Neck or chest surgery, shoulder or neck pain, neck injury, neuromuscular disease, cervical spine manipulation	Neck or chest surgery, shoulder or neck pain, neck injury, neuromuscular disease, manipulation of the cervical spine
Presentation	Asymptomatic, exercise limitation, unexplained dyspnea, incidental radiographic finding	Exercise limitation, unexplained dyspnea, orthopnea, dyspnea at rest, dyspnea when bending, respiratory failure, prolonged mechanical ventilation, constitutional symptoms
Examination	No abdominal paradox	Abdominal paradox
Laboratory tests		
Vital capacity (% of predicted value)	>70	<50
Decline in supine vital capacity (%)	10–30	30–50
Fluoroscopy	Sniff test positive	Not helpful
Thickening of diaphragm on inspiration	No change	No change
Complications	Ocassional hypoventilation during sleep, atelectasis	Frequent hypoventilation during sleep, pneumonia, atelectasis, respiratory failure
Treatment		
Observation period for recovery (yr)	1.5–3	1.5–3
Treatment for coexisting conditions	Yes	Yes
Reversal of metabolic disturbance	Yes	Yes
Noninvasive positive pressure ventilation (NIPPV)	Usually not indicated	Often indicated
Plication of diaphragm	May be helpful	Not indicated
Phrenic pacing	No	Yes, in patients with high spinal cord injury (SCI)

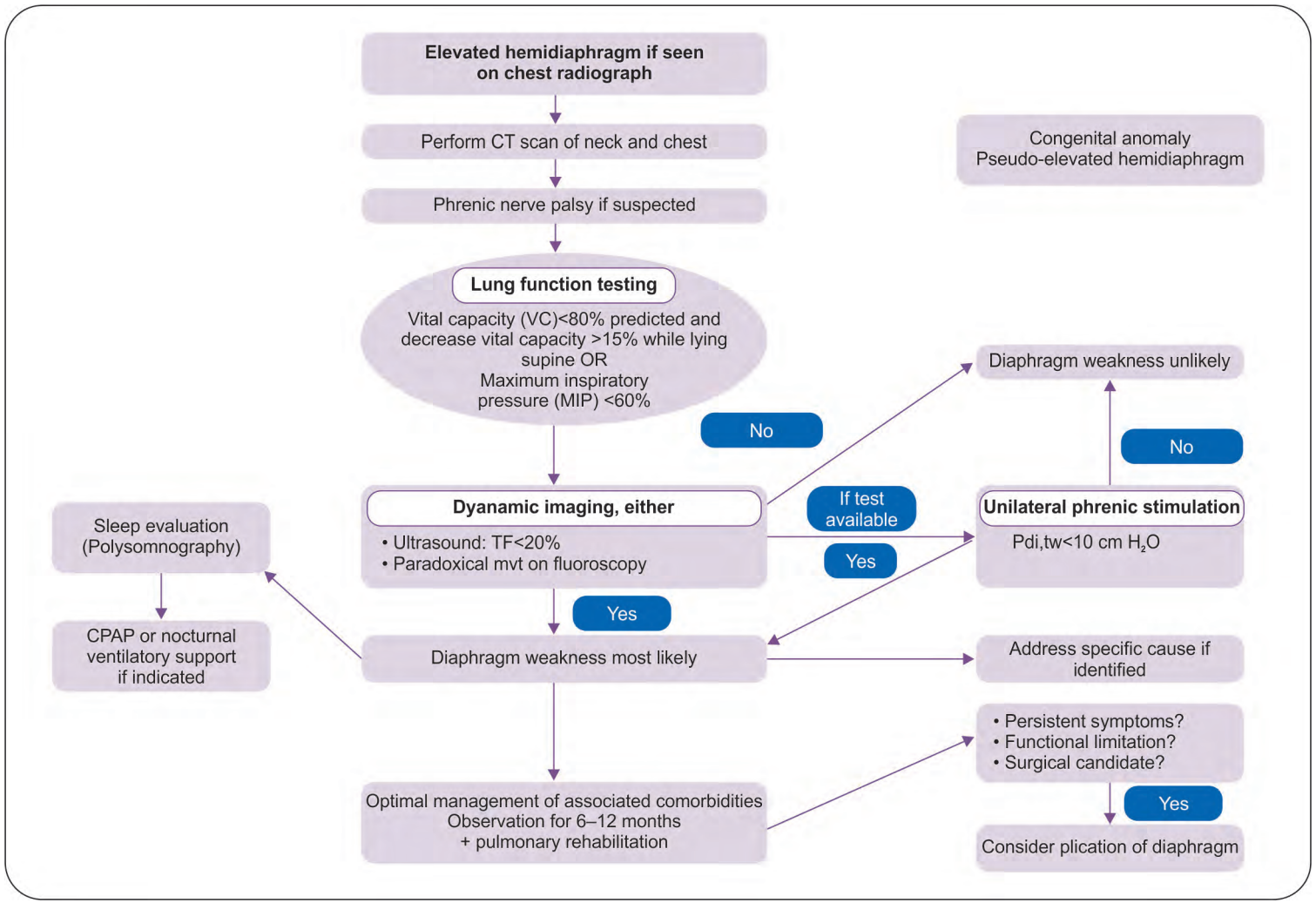
- *Arterial blood gas analysis:* Alteration of ABG is a late sign indicating severe functional impairment.
- *Computed tomography scan* of the abdomen, chest or both.
- *Magnetic resonance imaging (MRI)* to detect any pathology involving nerve roots or spinal column.

Therapeutic Management

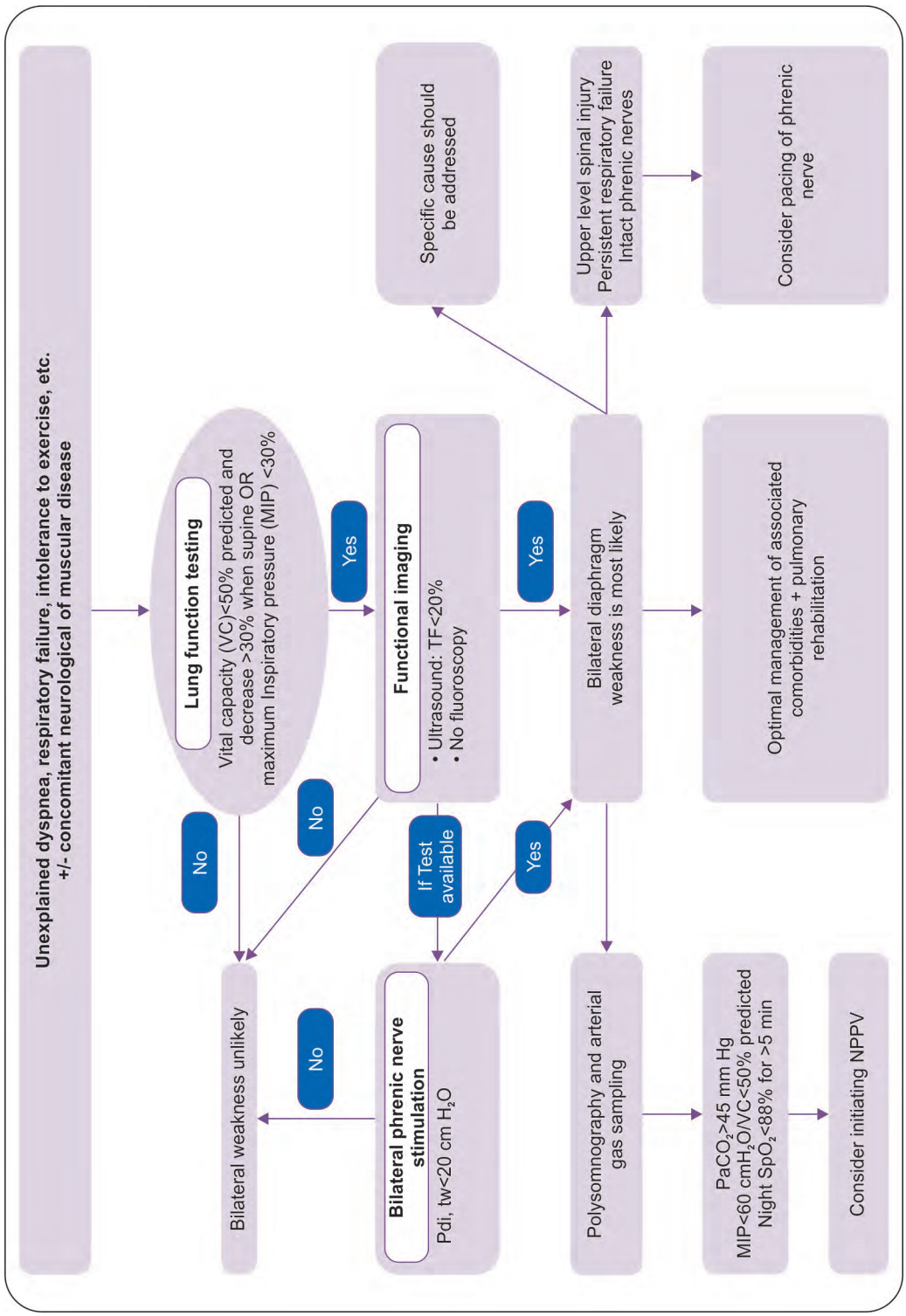
- Observation and supportive management
- Treatment of concurrent medical conditions
- Inspiratory muscle training (IMT)
- Noninvasive ventilatory support
- *Diaphragm pacemakers* can be used in case of functioning phrenic nerves such as patients with trauma to spinal cord or motor neuron disease
- Surgical procedure in the form of *diaphragmatic plication*
- *Tracheostomy* and *mechanical ventilation* in patients with a severe life threatening disease or in case of high cervical cord lesion causing quadriplegia

The comparison between unilateral and bilateral paralysis of diaphragm regarding the diagnosis and management has been described in **Table 3**. 'Diagnosis and therapeutic algorithm for unilateral and bilateral diaphragm weakness have been depicted in **Flowcharts 1 and 2**.

Flowchart 1: Diagnostic and therapeutic algorithm for unilateral diaphragm weakness



CPAP, continuous positive airway pressure; CT, computed tomography; MIP, maximal inspiratory pressure; PSG, polysomnography; TF, thickening fraction of the diaphragm; VC, vital capacity



Flowchart 2: Diagnostic and therapeutic algorithm for bilateral diaphragm weakness

MIP, maximal inspiratory pressure; NPPV, noninvasive positive pressure ventilation; TF, thickening fraction of the diaphragm; VC, vital capacity

Conclusion

Diaphragmatic weakness has been seen to be associated with poor clinical outcome in most instances. A detailed evaluation is often needed to find out the exact origin, to assess and plan to manage its impact on symptoms, exercise capacity, and sleep homeostasis. Diagnosis of bilateral or unilateral diaphragmatic dysfunction and management may be challenging for the physician as this is relatively rare, associated with subtle clinical features and difficulties faced in establishing the exact anatomical location and physiological alterations. Diaphragmatic dysfunction is often underdiagnosed but should never be neglected because it can be a very good prognostic indicator and this is often associated with a poor quality of life. Referral to a higher center with experience and expertise in this disease and access to phrenic nerve stimulation or pacing, diaphragm ultrasound and surgical expertise in diaphragm plication should be considered, where necessary.

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CHAPTER

121 Approach to Chest Pain in Emergency

Partha Sarkar, Adrija Chatterjee

Abstract

Chest pain is one of the most common problems faced in the emergency room. The challenge is to develop a strategy to identify more serious pathology from non serious ones, found in majority of patients. Assessment of patient history, physical examination, 12 lead ECG, and cardiac biomarkers form the basis of assessment of chest pain. First and foremost serious life threatening causes of chest pain such as acute coronary syndrome, aortic dissection, pulmonary embolism, tension pneumothorax, and cardiac tamponade have to be ruled out. History of characteristics chest pain have to be taken as per the pneumonic SOCRATES (site, onset, character, radiation, aggravating and relieving factors and severity) helps to differentiate the different causes of chest pain, cardiac versus non cardiac. Subsequently, for acute coronary syndrome, a 12-lead ECG will help to differentiate STEMI from non STEMI. Further the cardiac biomarkers such as highly sensitive cardiac specific troponin will help to identify unstable angina from NSTEMI.

Introduction

Chest pain is one of most frequent causes of attending the emergency department. It is also one of the most difficult diagnostic challenges which presents in an emergency room.

The differential diagnosis of chest pain syndrome is broad and disparate including disease processes that range from non urgent to life threatening. Furthermore within the consideration of life threatening causes patients may be suffering from coronary causes as well as pulmonary embolism, aortic dissection, aortic rupture, pneumothorax or even esophageal rupture. There are many other diagnoses, which are much less critical but as widely as musculoskeletal pain, zoster, pleurisy, pneumonia, or gastroesophageal reflux.[1]

Goals

- Early diagnosis of acute coronary syndrome (ACS).
- Recognition of other life threatening causes.
- Minimize cost and hospitalization in patient with chest pain of benign etiology.

Diagnostic assessment and triage based on the following etiologies:

- Myocardial ischemia
- Other cardiopulmonary causes—pericardial diseases, aortic emergencies, pulmonary conditions
- Non-cardiopulmonary causes

Differential Diagnosis

- *Cardiac:* Myocaridal ischemia, pericarditis, aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM)
- *Vascular:* Acute aortic syndrome, pulmonary embolism, pulmonary hypertension
- *Pulmonary:* Pneumonia, pleuritis, pneumothorax
- *Gastrointestinal:* Esophageal reflux, esophageal spasm, esophageal rupture, peptic ulcer, gallbladder disease

- *Neuromuscular:* Costochondritis, cervical disc disease, trauma, Herpes zoster
- *Psychiatric conditions*

Rule Out Deadly Causes

ACS, pericarditis, acute aortic syndrome, pulmonary embolism, pneumothorax, esophageal rupture.

These are the serious causes of chest pain not to be missed.

How to Approach a Patient of Chest Pain?

History

Evaluating clinicians should assess the quality, location, pattern, provoking and alleviating factors, associated symptoms, past medical history.

Quality of Pain

Angina pain of myocardial ischemia is described as tightness, squeezing, or heaviness. Whereas pain of pericarditis is described as sharp stabbing in nature.

Pericarditis of an infectious etiology causes simultaneous involvement of the adjoining pleura so patients experience pleuritic chest pain characterized by a localized sharp lancinating pain, which aggravates on inhalation, coughing. Pain of infectious pericarditis felt in shoulders and neck as central diaphragm attains sensory supply from phrenic nerve. However, a more lateral diaphragmatic movement may lead upper abdominal pain.

Involvement of pleura as in pneumothorax may produce pleuritic chest pain similar to infectious pericarditis.

Massive pulmonary embolism can present as heaviness.

Acute aortic dissection leads to excruciating ripping pain or "tearing" pain.

Epigastric burning pain like sensation suggests acid reflux or peptic ulcer disease. Esophageal spasm can be severe squeezing identical to angina. Gallbladder disease produces a colicky pain.

Musculoskeletal disorders produce an aching pain whereas herpes zoster produces a sharp burning pain.

Localization of Pain

Myocardial ischemia typically produces retrosternal discomfort with radiation to neck, jaw, shoulders, or arms. Inferior wall AMI typically produces substernal or epigastric discomfort.

Chest pain of pericarditis can mimic AMI but can radiate to trapezius, which does not occur with angina.

Chest pain due to myocardial ischemia is poorly localized and diffuse while pleuritic chest pain is localized.

Ascending and descending aortic dissection differ in their location of pain with anterior aortic dissection producing midline anterior chest pain and descending aortic dissection producing back pain.

Gastrointestinal conditions usually produce abdominal or epigastric discomfort exception being esophageal pain, which is retrosternal in location.

Chest pain of Herpes zoster has dermatomal distribution.

Pattern

Chest pain of myocardial ischemia develops over minutes and is precipitated by activity and relieved by rest. Pain of stable angina lasts for 2–10 minutes and subsides on rest whereas pain of unstable angina persists even on rest. In case of myocardial infarction pain lasts for more than 30 minutes.

Chest pain in pericarditis is episodic in nature. Chest pain in aortic dissection, pneumothorax is of sudden onset.

Pain of constant intensity over a prolonged period of time is more likely to represent peptic ulcer disease than myocardial ischemia.

Aggravating and Relieving Factors

Pain of myocardial ischemia is usually relieved by rest. However, one should be aware of the phenomenon of "warm up angina" in which pain seems to get relieved by continuing at same or greater level of exertion.

Administration of nitroglycerin may relieve both myocardial ischemia pain as well as pain produced by esophageal spasm.

Pain of musculoskeletal etiology changes in intensity with positional change of upper extremities and neck.

Pain of pericarditis worsened by supine position and relieved by sitting upright and leaning forward.

Pain due to gastroesophageal reflux may be exacerbated by alcohol, some foods or reclining position.

Worsening of pain with food suggestive of peptic ulcer disease or cholecystitis, which may be relieved by acid reducing therapies. However, in setting of a

severe coronary atherosclerosis redistribution of blood flow to splanchnic vasculature after eating can trigger postprandial angina.

Associated Symptoms

Symptoms associated with myocardial ischemia may include sweating, dyspnea, nausea, vomiting, and faintness.

Pulmonary embolism and pneumothorax should be considered in the background of sudden onset respiratory distress.

Hemoptysis usually points toward pneumonia. Blood tinged frothy sputum can be found in heart failure.

Syncope should prompt consideration of hemodynamically unstable conditions in pulmonary embolism and aortic dissection.

Although nausea and vomiting suggest a gastrointestinal disorder, these symptoms may occur in the setting of myocardial infarction, especially inferior wall AMI because of activation of vagal reflex.

Oesophageal rupture usually associated with forceful vomiting.

Past Medical History

Assess for risk factors of coronary atherosclerosis and venous thromboembolism.

History of connective tissue disorder such as Marfan's syndrome should increase the suspicion of acute aortic syndrome or spontaneous pneumothorax.

Physical Examination

General

Patients with AMI often appear anxious, pale, cyanotic, or diaphoretic.

Patients with AMI may describe their pain by clenched fist against sternum termed as "levine's sign."

Often body habitus is helpful. Like patients with Marfan's syndrome have young tall thin built.

Vital Signs

Tachycardia and hypotension are suggestive of hemodynamic instability should prompt a rapid survey for AMI, massive pulmonary embolism, pericarditis with tamponade, tension pneumothorax, acute aortic dissection.

Tachypnea and tachycardia with hypoxemia point toward a pulmonary cause.

Cardiac

Search for characteristic pattern of JVP in cardiac tamponade or right ventricular dysfunction.

S4 in case of myocardial ischemia and S3 in case of infarction can be found.

Murmur of mitral regurgitation is found in case of complications of AMI. Murmur of aortic dissection indicates complications of aortic dissection.

Pericardial friction rub suggests pericarditis.

Pulmonary

Decreased breath sound, hyper-resonant percussion note in case of pneumothorax or localized crepitation in pneumonia.

Esophageal rupture or "Boerhaave syndrome" is associated with subcutaneous emphysema and on being auscultated crackling sound is heard (Hamman's crunch).

Abdominal

Localized tenderness can be found in gastrointestinal conditions such as gallbladder stone or pancreatitis.

Abdominal findings such as hepatic congestion can be found in right ventricular dysfunction.

Musculoskeletal

Localized swelling, tenderness are useful clinical sign for costochondritis (Tietze's syndrome). Vesicular rash is found in the area of discomfort suggests Herpes zoster.

Battery of Tests

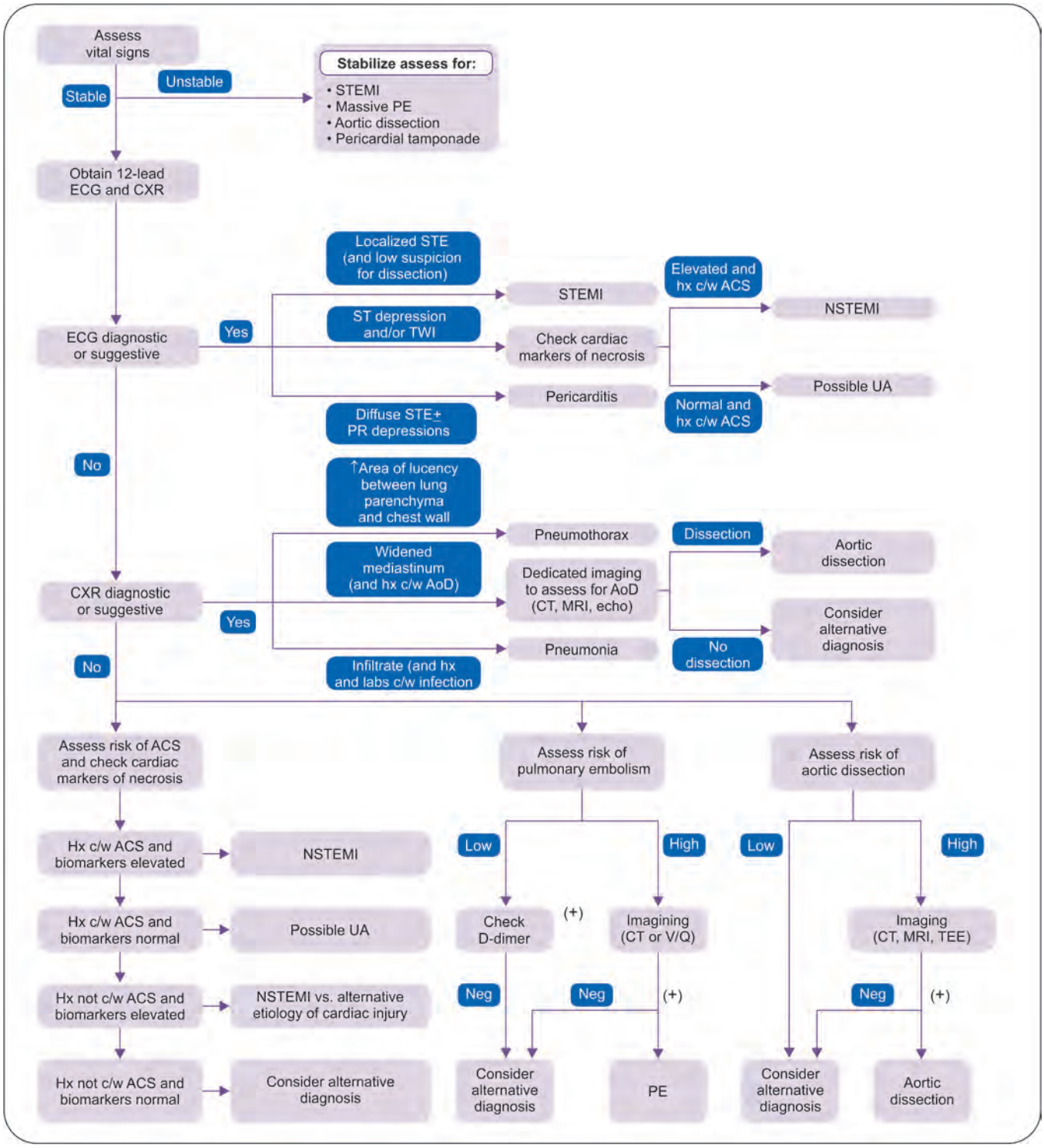
ECG

ECG is essential for identification of patients with ongoing ischemia as well as secondary cardiac complications of other disorders. ST segment elevation, ST segment depression, and symmetric T wave inversions are useful for detecting myocardial ischemia.[2] Serial evaluation of ECG every 30–60 minutes is recommended in emergency for evaluation of suspected ACS.[3]

Hyperventilation associated with panic disorder can also lead to nonspecific ST and T wave abnormalities.

Pulmonary embolism produces rightward shift of ECG axis manifesting as S wave in lead I, Q wave, and T wave in

Flowchart 1: How to approach a case of chest pain



ACS, acute coronary syndrome; STEMI, ST-elevation myocardial infarction; UA, unstable angina: CXR, chest X-ray; CT, computed tomgraphy, UA, unstable angina; ECG, electrocardiographic; TEE, transesophageal echocardiography; AoD, aortic dissection; c/w, consistent; hx, history; NSTEMI, non–ST-segment myocardial infraction; PE, pulmonary embolism; MRI, magnetic resonance imaging; V/Q, ventilation-perfusion; STE, stimulated echo.

lead III (S1Q3T3 pattern of acute cor pulmonale is classic, termed as McGinn-White sign).

ST elevation with diffuse lead involvement and PR segment depression distinguishes pericarditis from AMI.

CXR

CXR is most useful for detection of lung causes such as pneumonia, pneumothorax.

CXR findings commonly associated with pulmonary embolism include Hampton's hump or Westermark sign or Palla's sign.

CXR showing subcutaneous emphysema suggests "Boerhaave syndrome."

Cardiac Biomarkers

Circulatory proteins released from damaged myocardial cells are indicative of myocardial injury. Initially biomarkers may be normal even in patients with STEMI.

Cardiac troponin [cardiac specific troponin T (cTnT)] and cardiac specific troponin I (cTnI) are preferred biomarkers over creatine kinase MB and should be repeated in 3–6 hours in suspected ACS patients.

Serial changes in cardiac troponin are useful in discriminating acute causes of myocardial injury from chronic elevation due to underlying structural heart disease or end stage renal disease.[4]

Assessment of D-dimer test to aid in exclusion of pulmonary embolism.

Both B-type natriuretic peptide (BNP) and N terminal pro BNP (NT-probnp) is useful in diagnosis of heart failure.

Echocardiography

Patients with mechanical complications of MI or pericardial tamponade diagnosed easily with echocardiography.

Transesophageal echo is more sensitive of aortic dissection than transthoracic echo.

Provocative Tests

Exercise electrocardiography ("stress testing") is used for patients with low to intermediate risk of ACS who have not revealed a specific cause of chest discomfort on initial evaluation.[5]

Patients with ongoing chest pain should not be subjected to these stress tests.

Recent Advances

CT angiography has emerged as a sensitive technique for detection of obstructive coronary disease particularly in proximal third of major epicardial coronary arteries.[6]

CECT is useful for detection focal areas of myocardial injury.[3]

CT angiography can be used for exclusion of aortic dissection, pericardial effusion, and pulmonary embolism.

Cardiac MRI is an emerging technique for structural and functional evaluation of heart. Gadolinium enhanced MRI can provide early detection of MI and can define areas of myocardial necrosis accurately.

Early myocardial perfusion imaging can be performed for evaluating patients with low or intermediate risk of ACS.[7]

Flowchart 1 depicts the approach towards chest pain in the emergency room.

Don't Forget the Rare One

Takotsubo cardiomyopathy characterized by abrupt onset chest pain and shortness of breath, triggered by an emotionally stressful event. It mimics AMI because it is associated with ECG abnormalities and elevated cardiac biomarkers. But surprisingly coronary angiography is normal. It has predilection for women above 50 years.

Conclusion

Chest pain is one of the most common causes for admission to emergency departments. Emergency clinicians have a difficult task identifying, which patients to admit and which patients to discharge home.

Evaluation of acute chest pain in emergency is time consuming and expensive and often results in uncertain diagnosis.

A very small percentage of evaluated patients are eventually diagnosed with ACS. Most common diagnoses are gastrointestinal causes. Few of patients with chest discomfort discharged on the presumption of non-ischemic etiology from emergency are later deemed to have had a missed myocardial infarction.

So, rapid and precise identification, triage, and treatment of high-risk cardiopulmonary conditions are necessary, while low-risk patients can be safely observed with less intensive monitoring.

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CHAPTER

122 Approach to a Case of Anemia

Manoj Kumar Srivastava

Abstract

Anemia is the most common symptom present in most of the clinics of tropical country and it is usually a common symptom in females and during pregnancy! Anemia, which is a symptom and not a disease, is defined as a decrease in the circulating red blood cell mass to below age specific and gender specific limit. Evaluation for anemia is one of the most common clinical problems seen in the present hospital settings. The evaluation of anemia may be straightforward in an otherwise healthy individual with a single cause of anemia, but in many cases the cause is not readily apparent and multiple conditions may be contributing. The first step in diagnosis of anemia is detection with reliable and accurate tests, so that the important clue to underlying causes are not overlooked and patients are not subjected to unwanted laboratory tests.

Introduction

Anemia, which is a symptom and not a disease, is defined as a decrease in the circulating red blood cell mass to below age specific and gender specific limit. lt is difficult to directly measure RBC mass, so the hematocrit or the hemoglobin level in the blood are usually used instead to indirectly estimate the value.[1,2]

Evaluation for anemia is one of the most common clinical problems seen in the present hospital settings. The evaluation of anemia may be straightforward in an otherwise healthy individual with a single cause of anemia, but in many cases th cause is not readily apparent and multiple conditions may be contributing.

ln clinical practice, the use of proper standard method of history taking and clinical examination supported by laboratory investigations still form the best approach.[3] There are many ways to classify anemia, but none of them is perfect. The approach to find the cause of anemia differs for different groups depending on sex, age, and race. lt is important to reach the exact diagnosis of anemia to give the proper treatment. The common traditional ways to classify the anemia depend on

- Red cell morphology and indices
- Pathogenesis
- Clinical presentation of anemia[4,5]

Classification Based on RBC Morphology and Indices

The classification of anemia based on the red cell predominantly depends on the mean corpuscular volume (MCV) of RBCs. On the basis of MCV the anemia is classified as:

- Microcytic hypochromic anemia (MCV: <80 fL)
- Normocytic normochromic anemia (MCV: 80–100 fL)
- Macrocytic anemia (MCV: >100 fL)

Classification Based on the Clinical Presentation

- Acute: Due to hemolysis or bleeding
- Chronic Anemia: Due to various chronic diseases or due to bone marrow suppression

Flowchart 1 shows different types of anemia.

Classification Based on Pathogenesis of Anemia

- **Inadequate production:** These disorders may be due to:
  - Nutritional deficiency (vitamin B 12/folic acid deficiency, iron deficiency)
  - Stem cell disorders
  - Bone marrow infiltration
  - Defective bone marrow function of ineffective erythropoisis
- Excessive destruction of RBS (hemolysis)
- Bleeding—acute or chronic

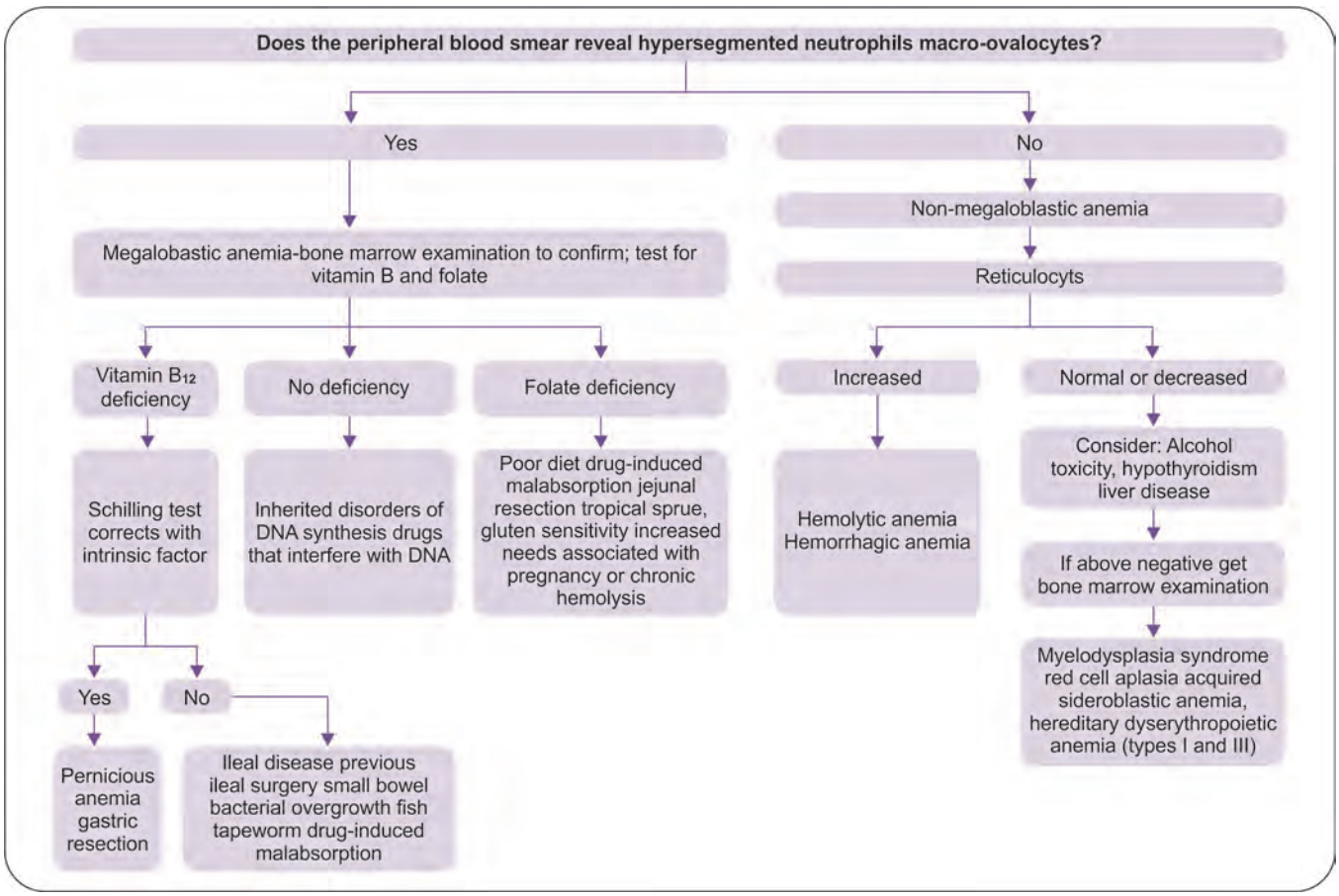
Microcytic Anemia (MCV <80 fL)

Microcytic anemia is defined as the presence of small, often hypochromic, red blood cell in a general blood picture as depicted in **Figure 1** (GBP and is characterized by a low MCV (<80 fL) **(Flowchart 2)**. Iron deficiency anemia is the most common cause of microcytosis. Overall, 50% of anemia is attributable to iron deficiency and accounts for approximately 8,41,000 deaths annually worldwide.[6,7]

Other causes of microcytic anemia are—

- Anemia of chronic disease
- Thalassemia
- Lead poisoning
- Sideroblastic anemia

Flowchart 1: Lab diagnosis cell morphology and type of anemia



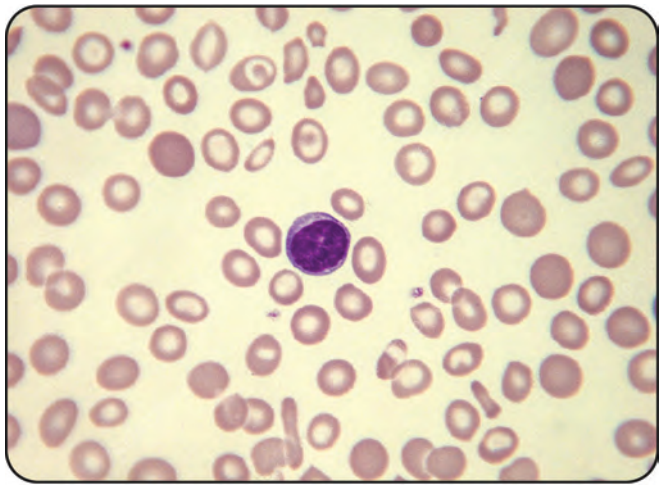


Fig. 1: Microcytic hypochromic anemia

Flowchart 2: Lab diagnosis cell morphology and bloodsmear

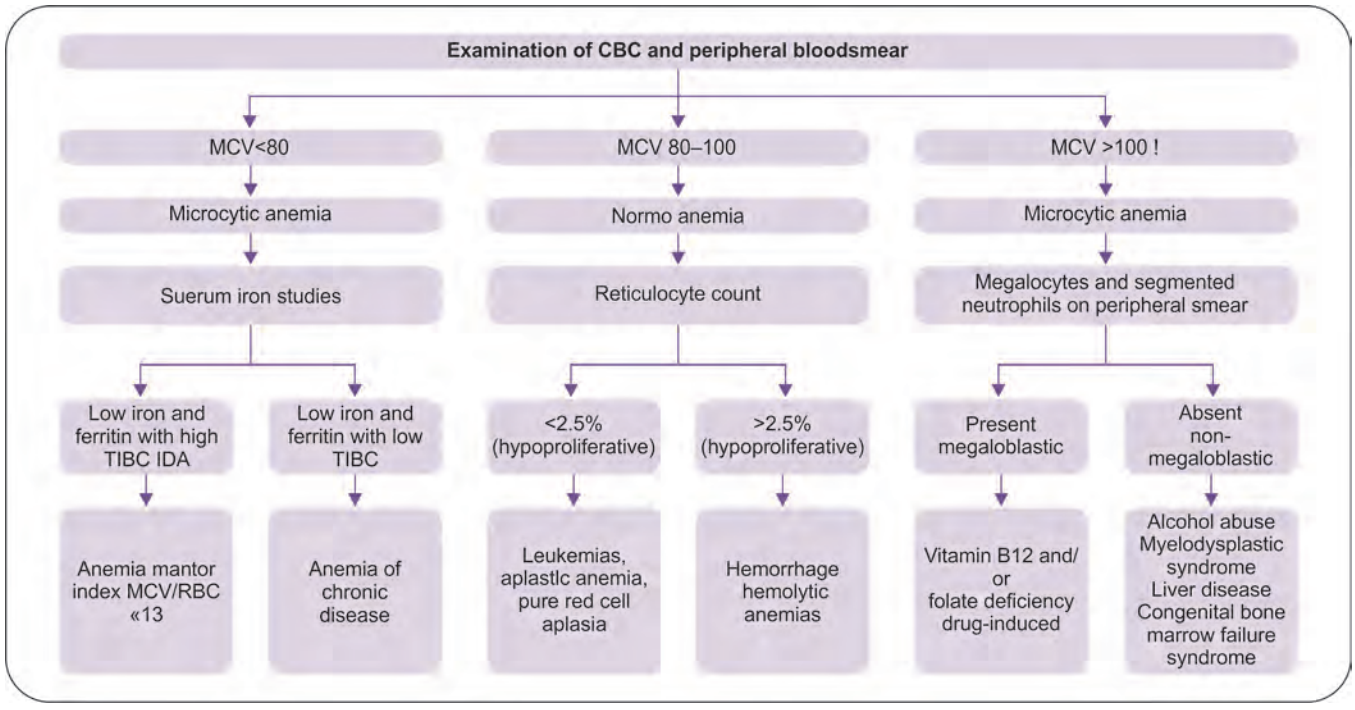


Table 1 and **Flowchart 3** show the different parameters to differentiate the discussed causes of microcytic anemia.

For megaloblastic macrocytic anemia refer **Figure 2**.

Non-megaloblastic Macrocytic Anemia

Causes of non-megaloblastic anemia are not related to defective DNA synthesis and it is characterized by the absence of megaloblasts and instead, the presence of large but mature red blood cells.

Causes of non megaloblastic macrocytosis includes—

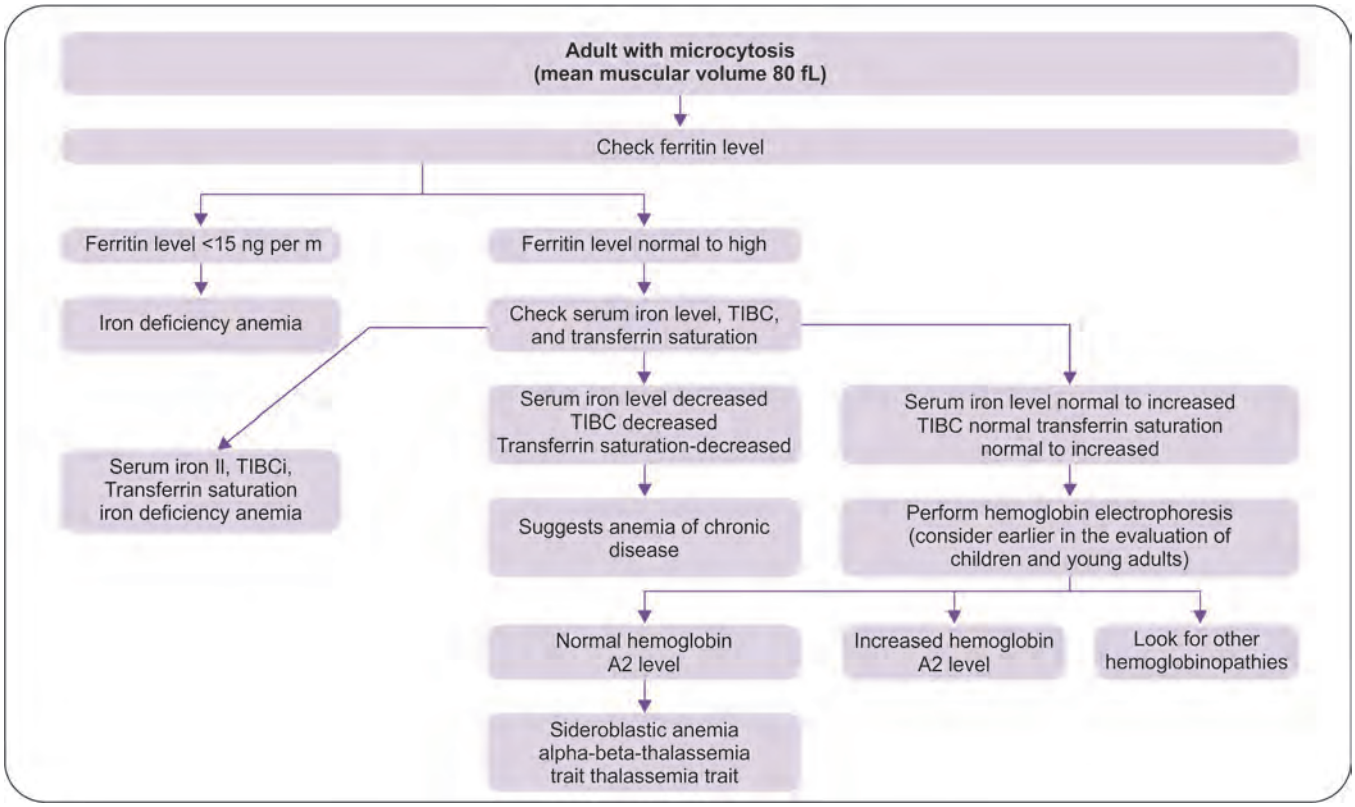
- Chronic alcoholism
- Liver disease
- Hypothyroidism
- Renal diseases

TABLE 1 Classification based on RBC morphology and indices

Parameters	*IDA*	*BT*	*Lead poisening*	*SA*	*CI*
Hgb	↓	N (or ↓)	N (or ↓)	—	↓
Se Ferritin	↓	N	N	N (or ↑)	N (or ↑)
Serum iron	↓	N	N	N (or ↑)	↓
FEP	↑	N	↑	—	↑
MCV	↓	↓	N or ↓	N	↓
RDW	↑	N	N	—	N
Reticulocyte	↓	—	—	—	N or ↓
MCV: RBC (mentzer index)	↑	↓	—	—	—
Lead	—	—	↑	—	—

BT, beta thalassemia; CI, chronic inflammation or infection; IDA, iron deficiency anemia; N, normal; SA, sideroblastic anemia

Flowchart 3: Lab diagnosis and cell morphology



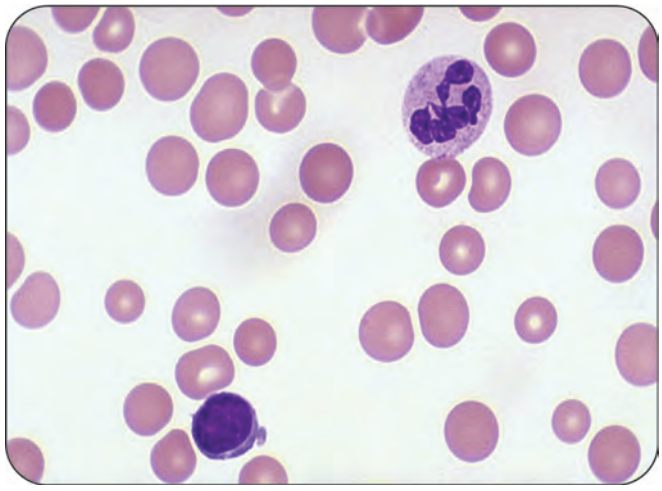
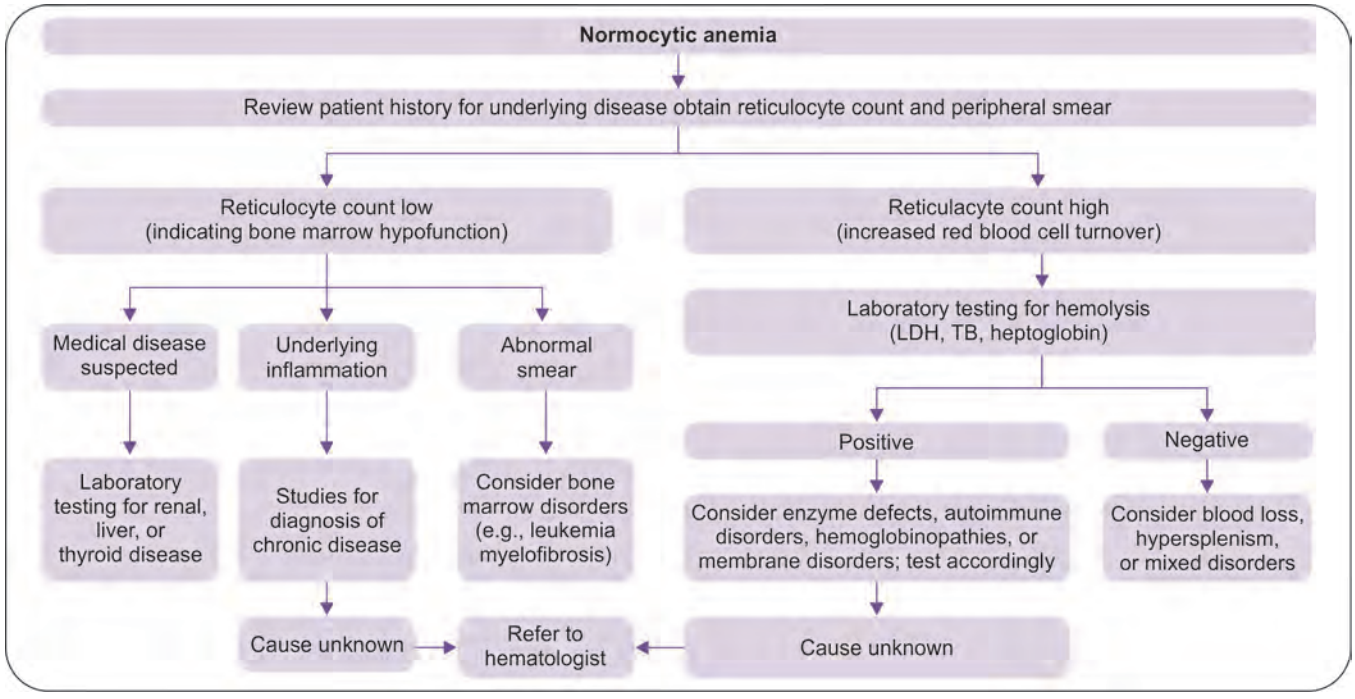


Fig. 2: Hypersegmented neutrophils and macroovulocytes (megaloblastic anemia)

Flowchart 4: Lab diagnosis cell morphology and peripheral smear



- Reticulocytosis
- Blood disorders like red-cell aplasia, aplastic anemia myelodysplastic syndromes, and myeloid leukemia, PNH
- Drugs such as azathioprine
- Pregnancy

Normocytic Anemia (MCV 80–100 fL)

A mild normochromic, normocytic anemia is a frequent finding and mostly due to a consequence of other diseases, including:

- anemia of chronic disorders associated with chronic infection, malignant disease, all forms of inflammatory

diseases. The exact mechanism is unknown, but likely to involve multiple factors, which leads to a reduction in the serum iron concentration along with concurrent reduction in the level of transferring. That's why saturation of the iron binding capacity is usually normal or only slightly reduced.

- Other disorders including renal failure, hypothyroidism, marrow failure (aplastic anemia, pure red-cell aplasia, infiltration), acute blood loss **(Flowchart 4)**.[8,9]

Conclusion

A good clinician diagnoses the type of anemia but a excellent clinician always tries to search out the cause of the disorder. So, to manage a patient of anemia, every effort should be given in searching the etiology of anemia. The first step in diagnosis of anemia is detection with reliable and accurate tests, so that the important clue to underlying causes are not overlooked and patients are not subjected to unwanted laboratory tests.

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CHAPTER

123 Approach to Aphasia

Jyotirmoy Pal, Tarun Kumar Paria, Purbasha Biswas, Manisankar Bhattarcharya

Abstract

Aphasia refers to a disorder of language processing caused by a dysfunction in specific regions of the brain. It is common after stroke and associated with relevant disability and higher mortality. Evaluation of language function (spontaneous speech, auditory comprehension, naming, repetition, reading, and writing) allows classification of aphasia. Most patients present some degree of recovery. Speech and language therapy is an effective treatment for aphasia following stroke. Other approaches, e.g., pharmacotherapy, transcranial magnetic stimulation, are being investigated.

Introduction

While assessing a patient in a neurological ward or outpatient department, one has to frequently come across cases with communication disorders. It is important to distinguish among different types of communication problems which may range from language disorder to speech production at different levels.

Broadly, communication disorders are divided into two basic groups:

- Speech defect: consisting of Dysarthia and Dysphonia
- Language dysfunction: consisting of Dysphasia/Aphasia

The fundamental difference between a speech defect and aphasia remains as follows: if one transcribes the patient's verbal expression into writing, it will read as combination of normal and grammatically correct sentences in speech defect which is not the case for aphasic participants. Thus, a language defect can simply be considered a more fundamental disturbance in communication machinery, which hinders appropriate expression of thoughts by any means, whereas in speech disorders thoughts can be properly expressed by the agency of nonverbal ways of communication, for instance writing **(Fig. 1)**.

- *Dysarthia:* It is a disorder of the motor production or articulation of speech mainly of neurologic origin.
- *Dysphonia:* It is a term that describes voice disorders, for example, involuntary tightening or constriction of vocal cords causing interruptions of speech and voice quality.
- *Aphasia/Dysphasia:* It is an acquired disorder with loss or defective language content of speech resulting from damage to speech centers of dominant hemisphere (usually left in 97%).

Language has two parts:

- Expression
- Understanding

Expression

Expression has got three components:

- Emotional component: This component of expression does not require any learning and is an expression of inner suppressed emotions

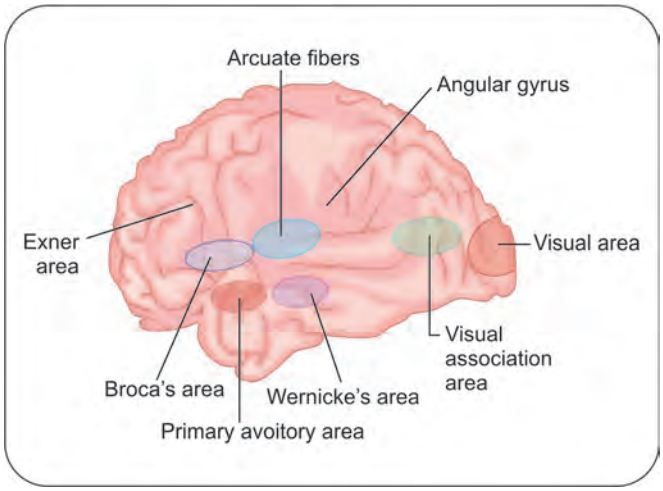


Fig. 1: Language areas of brain

- Automatic component: This component of expression occurs automatically and is generally acquired through learning
- Proposition: This is the actual speech component

Understanding

This occurs through a series of steps **(Flowchart 1)**.

Examination

Examination of speech consists of testing of the following components:

- Spontaneous speech
- Comprehension (auditory)
- Naming
- Repetition
- Writing
- Reading

Spontaneous Speech

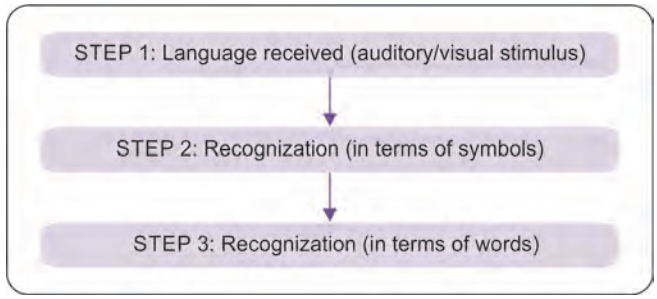
Generally motor speech defect (damage of Broca's area) manifests as loss of spontaneous speech.

- Types:
  - Complete loss : Mutism (no speech)
  - Incomplete Broca's area damage: This manifests in four forms **(Flowchart 2)**:
- *MONOPHASIA: Repetition of the same word*
- PARAPHASIA: Single letter of a word or the entire word is substituted with similar sounding words

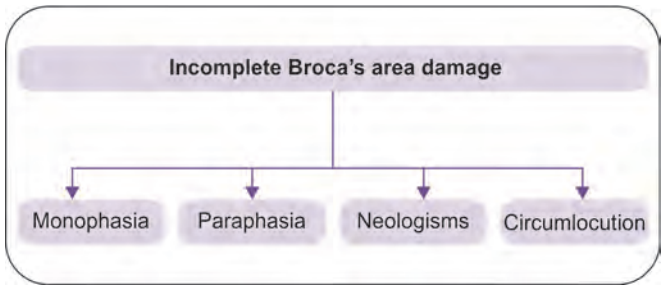
  Example 1: "Tarun" → "Arun" : single letter substitution
  Example 2: "Harry" is a bad boy. → "Tom" is a bad boy : entire word substitution
- NEOLOGISMS: New words without any meaning
- CIRCUMLOCUTION: The patient can name an object but uses different descriptions to describe a particular object

  Example: A cell phone when put infront of the patient, he can't name the object but says "this is an object used to call someone"

Flowchart 1: Pathway of understanding



Flowchart 2: Effects of incomplete Broca's area damage



Tests for Spontaneous Speech

- Fluency: Normal fluency is 100–150 words per minute or more than 7 words in a sentence, while non fluency refers to less than 10–15 words per minute
- Pronunciation
- Capability of words/sentence formation
- Speech disorder like paraphasia

Comprehension

The patient's responses to verbal requests and commands and to everyday questions and comments give information about his ability to understand speech.

Comprehension may be tested by having the patient follow verbal commands ("show me your teeth", "stick out your tongue"). Comprehension can be judged to be reasonably intact if the patient follows a complicated multistep command. However, failure to follow a command does not necessarily prove that comprehension is impaired. A patient may not comply because of apraxia. Patients with left hemisphere lesion may even have apraxia for functions of their nonparietic left hand. When the patient doesnot follow simple commands, establish whether he can say or shake his head yes or no.

Naming

Some caution is necessary while testing for naming, as there are influences of age, culture, and education.

Naming is the function of parietal lobe.

Test for Naming

While testing naming, always use common object. Naming is said to be intact when patient is given several objects to identify and can name 12 items in 1 minute.

If the patient says less than 12 items, there are three possibilities:

- Can't say name
- Can recognize the item, but can't say the function
- Can say only 4 out of 12 items

Repetition

Repetition is the function of lower parietal lobe (arcuate fibers). The ability to repeat may be selectively involved or paradoxically preserved in certain aphasic syndromes. A patient's repetition span (i.e., the number of words he can repeat) is usually two more than his digit span.

Types of repetition disorders include:

- Can't repeat
- Can repeat only a part
- Can substitute with a new syllable or word

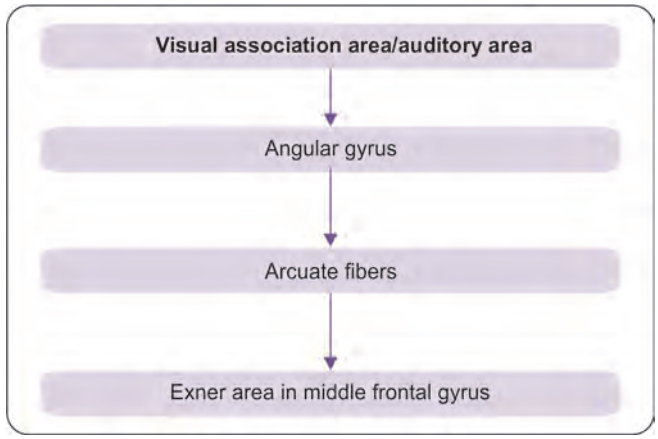
Repetition is preserved in anomic, transcortical, and some cases of subcortical aphasia.

Writing

Pathway of Writing

The patient's ability to use written language should also be assessed. It may be disturbed in conjunction with abnormalities of spoken language, or separately. Patients who are aphasic in speech are also aphasic in writing, but writing may be preserved in patients with dysarthria or verbal apraxia. The ability to write to dictation is analogous to the ability to repeat verbal material. Copying written material also assesses the ability to transfer information from visual system to language area. Having the patient copy written material may also test the connections between the receptive language areas and Exner's writing center **(Flowchart 3)**.

Flowchart 3: Pathway of writing



Reading

The patient's ability to comprehend written language symbols can be tested by having him read. Written language is perceived by the visual system and the information is conveyed to the perisylvian language centers. Dysfunctions of the language centers or interruption of the connections with visual system may cause inability to read (alexia).

Pathway of Reading

Visual association area → Angular gyrus

Alexia (Fig. 2)

- Alexia with lesion in Wernicke's area: Reading and understanding impaired, can't write dictation.
- Alexia without lesion in Wernicke's area: Reading impaired but auditory understanding preserved. This is called PURE WORD BLINDNESS.

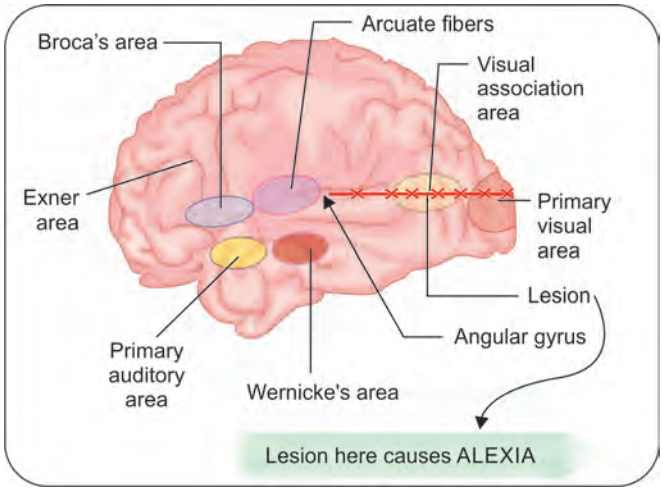


Fig. 2: Pathway of pathology of alexia

Types of Aphasia

- *Sylvian aphasia:* repetition will be lost
  - Broca's aphasia
  - Wernicke's aphasia
  - Conduction aphasia
  - Global aphasia
- *Perisylvian aphasia:* repetition is preserved
  - Anomic aphasia
  - Transcortical aphasia
  - Subcortical aphasia
  - Mixed aphasia

Sylvian Aphasia (Table 1)

Broca's Aphasia

- Fluency lost, patient will be frustrated but aware
- Communicate with small sentences with few words and with gestures
- Reading will be lost
- Writing preserved
- If there is combined damage of Broca's area and Exner's area, then both reading and writing will be lost
- *Associated* with corticospinal tract sign (Faciobrachial)

Wernicke's Aphasia

- Lesion involves:
  - Angular gyrus
  - Supramarginal gyrus
  - Wernicke's area
- Characteristics:

TABLE 1 Motor and sensory areas of brain and their connection

Wernicke's area (area 22)	*Arcuate fasciculus*	*Broca's area (area 44)*
Decoding of sounds into language information (Comprehension)	Communication between the Broca's and Wernicke's area. Needed for speech repetition	Responsible for spontaneous speech output, i.e., fluency

  - Damage to Auditory Association Area—**WORD DEAFNESS**
  - Damage to Angular Gyrus—**WORD BLINDNESS**
  - Fluency preserved
  - No appropriate response to any command (increased spoken words—**HYPERLABIA**)
  - Repetition lost

Conduction Aphasia

- Lesion involves the Arcuate fibers
- Characteristics:
  - Repetition lost
  - Fluency preserved
  - Comprehension is unaffected
  - Reading is lost
  - Writing is lost

Global Aphasia

- Features of above three aphasias
- *Associated* with hemianopia, hemisensory loss, hemiparesis

Perisylvian Aphasia

Anomic Aphasia

- Naming difficulty
- All other modalities preserved
- *Circumlocution* will be present

Subcortical Aphasia

- Repetition preserved
- Lesion involves:
  - *Caudate nucleus:* Features of Broca's aphasia with preserved repetition
  - *Thalamus:* Features like Wernicke's aphasia with preserved repetition

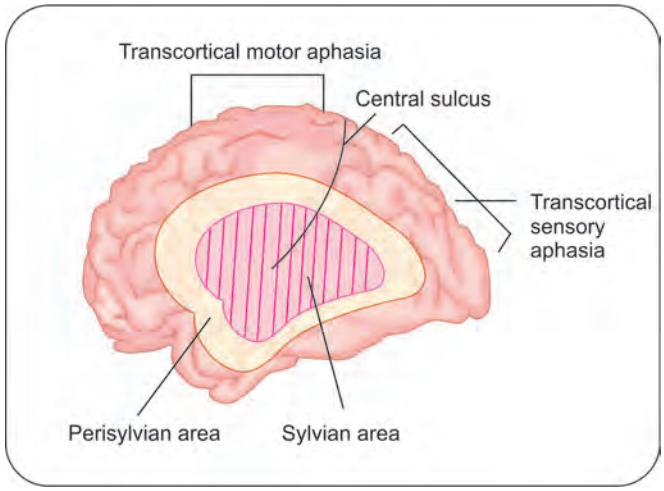


Fig. 3: Areas of transcortical aphasia

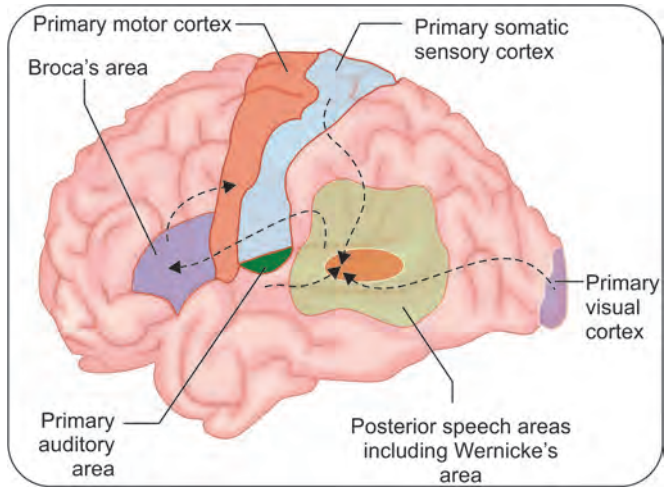


Fig. 4: Language areas of the brain

Transcortical Aphasia

This is of two types **(Fig. 3)**:

- **Transcortical sensory aphasia**:
  - Features like that of Wernicke's aphasia with preserved repetition
  - Lesion involves the area posterior to central sulcus
- **Transcortical motor aphasia:**
  - Features like that of Broca's aphasia
  - Lesion involves the area anterior to the central sulcus

Anatomy of Speech Areas

The classical model proposed by Wernicke consists of the following parts **(Fig. 4)**:

- Primary auditory area
- Secondary auditory area
- Wernicke's area (Sensory speech area)
- Broca's area (Motor speech area)
- Arcuate fasciculus
- Primary visual cortex
- Primary somatic sensory cortex
- Primary motor cortex
- Angular gyrus
- Exner's area

However, this classical model has been expanded and modified by recent reviews and are now part of *Dual Stream Model of Hickok and Poeppel.* Some of its components include:

- *Spoken speech processing:* Heschl's gyrus (bilateral superior temporal gyrus)
- *Decoding of sounds into language information:* Wernicke's area (area 22), in left superior temporal gyrus in its posterior part, as well as posterior parts of middle and inferior temporal gyri.
- *Phoneme processing:* Inferior parietal lobule, especially the supramarginal gyrus.
- *Readind comprehension:* Parieto-occipital cortex, especially the angular gyrus.
- *Spontaneous speech output:* Broca's area in the posterior inferior frontal gyrus (areas 44, 45), and the premotor cortex which program the motor cortex to produce sounds.
- *Speech repitition:* Communication between the posterior and anterior speech regions via the arcuate fasciculus and uncinate fasciculus.
- *Alerting the language network:* Anterior thalamus, basal ganglia.

Auditory Pathway and Speech

- The auditory pathway conveys the special sense of hearing. Information travels from the receptors in the Organ of Corti of the inner ear (cochlear hair cells) to the central nervous system carried by the vestibulocochlear nerve.
- This pathway ultimately reaches the primary auditory cortex for conscious perception. In addition, unconscious processing of auditory information occurs in parallel **(Figs. 5 and 6)**.

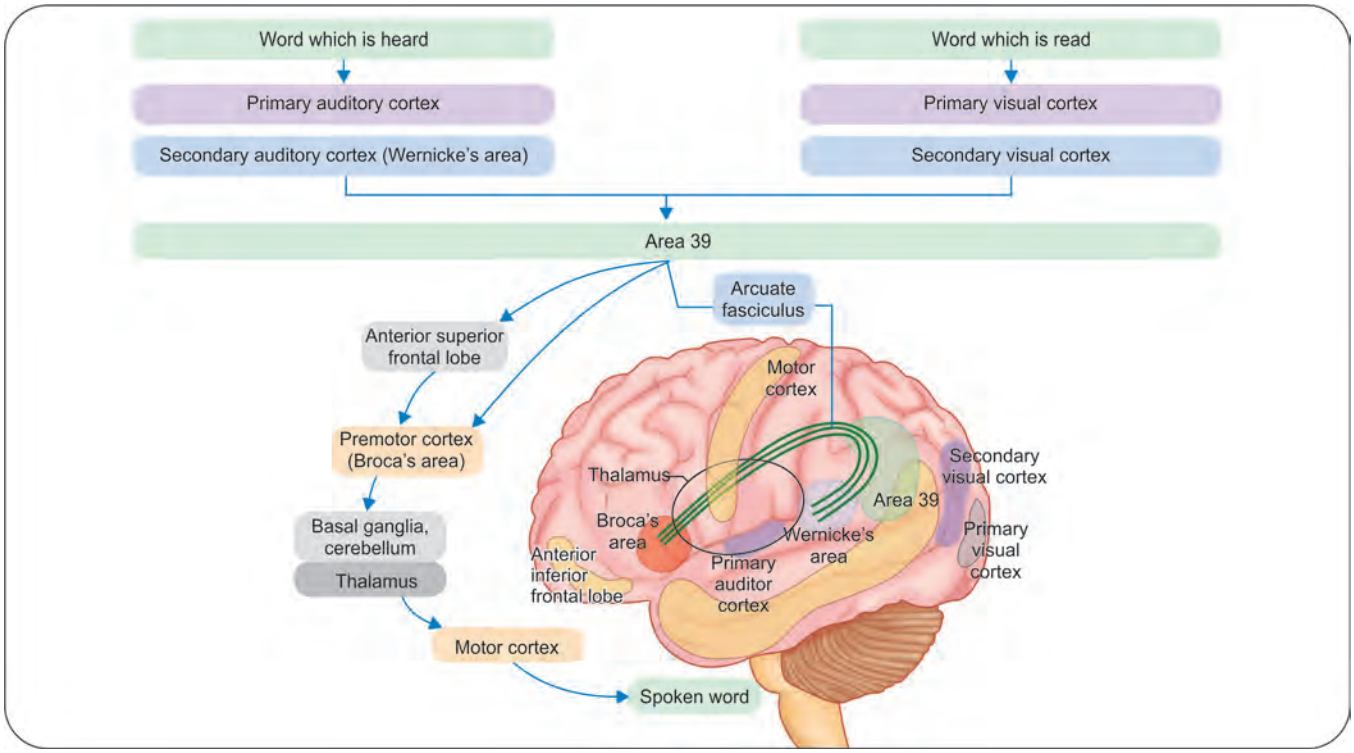


Fig. 5: Genesis of speech

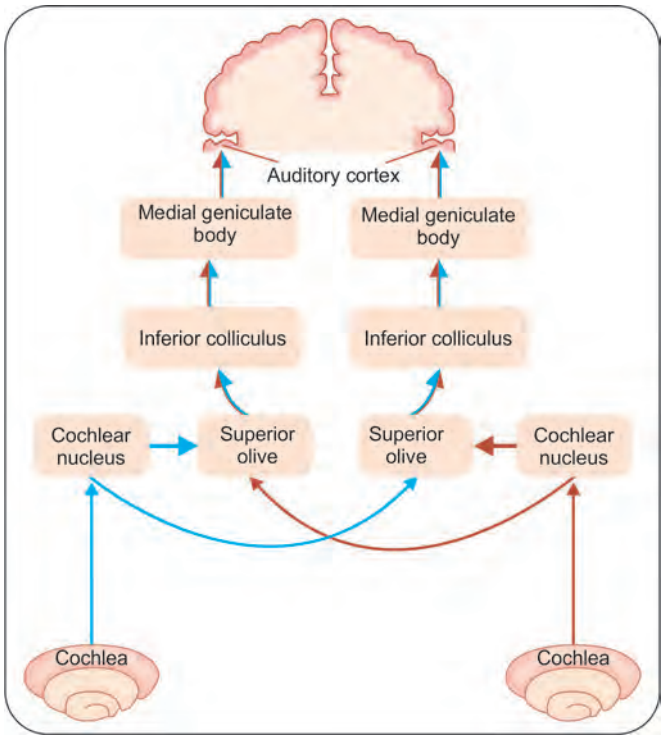


Fig. 6: Auditory pathway

Aphasia

Aphasia as mentioned earlier is a loss or impairment of language production and/or comprehension, often accompanied by a loss of ability to read and/or write resulting from damage to speech centers within the dominant (usually left in 97%) hemisphere **(Fig. 7)**.

A language disturbance occurring after a right hemisphere lesion in a right-handed person is known as *Crossed aphasia*.

Aphasia can be categorized according to whether the speech output is fluent or nonfluent:

- *Fluent aphasia (receptive aphasia):* It is the impairment mostly due to the input or reception of language with difficulties either in auditory verbal comprehension or in the repetition of words, phrases, or sentences spoken by others. For example, Wernicke's aphasia.
- *Nonfluent aphasia (receptive aphasia):* These are difficulties in articulating with relatively good auditory, verbal comprehension. For example, Broca's aphasia.

Normal fluency: Between 100–150 words/min, sentence length >7 words.

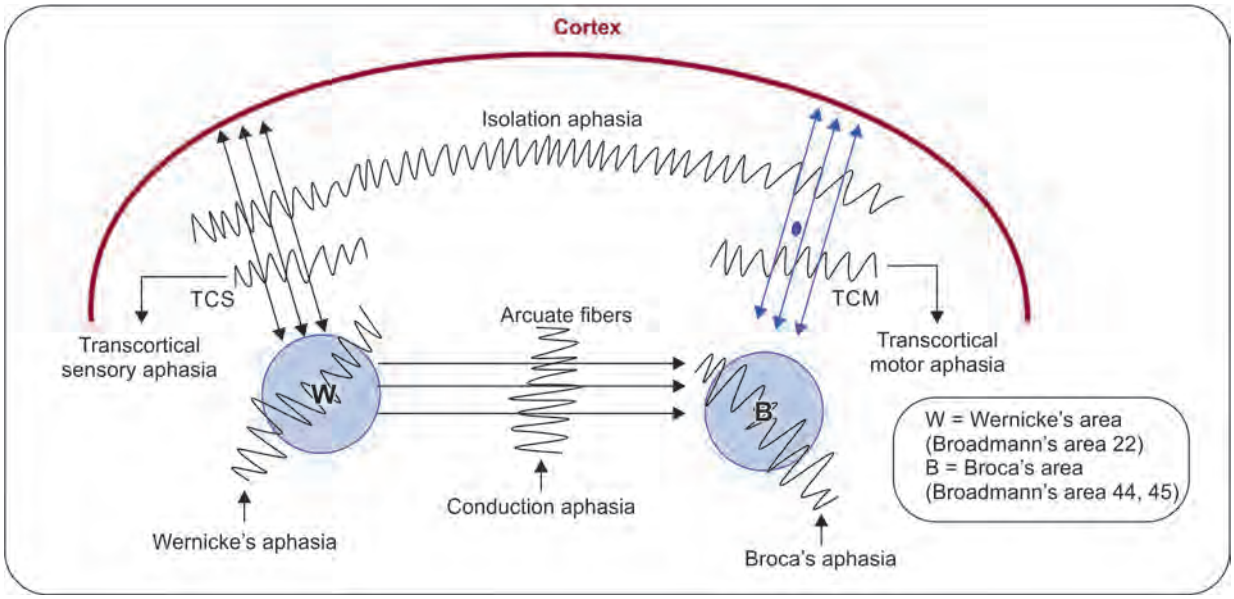


Fig. 7: Schematic representation of aphasias and associated lesions

TABLE 2 Domains of speech

Domains	*Methodology*	*Observations*
Spontaneous speech	• Observe the speech and language during routine conversation • Ask open ended questions. Example: – Why have you come to the hospital? – Describe the nature of your job • If the patient is not communicative try recitation list. Example: – List the days of a week – List the months of the year	• Initiation difficulty • Articulation • Fluency • Prosody (the melodic intonation) • Grammatical correctness (agrammatic speech sounds like telegraphic language) • Paraphasias:[1] If present, literal[2] or semantic[3]? • Neologisms[4] • Word finding pauses, circumlocution
Naming	Show different categories like objects, body parts, colors, pictures of animals Example: pen, watch, key hand, thumb, dog , cat, red/blue/ yellow colors, names of familiar people	• Impaired naming, in spite of recognition of the object or the person • Impaired naming restricted to certain category • Confabulation • Word finding difficulty, pauses, circumlocution
Auditory comprehension	• One step commands (beware of apraxias) – Stick out your tongue – Point to your nose – Open your mouth • Two steps commands (beware of body part agnosias, right left disorientation) – With your right hand, point to your left ear – Point to the ceiling and then to the floor – Raise your hand and close your eyes • Yes or no responses (inform that patient should say yes or no) – Is your name xxx? (use a wrong name) – Is your name zzz? (use correct name) – Do you live in xxx? (use wrong place) – Do you live in zzz? (use correct place) – Does Sunday come after Saturday?	• Impaired comprehension to spoken commands • If apraxia/body part agnosia interferes with body part commands, impaired "yes/no" responses

Contd...

Domains	*Methodology*	*Observations*
Repetition	• Single words: – Brown – Chair – Five hundred and fifty-five • Sentence repetition (there should be no errors of omission or commission) – It is 4 o'clock – He locked the doors – He searched for keys in his pocket – No ifs, ands, or buts – He opened the sports page of the newspaper for cricket score	• Impaired for difficult consonants in dysarthria • Impaired for complex grammatical sentences in aphasia
Reading	• Simple letters and words: – Alphabets (G, C, K, M) – Numbers (3, 8, 6, 9) – Simple words (ear, ant, car, etc.) • Obeying written commands (carry cards with these commands written) – Make a fist – Open your mouth – Point to the floor then point to the ceiling – With your right hand point to the left knee • Reading aloud with comprehension – Ask patient to read a newspaper item and ask him relevant questions	• Impaired letter formation • Spelling errors (most useful in mild Wernicke's aphasia) • Impaired grammar • Impaired reading comprehension, in spite of good speech comprehension in Broca's aphasia • Relatively preserved reading comprehension in spite of impaired auditory comprehension in Wernicke's aphasia
Writing	• Ask patient to write few sentences about why he has come to the hospital • Ask him to write about his job/business • Show him a picture and ask him to write a few sentences about it • If the patient has right sided hemiparesis, ask him to use left hand	

[1]Paraphasia: It is a phenomenon of substitutions in speech components.
[2]Literal paraphasia (Substitution of one phoneme for another; e.g., foon for spoon)
[3]Semantic paraphasia (Substitution of one word for another; e.g., pan for spoon)
[4]Neologisms: Use of non-existent words

TABLE 3 Interpretation of language assessment

C-Comprehension (requires intact Wernicke's and transcortical sensory area)
R-Repetition (requires intact Wernicke's, arcuate fibres, and Broca's areas)
F-Fluency (requires intact Broca's and transcortical motor area)

Aphasia	*Site of lesion*	*C*	*R*	*F*	*Reading*	*Writing*	*Associated signs*
Wernicke's-sensory/receptive/posterior	Involvement of inferior division of middle cerebral artery	–	–	+	**Impaired, but sometimes relatively preserved (opposite of Broca's aphasia**)	Impaired, good letter formation, spelling errors, and poor grammars	Visual field defect
Broca's-motor/expressive/anterior	Involvement of superior frontal branch of middle cerebral artery	+	–	–	Impaired with preserved speech comprehension, especially for syntax ("third alexia")	Impaired with poor letter formation and poor grammar	Right sided hemiparesis, apraxia of left limbs

Contd...

Contd...

Conduction/arcuate	Arcuate fasciculus	+	_	+	Inability to read aloud, reading comprehension usually intact	Impaired variably	Mild right hemiparesis, apraxia of left limbs, right hemisensory loss, visual field defect
Transcortical sensory	Posterior watershed zone	_	+	+	Impaired	Impaired	----------
Transcortical motor	Anterior watershed zone	+	+	_	May or may not be intact	May or may not be intact	----------
Isolation aphasia (mixed transcortical aphasia)	Both anterior and posterior watershed zone	_	+	_	Impaired	Impaired	----------
Global aphasia	Dominant frontal, parietal, and superior temporal lobe, left MCA involved	_	_	_	Impaired	Impaired	Right hemiparesis, hemisensory loss, hemianopia

Once the comprehension, repetition, and fluency are intact, we look for Reading, Writing, and Naming disorders associated with reading, writing, and naming.
R-Reading
W-Writing
N-Naming

		R	*W*	*N*
Alexia without agraphia	Occipitotemporal region	_	+	+
Alexia with agraphia	Left angular gyrus	_	_	+
Nominal/anomic/amnesic	Temporoparietal	+	+	_

TABLE 4 Lesion localization

Aphasia	*Site of lesion*
Transcortical motor aphasia	• Left frontal lobe anterior to Broca's area • Frontal deep white matter • Medial frontal region neat SMA (in the anterior cerebral artery territory)
Transcortical sensory aphasia	Left temporo-occipital region
Transcortical mixed aphasia	Large watershed infarctions in the left hemisphere, sparing the perisylvian cortex, but disconnecting them from other cortical regions
Conduction aphasia	Lesion involving either the arcuate fasciculus or the superior temporal gyrus or the inferior parietal region (supramarginal gyrus)
Wernicke's aphasia	Lesion involving Wernicke's area and adjacent temporoparietal region (inferior parietal lobule, superior temporal gyrus)
Single word comprehension defect	Lesion limited to Wernicke's area
Broca's aphasia	Lesion involving the Broca's area and adjacent cortex and subcortical white matter
Isolated speech initiation defect	Lesion limited Broca's area
Global aphasia	Large lesion involving the left frontal, temporal, and parietal lobes
Anomic aphasia	Non-localizing left hemispheric disease. Usually superior temporal gyrus, but also frontal or parietal lobe near angular gyrus
Alexia with agraphia	Left angular gyrus lesions
Alexia without agraphia	Disconnection (of language areas from right occipital cortex) by splenial lesion plus left occipital lesion. Patient has intact left hemifield, but written information presented in that hemifield is not conveyed from right occipital cortex to the language areas
Third alexia	Impaired reading comprehension in Broca's aphasia
Speech alexia	Left frontal or insular lesion

Domains of Language (Table 2)

Language has to be assessed in six domains, which are as follows:

- Spontaneous speech
- Naming
- Auditory comprehension
- Repitition
- Reading
- Writing

Interpretation of Language Assessment

See **Table 3**.

Lesion Localization

See **Table 4**.

Conclusion

A social approach of language assessment that prioritizes subjectivity is possible when we use a fourth-generation method (Campos and Furtado, 2011), which goes beyond individual evaluation and rehabilitation, providing a more effective improvement. The plasticity of the human brain and training-induced learning improve the quality-of-life due to interference in the process of cognition of individuals with dysgraphia. Although their learning tends to be specific to the trained function and not transferred to similar tasks, there are no obstacles that prevent the discussion of new training schemes. These trainings can lead to the acquisition of new knowledge and to the development of new strategies so that they are used flexibly in various tasks and contexts. These challenges are responsible for increasing learning, for progressing the task difficulty, for the motivational state of the individual, and also for reflecting on the type of feedback that the training provides.

Suggested Readings

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Section 10

Section Editor: Rajesh Upadhyay

Gastroenterology

CHAPTER

124 Type 2 Diabetes Mellitus Originates from Fatty Liver

Rajesh Upadhyay, Ankit Gupta

Abstract

The relationship between diabetes mellitus and liver disease is bidirectional, both supporting and accelerating the development of each other. The key pathogenic mechanism is insulin resistance (IR). The main factor leading to IR is accumulation of fat in the liver. The hepatic fat predominately comes from three sources

- Dietary fat,
- De-novo lipogenesis due to high insulin level and
- Fatty acid generation from adipose tissue lipolysis.

Fat in the liver impairs insulin signaling, leading to IR. Liver is the largest metabolic organ leading to IR. The resultant IR worsens hyperinsulinemia, which affects various metabolic processes in the liver. The IR prevents glucose transport from blood to liver, thus leading to poor trapping in liver and consequent rise in blood sugar. In addition increased free fatty acids inhibit the insulin action on liver, and insulin-induced suppression of glucagon is impaired, thus leading to increased production of hepatic glucose which has a major contribution in fasting hyperglycemia. Evidence suggests that improvement in fatty liver reduces IR and prevents development and/or improvement of diabetes mellitus. There are numerous observational studies suggesting that fatty liver is an independent risk factor for development of diabetes. Chronic liver disease is associated with development of diabetes (secondary diabetes). Glucose intolerance can be seen in about 80% of patients, and diabetes in about 30% of patients with chronic liver disease. Thus, fatty liver may be considered the main organ responsible for IR and T2DM. Diabetes should be considered a reversible metabolic state due to excess intra-organ fat, especially fatty liver.

Introduction

The interest in relationship between chronic liver disease and diabetes mellitus has increased since last decade. Chronic liver disease particularly NAFLD is associated with diabetes mellitus. In the United States, NAFLD is the most common cause of chronic liver disease and affects between 80–100 million individuals.[1] According to an estimate in India, approximate 30% of the population is having NAFLD and its prevalence approaches to 64% in diabetics.[2] The association is based on insulin resistance (IR), which is the common underlying mechanism for both T2DM and NAFLD. The relationship between diabetes mellitus and liver disease is bidirectional, both supporting and accelerating the development of each other. What remains unclear is the chicken-egg conundrum—which comes first? In other words, does diabetes lead to fatty liver or fatty liver causes diabetes? An understanding of this requires a deep study of the physiology and pathogenesis of both conditions and developing clear concepts. Although IR is the common pathogenetic mechanism for both these conditions; however, it is the liver which is the key player for IR.

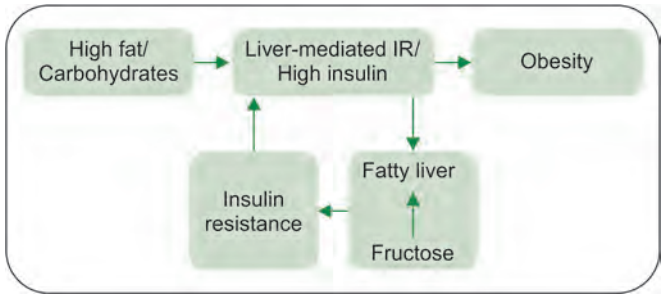
Liver is the Main Organ Producing IR

Being the largest metabolic organ of human body, it plays an important role in glucose metabolism. It is the site for glycogenesis, glycogenolysis, and gluconeogenesis. It has an immense capacity to store sugar in times of excess and push out glucose into circulation in deficient condition. Therefore, in states of fasting or hypoglycemia, liver releases glucose into the circulation by glycogenolysis and/or gluconeogenesis. On the other hand, it is also the main organ which prevents rapid rise of blood glucose after food ingestion. Whatever glucose is absorbed from the intestines it goes through the portal vein to the liver where, almost all of it is retained. The rise in prandial plasma glucose reflects only a minor component of the absorbed glucose. It is pertinent to note that the first glycemic abnormality in T2DM is postprandial hyperglycemia, which may actually indicate insufficient trapping of glucose by the liver. The insufficient trapping of glucose in the liver is due to the liver mediated IR. The main factor leading to IR is accumulation of fat in the liver. This brings us to the basic question as to what causes fatty liver **(Flowchart 1)**. High carbohydrate/high fat diet increases insulin production, which pushes sugar from blood into liver. The liver cells are filled up with stored glycogen. The hepatic fat predominately comes from three sources:

- Dietary fat,
- De-novo lipogenesis due to high insulin level, and
- Fatty acid generation from adipose tissue lipolysis.

In addition the role of absorbed fructose is also important. Fructose unlike glucose can only be metabolized by the liver and not by other tissues. In fatty liver, there is already high hepatic glucose/glycogen; hence, fructose can only be converted into fat which adds to the fatty pool. Fatty acid accumulation occurs in the liver cells which would normally be oxidized to produce energy. However, the oxidative stress and mitochondrial dysfunction in fatty liver prevents oxidation. The fatty acid is therefore esterified into triglycerides and stored in the liver cells. Fat in the liver impairs insulin signaling, leading to IR. The resultant IR worsens hyperinsulinemia, which affects various metabolic processes in the liver. First, it stimulates the enzyme hexokinase, which phosphorylates glucose. In addition, it also activates the enzymes phosphofructokinase and glycogen synthase, which are involved in glycogen synthesis. When glycogen stores are saturated, the excess glucose is then shunted to fatty acid synthesis, which further adds to liver fat.

Flowchart 1: What causes fatty liver?



The liver mediated IR is a manifestation of the inherent ability of liver to protect itself from ongoing onslaught of further sugar/fat accumulation in liver cells, which is likely to cause cell disintegration. The stored fat is therefore transported out from the cell in the form of free fatty acid and VLDL, which causes tissue IR in various organs **(Fig. 1)**. The IR prevents glucose transport from blood to liver, thus leading to poor trapping in liver and consequent rise in blood sugar.

Increased Hepatic Glucose Output in Diabetes

It is also well known that hepatic glucose output is increased in T2DM, and it has a major contribution in fasting hyperglycemia. Increased free fatty acids inhibit the insulin action on liver, and insulin-induced suppression of glucagon is impaired, thus leading to increased production of hepatic glucose excessive release of glucose from liver further increases blood sugar levels although the levels may still be maintained within the normal range due to compensatory high pancreatic beta cell production of insulin.

Phases of T2DM and the Role of Pancreatic Fat

It is well known that in diabetics, there is a prolonged period of 12–14 years of IR with compensatory hyperinsulinemia keeping the blood sugar within the normal range with gradually increasing HbA1c to prediabetic levels. Then comes the pancreatic beta cell failure resulting in reduced

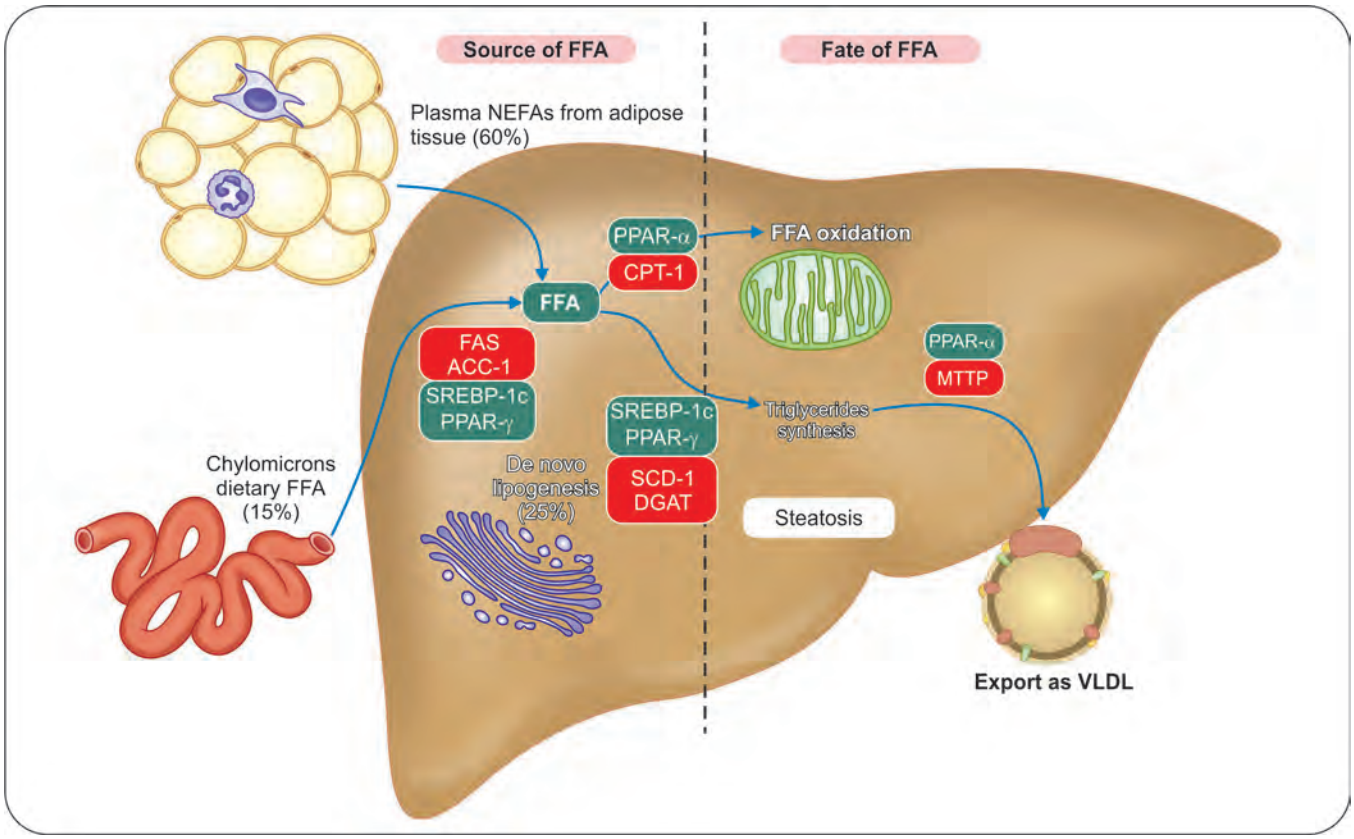


Fig. 1: Sources and fate of free fatty acids in liver

insulin production causing overt diabetes **(Fig. 2)**. The question is what causes beta cell failure? Various theories in literature have been suggested especially the burnout theory due to persistent insulin overproduction by the pancreatic beta cells leading to cell death causing reduced insulin production. If this was so then T2DM would clearly be an irreversible condition. On the contrary, there is evidence of increase in insulin secretion post-bariatric surgery or following a hypocaloric diet.[3,4] Such interventions have the ability to reverse diabetes completely. Hence, a more plausible explanation would be that the beta cells have been rendered metabolically inactive due to reversible factors. Evidence suggests that fatty acids prevent beta cell proliferation. In the genetic model, Zucker diabetic fatty rats rapid increase in pancreatic fat leads to development of diabetes. When food intake is restricted in this model, diabetes did not develop. This also suggests that a significant

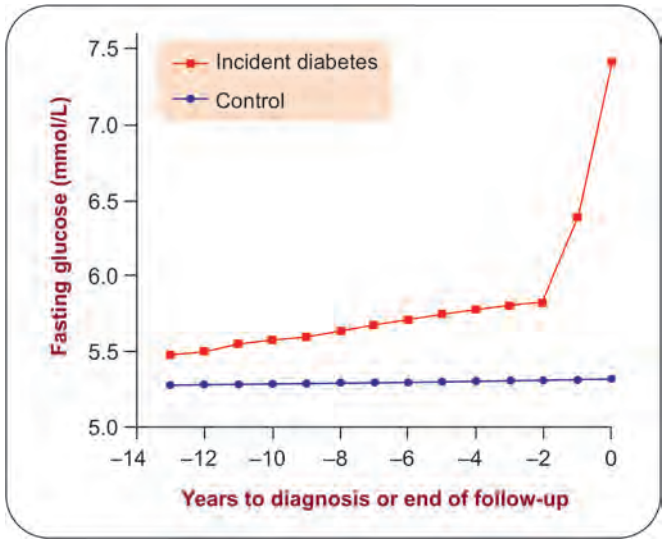


Fig. 2: Two phases of type 2 diabetes

mass of beta cells is not permanently damaged but became metabolically inactive. Thus, pancreatic fat (PF) accumulation is an important precursor for development of diabetes. The amount of PF is greater in diabetics and increases with the duration of diabetes. Patients with PF have a higher prevalence of T2DM than non-PF controls (12.6% vs. 5.2%) and T2DM was independently associated with PF.[5] A cohort of patients with biopsy proven NASH had more PF in diabetics compared to patients without diabetes.[6] The fatty liver cells are overdistended with fat which is then transported to different organs including the pancreas as free circulating fatty acids and VLDL particles which lead to tissue IR and PF accumulation. There is evidence to suggest this cross talk between the fatty liver and PF.[7] Fat in pancreas may lead to metabolic suppression of beta cells causing pancreatic failure and reduced insulin production leading to T2DM. This hypothesis appears attractive but needs to be evidence based. There are studies on post-bariatric surgery patients demonstrating lowering of pancreatic triglyceride content with simultaneous increase in insulin secretion. Bariatric surgery leads to fat mobilization from various tissues and liver/pancreas are the earliest targets of mobilization leading to reduction in liver and PF causing improvement in insulin sensitivity and insulin production. Hence, improvement in blood glucose in post-bariatric surgery patients occurs early even before body weight loss and this improvement in blood glucose has linear correlation with reduction in fat content of liver and improved sensitivity to insulin and the normalization of fasting blood glucose which occurred within 7 days.[8] PF content reduction occurred in 8 weeks and was accompanied by restoration of first phase insulin.[9]

Treatment of Fatty Liver can Ameliorate IR and Prevent Diabetes

In a rodent model, it was found that there was early development of hepatic IR without significant changes in insulin-stimulated glucose utilization or body weight in rodents fed with high fat diet.[10] In a study in T2DM patients subjected to a moderately hypocaloric and very low-fat diet, 81% reduction in intrahepatic fat content and improvement in basal and insulin-stimulated hepatic glucose metabolism was noted; however, effects on insulin-stimulated peripheral glucose uptake were not significant.[11] So dietary modification can improve hepatic insulin sensitivity. Weight loss interventions are also associated with improvement in liver histology and transaminases. Metformin an oral antidiabetic drug reduces plasma glucose via activation of AMP kinase, and reduces hepatic glucose synthesis. This enzyme also decreases lipid synthesis and enhances fat oxidation. Metformin treatment thus can improve insulin sensitivity and liver transaminases in patients with fatty liver disease. Thiazolidinediones are insulin sensitizers and can improve hepatic as well as peripheral insulin sensitivity. They can induce adipocyte differentiation, reduce free fatty acid levels, and thus decrease their delivery to liver. They also increase adiponectin levels and can increase lipid oxidation of fatty acid in liver. They also reduce TNF-alpha and C-reactive protein, which play important role in IR. Therefore, there are ample evidences to suggest[2] that targeting fatty liver can lead to improvement of IR. It is a well-known fact that persons with fatty liver have higher prevalence of T2DM (22.4%) and NASH (43.6%) as compared to 8.5% in general population.[12] This suggests that fatty liver is a risk factor for T2DM and increases the risk of development of T2DM by 2–3 folds. The risk of development of T2DM may be even higher in patients with more severe liver disease which suggests that fibrosis increases the risk. About 30% patients with cirrhosis of liver have diabetes.[13]

Evidence Suggesting Fatty Liver Leads to T2DM

Over the past 15 years there have been numerous observational studies suggesting that fatty liver is an independent risk factor for development of diabetes **(Table 1)**.

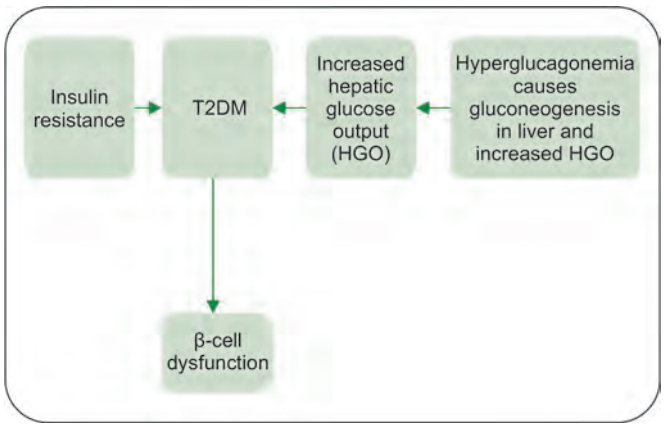
Secondary Diabetes is Related to Liver Disease

Liver is the most important organ for regulation of blood sugar. It is therefore, a simple understanding that chronic liver disease is associated with impaired glucose tolerance and development of diabetes. Glucose intolerance can be seen in about 80% of patients, and diabetes in about 30–60% of patients with chronic liver disease.[14,15] Apart from fatty liver disease, other conditions like hemochromatosis, cystic fibrosis, chronic liver disease due to alcohol abuse, chronic hepatitis C, and glycogen storage disorders are also associated with development of diabetes.

TABLE 1 Observational studies of the association between NAFLD and T2DM

Study	*Study population*	*Length of follow-up (diagnosis)*	*Main findings*
Fan et al. (2007) Chinese study	Age and sex matched 1,146 individuals with and without NAFLD	7 years, ultrasound based NAFLD diagnosis	Higher incidence of T2DM in NAFLD group (OR 4.6, 95% CI 3.0–7.1)
Shibata et al. (2007) Japanese study	3,189 male ≥ 40 years age	8 years, ultrasound based NAFLD diagnosis	NAFLD significantly increases the risk of T2DM (HR 5.5, 95% CI 3.6–8.5)
Kim et al. [2008] South Korean study	5,372 individuals	5 years, ultrasound based NAFLD diagnosis	NAFLD was independent risk factor for T2DM (HR 1.51, 95% CI 1.04–2.20).
Yamada et al. (2010) Japanese study	12,375 individuals	5 years, ultrasound based NAFLD diagnosis	Fatty liver is independent risk factor for development of T2DM (OR 1.91, 95% CI 1.56–2.34)
Sung et al. (2011) South Korean Study	11,091 individuals	5 years, ultrasound based NAFLD diagnosis	Increased risk of T2DM in NAFLD (OR 2.05, 95% CI 1.3–3.1)
Bae et al. (2011) South Korean Study	7,849 individuals	5 years, ultrasound based NAFLD diagnosis	Increased risk of T2DM in NAFLD (HR 1.33, 95% CI 1.07–1.66)
Sung et al. (2012) South Korean Study	12,853 individuals	5 years, ultrasound based NAFLD diagnosis	NAFLD was independently associated with incident T2DM (OR 2.42, 95% CI 1.7–3.36)
Ekstedt et al. (2006) Swedish study	Retrospective study, 129 individuals	13.7 years, liver biopsy based NAFLD diagnosis	At follow-up, 58% of patients developed T2DM and 20% developed impaired glucose tolerance
Alessandro Mantovani, et al. (2018) Meta-analysis	19 observational studies (296,439 individuals)	Median 5 years	NAFLD associated with two fold increase risk of diabetes
Sung et al. (2019) South Korean Study	70,303 adults	3.3 years	Diabetes risk increased with increasing insulin resistance (HR-6.6)

Flowchart 2: Triumvirate pathology of T2DM



Conclusion

The traditional triumvirate features in the pathogenesis of diabetes, viz. IR, diminished insulin release from pancreatic islet beta cells and increased hepatic glucose output **(Flowchart 2)** gave way to the ominous octet proposed by deFronzo in his Banting Lecture a decade back.[16] However, it is imperative to note that the triumvirate features had the liver contributing to categorically all the features. The octet may provide the treating physicians with different ways to tackle the treatment of diabetes, but it will be pertinent to understand that the liver-pancreas axis is involved in most of the features of the octet. Thus, liver is an important organ involved in glucose homeostasis and plays an important role in the pathogenesis of T2DM. In fact, reversal of fatty liver may help ameliorate IR, and may aid in the prevention of development of type 2 diabetes. Thus, fatty liver may be considered the main organ responsible for IR and T2DM. Diabetes should be considered a reversible metabolic state due to excess intra-organ fat especially fatty liver.

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CHAPTER

125 Non-Pharmacological Management of NAFLD/NASH (Diet, Exercise, and Role of Intermittent Fasting)

Sundeep Kumar Goyal

Abstract

Nonalcoholic fatty liver disease (NAFLD) and its complications are growing with increasing prevalence of obesity. Multiple factors and pathways are involved in pathogenesis of disease. In the absence of effective pharmacotherapy that addresses all or most of the components of disease and reverses the inflammation and fibrosis, primary approach to treat NAFLD focuses on promoting weight loss through diet and lifestyle interventions. The choice of therapy is dependent on degree of overweight, comorbidities, and patient preferences. This chapter will review the dietary therapy and lifestyle changes of NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) and its complications are growing with increasing prevalence of obesity worldwide. Under the umbrella of NAFLD, there are two histological phenotypes:

- Steatosis (nonalcoholic fatty liver, NAFL) and
- Steatosis with inflammation, ballooning and fibrosis (nonalcoholic steatohepatitis, NASH).

NAFLD often occurs concomitantly with other end organ diseases like diabetes, hypertension, coronary artery disease, and chronic kidney disease. These are often connected to common biology linked to metabolic stress and systemic inflammation. So term NAFLD is proposed to rename as metabolic dysfunction associated fatty liver disease (MAFLD) to give clearer concept of liver manifestations of this multisystem disease.[1] Natural history of disease is influenced by various factors like age, sex, ethnicity, diet, hormonal status, genetic, epigenetic factors, gut microbiome, alcohol, and metabolic status and leads to heterogeneous clinical phenotype.

Aim and objectives of dietary restriction and exercise: Patients with NAFLD/MAFLD are metabolically unhealthy with imbalance between calorie intake and expenditure that leads to obesity, insulin resistance, and other metabolic disorders.[2] Obesity doubles the prevalence of NASH and its progression to cirrhosis, liver failure, and hepatocellular carcinoma (HCC).[3] Prior to development of cirrhosis, clinical outcomes of disease are mostly related to cardiovascular system. With the advancement of fibrosis stage or cirrhosis development, liver-related outcomes increase exponentially.[4] The ideal goal of treatment is to subside inflammation, regression of fibrosis, and cirrhosis with simultaneously addressing concomitant metabolic disorders and cardiovascular mortality.[5] Histology based data have showed that weight loss is the only modality at present that has favorable impact on reducing hepatic as well as extrahepatic complications.[6,7] In a prospective study of 293 patients, degree of weight loss was independently associated with improvements in all NASH-related histological parameters.[8] Nevertheless, in the study just 10% of patients reached a 10% weight loss and 70% of the cohort did not lose 5% of total body weight **(Fig. 1)**.

Approximately 22 kcal/kg (±20%) is required to maintain a kilogram of body weight in a normal-weight

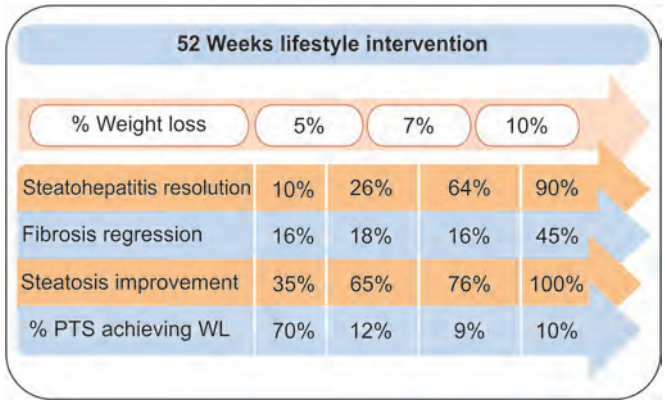

Fig. 1: Effect of weight loss on NASH[8]

adult. An average deficit of 500 kcal/day should result in an initial weight loss of about 0.5 kg/week. Both lean body mass and body fat decreases with weight loss and reach plateau after 3–6 months. Further caloric restriction and increased physical activity required to overcome this plateau effect.[9] Aim of weight loss is to preserve muscle mass and decrease visceral fat.

Types of diet: Planning a diet requires the selection of caloric intake and then choice of foods according to local culture and palatability. Replacement of food by low-calorie meals containing 250–350 kcal/package in form of nutrition bars, frozen food, and prepackaged meals resulted in early initial weight loss, which then was maintained over long term (4 year follow-up).[10] The Mediterranean diet includes consuming high level of monounsaturated fat relative to saturated fat; moderate consumption of alcohol, mainly as wine, a high consumption of vegetables, fruits, legumes, and grains, a moderate consumption of milk and dairy products, mostly in the form of cheese, and a relatively low intake of meat and meat products. Adherence to the Mediterranean dietary pattern leads to a significant decrease in liver fat and insulin resistance among overweight patients with NAFLD.[11]

Dietary Composition

Carbohydrate: Low- and very low-carbohydrate (60–130 gm and <60 gm, respectively) diets have been more effective for short-term weight loss than low-fat diets, but not for long-term weight loss, compared with a low-fat diet.[12,13] Restriction of carbohydrates less than 50 gm/day-cause rapid weight loss, due to breakdown of glycogen, ketosis development, and fluid loss. In addition, very low-carbohydrate diets are associated with a small increase in energy expenditure.[14] Side effects may be more with low-carbohydrate diet like constipation, headache, muscle cramps, diarrhea, weakness, and rash. There is some data to suggest that low-carbohydrate diet have early weight independent effect on liver steatosis and insulin resistance but after more than 7% weight loss this benefit is similar like hypocaloric low-fat diet.[15]

A low-carbohydrate diet may be planned either by reducing the total amount of carbohydrate or by consuming foods with a lower glycemic index (GI) or glycemic load. High-glycemic-load foods increase postprandial glycemia and insulinemia, particularly in patients with insulin resistance. Since the duration of post-meal satiety is related to postprandial glycemia, low-GI foods have been hypothesized to reduce hunger signals and delay the onset of the next meal. Meals with high GI were found to be associated with high-grade liver steatosis (assessed by ultrasound), particularly in insulin-resistant subjects.[16]

Fructose: Fructose mainly derived from table sugar (50% fructose) and corn syrup (55% fructose). High intake of sugar-sweetened foods in general contributes to weight gain and high liver fat due to their high-energy density, glycemic load, and palatability. Fructose role has been implicated in alteration of gut microbiome, increasing gut permeability, endotoxemia and hyperuricemia.[17,18] Soft drinks contain caramel coloring rich in advanced glycation end products, which increases insulin resistance and liver injury.[19]

Fat: The quality of fat consumed and its food sources appear to be more important for health than total fat intake. Trans fatty acids and saturated fatty acids have been associated with metabolic derangement (increase LDL, low HDL), and an elevated cardiovascular risk.[20] Saturated fat promotes visceral and liver fat deposition.[21] Assessment of dietary pattern in NASH patients showed higher saturated fat and cholesterol intake and lower polyunsaturated fatty acids (PUFA), fiber, vitamin C and E consumption.[22]

Monounsaturated fatty acids (oleic acid, palmitoleic acid in canola and olive oil) consumption favors accumulation of fat in adipose tissues rather than the liver in animal models.[23] In type 2 diabetic patients, an

isocaloric diet enriched in MUFA compared with a diet higher in carbohydrate and fiber was associated with a significant fat reduction in liver (measured by proton magnetic resonance spectroscopy) despite a stable weight in both groups.[24] Polyunsaturated fatty acids (n-6: linoleic acid, arachidonic acid and n-3: α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid) are abundant in fish oil. Low intake n-3 fatty acids and higher n-6/n-3 ratio is found in NAFLD patients than healthy controls.[25] It is associated with a proinflammatory state and increased lipogenesis leading to steatosis.[26] Conversely, n-3 PUFAs down-regulate sterol regulatory element binding protein 1c (SREBP-1c) and up-regulate peroxisome proliferator activated receptor α (PPAR-α) that would favor fatty acid oxidation and reduce steatosis.[27] PUFA Supplementation is effective in reducing total liver fat but not beneficial in histological improvement in terms of inflammation and fibrosis.[28]

High cholesterol consumption (>500 mg/day) was associated with higher risk of cirrhosis or liver cancer, instead of total fat consumption.[29]

Protein: High-protein diets have been recommended for the treatment of obesity because they are more satiating and stimulate thermogenesis. Higher-protein diets may improve weight maintenance. Total red meat and processed red meat intake are both positively associated with risk of coronary artery disease.[30]

Fiber has several beneficial metabolic effects, including increased satiety, increased incretin secretion, reduced absorption rate of CHO and proteins, modulation of gut microbiota, and increased fermentation products, such as butyrate.

Increased coffee consumption has been associated inversely with the risk of cirrhosis or progression of fibrosis but not with steatosis.[31] In epidemiological studies, coffee consumption is associated with a lower risk of metabolic syndrome.[32] Animal studies suggest, coffee exerts its effects by reducing hepatic fat accumulation, systemic and liver oxidative stress and liver inflammation.[33] Drinking coffee reduces HCC risk.[34] For the majority of healthy adults, consuming less than 400 mg of caffeine a day appears to be safe.

Intermittent Fasting

Intermittent fasting strategies, including alternate-day fasting (25% of total energy consumed on "fast" days and 125% consumed on "feast" days) and time-restricted feeding (TRF) (cessation of eating by a certain time each day) have been used as approaches to weight loss. Short-term TRF trials have shown that the alignment of the feeding period with circadian rhythms may result in weight loss and improve metabolic parameters.[35] The mechanisms by which intermittent fasting affect health may include improved insulin sensitivity and anti-inflammatory effects.

Summary of diet recommendations for NASH:[2]

- Calorie restriction (500–1000 kcal/day)
- Low-carbohydrate (<40%) diet—replace calories with PUFA, MUFA
- Low-fat diet—replace calories with low-GI foods
- Reduce trans FA (<1%), saturated fats (<7%), and cholesterol (<200 mg/day)
- Proteins from fish, poultry, nuts, and legumes & restrict unprocessed red meats (<300 g/week), processed meats (<2/week)
- Increase the intake of cereal-derived non-soluble fiber (whole grain) (25 g/day)
- Vegetables (3–5 servings/day), fruits (2–4 servings/day), nuts (4 servings/week), olive oil, and low-fat dairy products.

Physical Activity

Sedentary behavior is a component of reduced life expectancy. The energy expenditure is sum of resting metabolic rate (RMR), the thermic effect of feeding (TEF), and physical activity. Exercise (aerobic and resistance) is planned form of physical activity. While it may be difficult to lose weight with exercise alone, exercise programs added to moderate to severe caloric restriction have additional effect upon weight loss.[36] If a patient burn 100 calories during exercise each day (700 calories per week), it would take almost 5 weeks to utilize the energy (3,500 calories) in half kg of fat. Exercise alone, in the absence of any change in body weight or composition, may enhance peripheral insulin sensitivity and glucose homeostasis mediated by insulin-receptor up regulation in muscle tissue, enhancing whole-body lipid oxidation, decreased hepatic triglyceride accumulation and lower hepatic FFA uptake **(Fig. 2)**. Increased physical activity attenuates the diet-induced loss of muscle mass, which in turn increases physical functioning and insulin sensitivity.[37] Both aerobic or resistance exercise are effective in reducing liver

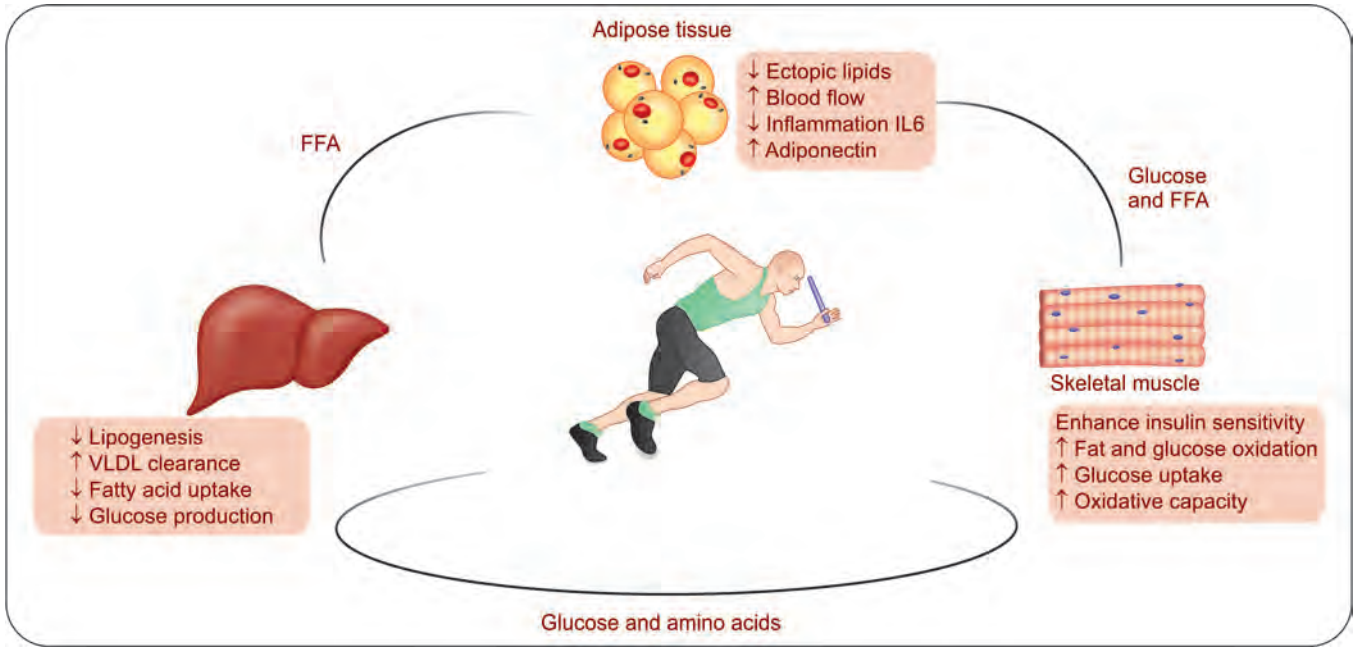

Fig. 2: Exercise effect in NAFLD and effect on liver, adipose tissue, and muscles

fat.[38] The addition of resistance exercise to weight-loss programs can help prevent the reduction in muscle and bone mass. Patients with poor cardiorespiratory reserve may better tolerate resistance exercise. Weight training results in greater increases in fat-free mass.[39]

The recommendation by American Heart Association of intense cardiorespiratory activity (aerobic & resistance) for at least 150 minutes (preferably 300 minutes) per week, or at least 75 minutes (preferably 150 minutes) is adapted by EASL for NASH patients.[40] The clinician needs to be aware for identifying high-risk patients who may require a more thorough evaluation before beginning an exercise program. The major hurdle is obtaining long-term compliance—especially in individuals who are not accustomed to regular intense exercise.

Conclusion

The primary approach to treat NAFLD focuses on the control of the underlying risk factors like diabetes, hyperlipidemia, obesity, and other comorbidities through diet and lifestyle changes. After the initial weight-loss phase, the weight-maintenance phase is key for preventing long-term complications. Strategies to enhance long-term adherence to lifestyle interventions, with a multidisciplinary approach should be included.

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CHAPTER

126 Medical Management of Acute Pancreatitis

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Abstract

Acute pancreatitis is a common disease, major etiologies being gallstones or alcohol ingestion. Diagnosis is based on clinical symptoms, elevated pancreatic enzymes, and imaging findings. Revised ATLANTA classification (2013) has defined the types, severity, organ failure, and complications of acute pancreatitis. Majority of patients have self-limiting disease while some may develop severe disease, causing organ failure and complications such as pseudocyst or wall-off necrosis (WON). Treatment involves early enteral nutrition, intravenous fluids, analgesics, with avoidance of use of antibiotics. Endoscopic and/or surgical interventions are required in case of complicated unresolving pancreatic collections.

Introduction

Acute pancreatitis (AP) is a common gastrointestinal tract (GIT) disease causing enormous physical, emotional, and socioeconomic human burden. The first clinical description of AP was given by Dutch anatomist Nicholaeus Tulp in 1652. Incidence of AP varies from 30–80/100,000 population. In India, approximately 74% of patients of AP are men with the mean age being 40 years, which is a younger age group compared to other parts of the world.

Definitions[1]

ATLANTA classification defining the severity and complications of AP was first described in 1992. Since then there has been continuing research in this field and has resulted in improvement of knowledge about the disease process, and hence management of AP. Also, there has been a major improvement in imaging modalities, which has helped to classify and define disease severity and complications in a clarified way as a part of revised ATLANTA classification proposed in 2013. This revision includes assessment of the severity clinically and provides objective terms to define the local complications of AP, which are described as follows.

Definitions and Classification: Proposed to be Used in Clinical and Research Communications

Diagnosis of AP

The diagnosis of AP requires two out of following three features:

- Pain abdomen suggestive of AP (acute onset severe, persistent, epigastric pain, aggravated with food intake, and radiating to the back);
- Pancreatic enzymes activity (serum lipase and serum amylase) more than three times elevated than normal range; and
- Imaging findings on contrast-enhanced computerized tomography (CECT), magnetic resonance imaging (MRI), or trans abdominal ultrasonography, showing characteristic changes of AP.

Routinely use of CECT in patients of AP is unjustified, as the diagnosis is apparent and most patients have a mild, non-complicated course. But if there is lack of improvement after 48–72 hours (e.g., persistent pain, nausea, fever, inability of start oral feeds), imaging using CECT or MRI is recommended for assessment of local complications such as peripancreatic fluid collection or pancreatic necrosis.

Onset of AP

The onset of AP is defined by the time when the typical abdominal pain first begins and not by the time when patient first seeks hospital care. This time of onset of pain abdomen is crucial to define the further complications of AP.

Types of AP

AP can be subdivided into two types based on presence or absence of necrosis:

- *Interstitial pancreatitis*—in the absence of pancreatic necrosis, the edematous pancreas in mild disease, is defined as interstitial pancreatitis;
- *Necrotizing pancreatitis*—in about 5–10% of patients, AP evolves to produce necrosis of pancreatic parenchyma, the peripancreatic tissue or both.

Pancreatic necrosis is defined as focal or diffuse areas of nonviable parenchyma which is 30% of the pancreas or 3 cm in size.

Complications

Organ Failure—Definition

Organ failure is defined based on the assessment of three major organ systems:

- Cardiovascular
- Respiratory, and
- Renal. Modified Marshall scoring system **(Table 1)** is used to define organ failure.

Local Complications—Definition

The concept of local complications following AP was defined by the Original ATLANTA classification (1992). Since then with the advancement of the understanding of pathophysiology and improvement of imaging has led to better characterize the local complications as acute peripancreatic fluid collection, pancreatic pseudocyst **(Fig. 1)**, acute necrotic collection, and walled-off necrosis **(Fig. 2)** based on the presence and absence of necrosis and time from the onset of pain abdomen, each of which has been defined by the revised ATLANTA classification[1] (2013) **(Table 2)**. Gastric outlet obstruction, splenic vein and portal vein thrombosis are some of the other local complications of AP.

Systemic Complications—Definition

Any exacerbation of previous comorbid conditions such as chronic lung disease, or coronary artery disease, by AP is defined as systemic complications.

TABLE 1 Modified Marshall scoring system[1]

Organ systems	*Scores*				
	0	*1*	*2*	*3*	*4*
Respiratory (FiO_2/PaO_2)	>400	301–400	201–300	101–200	≤100
Renal (creatinine mg/dL)	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic BP mm Hg)	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH<7.3	<90, pH<7.2

FiO_2 calculation for non-ventilated patients	
Supplemental oxygen (L/min)	*FiO_2 (%)*
Room air	21
2	25
4	30
6–8	40
9–10	50

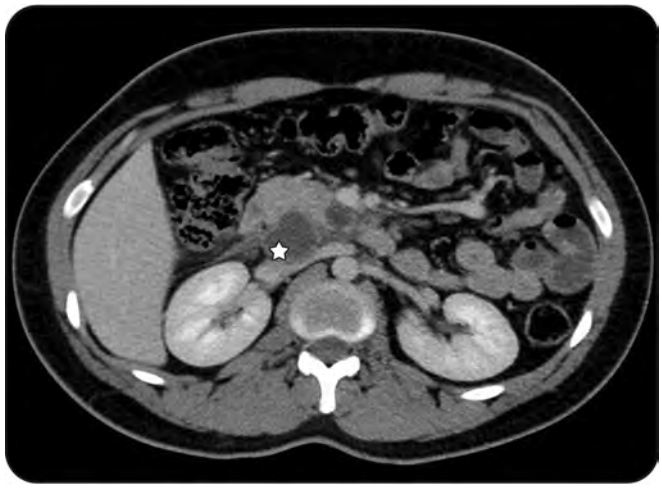


Fig. 1: Contrast enhanced CT axial images showing small pseudocysts in the uncinate process and neck of pancreas

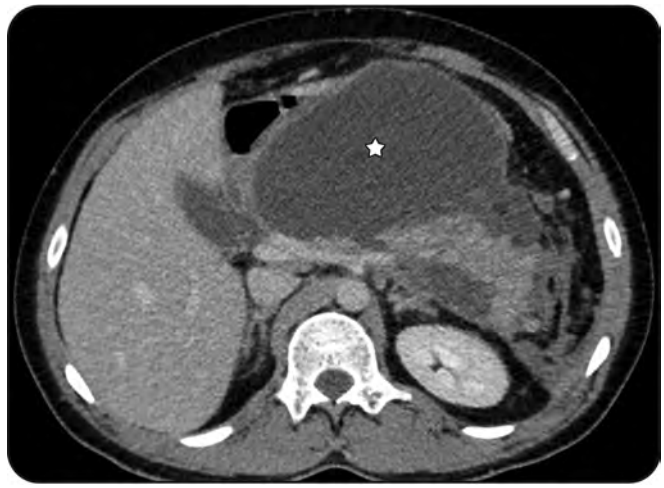


Fig. 2: Contrast enhanced CT axial images showing large peripancreatic walled off necrosis (WON) around body and tail of pancreas

TABLE 2 Terminology based on fluid collection[1] (local complications)

Type of pancreatitis	*First 4 weeks*	*After 4 weeks*
Interstitial pancreatitis	Acute peripancreatic fluid collection	Pseudocyst
Necrotizing pancreatitis	Acute necrotic collection (ANC)	Walled off necrosis (WON)

Phases[2]

The disease process of AP is not fixed and can vary from patient to patient. Arbitrarily the disease course can be divided into two overlapping phases with two peaks of mortality: Early and Late phase. These two phases are considered separately.

Early Phase

The early phase involves first week of disease presentation, but may sometimes be prolonged into the second week also. During the early phase, manifestations are due to the response to local pancreatic inflammation and injury. Pancreatic inflammation, in turn, activates cytokine cascade, which clinically manifests as systemic inflammatory response syndrome (SIRS) **(Table 3)**. There is an increased risk of developing organ failure if SIRS is persistent. The presence and duration of organ failure in the early phase determines the severity of AP. If the organ failure resolves within 48 hours, it is defined as "Transient organ failure," and if it persists for more than 48 hours, it is defined as "Persistent organ failure." Multiorgan failure (MOF) is defined when more than one organ develops failure.

Late Phase

By definition, the late phase occurs only in patients with moderately severe or severe AP. It is characterized by the persistence of local complications or systemic signs of inflammation.

Severity of AP—Definition

It is prudent to define and distinguish patients of AP based on severity. The ATLANTA classification has defined three major types of severity—mild, moderate, and severe AP **(Table 4)**.

Etiology[2]

The most common causes of AP are gallstones (40–70%) and alcohol (25–35%). Other etiologies being post ERCP (5%), post trauma, especially in children (1%), idiopathic (25%), and miscellaneous (5%). Alcohol-related

TABLE 3 SIRS[1]

Signs of systemic inflammatory response syndrome (SIRS)
SIRS—defined by presence of two or more criteria: • Heart rate >90 beats/min • Core temperature <36°C or >38°C • White blood count <4000 or >12000/mm^3 • Respirations >20/min or PCO_2 <32 mm Hg

TABLE 4 Grades of severity[1,2]

Severity	*Local/systemic complications*	*Organ failure*
Mild acute	No	No
Moderately acute	Yes	Transient (<48 hrs)
Severe acute (15–20%)	Yes	Yes (>48 hrs)

pancreatitis usually manifests as a spectrum, ranging from distinct episodes of AP to chronic pancreatitis causing irreversible changes silently.

Risk Stratification and Predicting Severe AP

For initial management and hospitalization, laboratory investigations and imaging studies can be useful but are unreliable to predict the severity of AP. Laboratory investigations like hematocrit, blood urea nitrogen (BUN), creatinine or CRP in the 1st 48 hours can be normal. Also, cross sectional imaging cannot determine severity early in disease course as necrosis is usually absent on admission and may take 2–3 days to develop. Thus, as there is an absence of any definite test to determine the severity of AP, clinical assessment of third space fluid losses, shock and signs and symptoms suggestive of organ dysfunction is of paramount importance.

Management (Flowchart 1)

Pain Management (Analgesia)

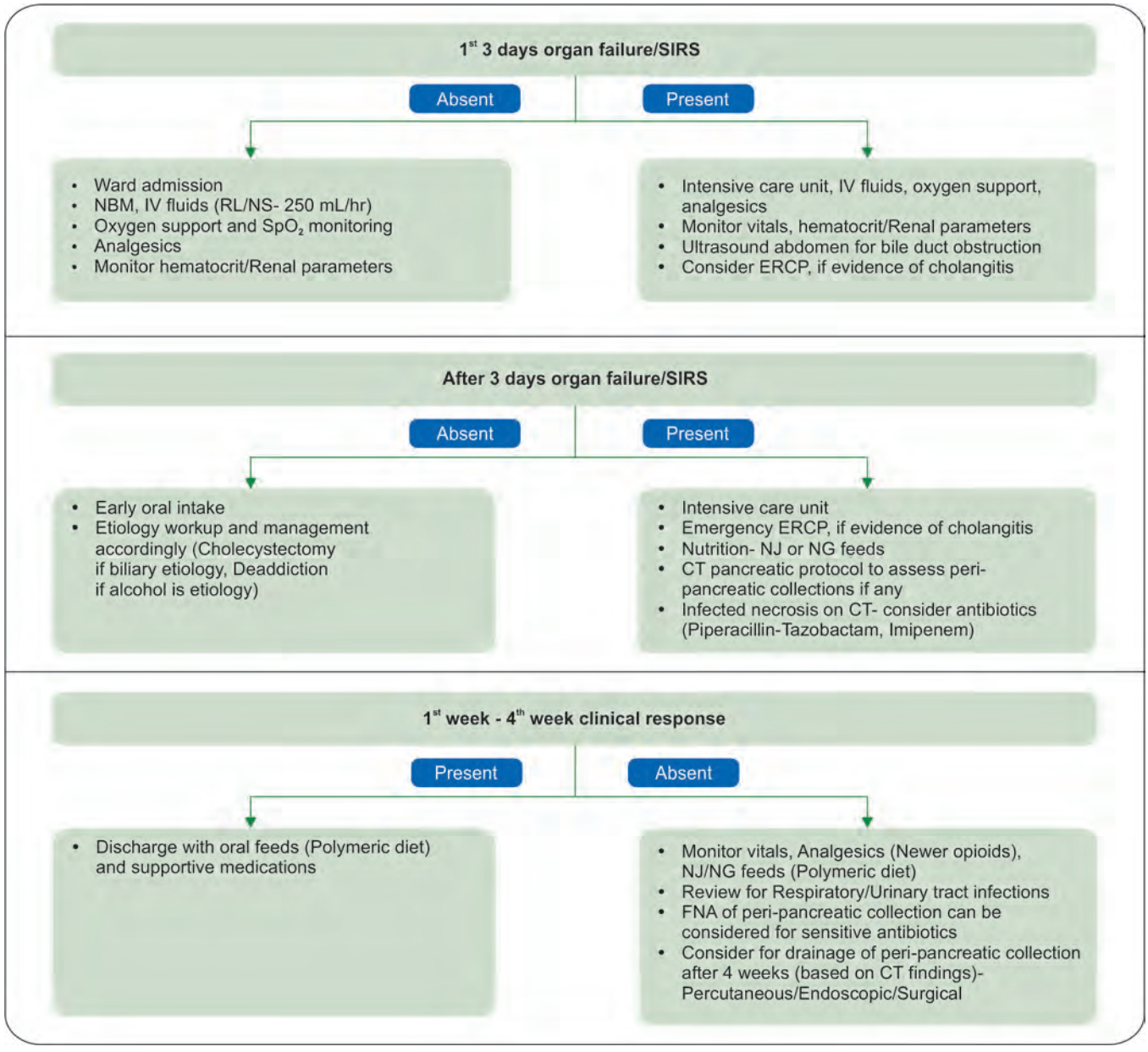
Abdominal pain is the presenting and distressing symptom in patients with AP. Effective and successful analgesia is an important component of the management of AP. An added desirable effect of the analgesic could be its impact on the underlying inflammatory process. Both opioid analgesics and nonsteroid anti-inflammatory agents (NSAIDs) have been used in patients with AP for pain relief. However, the evidence for their efficacy and safety profile is limited. The concern with NSAIDs is adverse events such as gastrointestinal bleeding and acute kidney injury. Opiates have shown by a randomized controlled trial to have better analgesic effect and safety profile compared to NSAIDs[3] for AP. Nalbuphine (an opioid with μ receptor antagonism) is a latest armamentarium useful for AP pain.

Fluid Resuscitation—Importance of Intravenous Hydration

Multiple factors are responsible for often causing hypovolemia in patients affected by AP, such as vomiting, third space loss, decreased oral intake, diaphoresis, and increased respiratory losses. Besides, inflammation of pancreas causes pancreatic edema and microcirculatory effects causing decreased blood flow, which in turn causes cell death, pancreatic tissue necrosis and pancreatic enzymes release, activating further numerous inflammatory cascades.

In AP, there is a median fluid loss of 3.2 liters.[4] The fluid should be given as 15–20 mL/kg bolus dose followed by 1.5–3 mL/kg/hour, depending on the response for the first 12–24 hours. Although the most effective approach to early fluid resuscitation has yet to be determined, studies have suggested that lactated Ringer's maybe the preferred solution for initial hydration.[5] Owing to its bicarbonate content and stable pH, this isotonic solution, when compared to normal saline, may prevent the development of metabolic acidosis, which can complicate care in patients receiving large-volume resuscitation using isotonic saline. Also, there are theoretical advantages in stabilizing the pancreas by preventing acidosis, which increases degranulation, enzyme release. The goal of fluid therapy is to achieve a mean arterial BP of minimum 70 mm Hg, hematocrit of 40–42, urine output—0.5–1 mL/min.[6] Monitoring of fluid therapy can be done using invasive methods like central venous pressure, stroke volume, arterial pressure wave-form, and noninvasive methods like IVC diameter: <1.5 cm or >50% index-deficit, lung ultrasound for fluid overload. Elderly patients and those with history of cardiac and/or renal disease should be taken carefully resuscitated.

Flowchart 1: Management of acute pancreatitis



CT, computerized tomography; ERCP, endoscopic retrograde cholangiopancreatography; FNA, fine needle aspiration; IV, intravenous; NBM, nil by mouth; NG, nasogastric; NJ, nasojejunal; SIRS, systemic inflammatory response syndrome[12]

Antibiotics—Role in AP Management

Routine use of prophylactic antibiotics in patients with mild AP and also severe AP is not recommended. Also, in patients having sterile necrosis, the use antibiotics to prevent the evolution of infection is not recommended. After 7–10 days of hospital stay, in patients with lack of improvement and having persistent fever and increasing WBC counts, infected pancreatic or peripancreatic necrosis should be suspected. Serum procalcitonin may be helpful as a useful marker. In these patients, there are two ways to manage: (a) CT-guided fine needle aspiration (FNA) with culture sensitivity can be used to start suitable

antibiotics, or (b) Empirical use of antibiotics can be done after obtaining necessary blood or urine culture sensitivity for disease causing agents, without CT-guided FNA. Infected necrosis warrants use of antibiotics which can penetrate the necrosis, such as carbapenems, quinolones, and metronidazole, as per the local pattern of sensitivity of organisms. Timely use of antibiotics in such cases can delay or sometimes avoid interventions, hence reducing morbidity and mortality. Evidence of extra-pancreatic infections like urinary tract infections, cholangitis, catheter-acquired infections, bacteremia, and pneumonia necessitates antibiotics. Routinely antifungal agents along with antibacterial agents (used for prophylaxis or treatment) are not recommended.

Nutrition in AP

Traditionally patients having AP were kept nil per mouth (NPO) to theoretically provide rest to the organ. Multiple experimental and clinical studies have subsequently shown that bowel rest causes mucosal atrophy and increases infectious complications due to bacterial translocation from the gut. Also, studies have shown that early enteral feeding in the course of AP reduces hospital stay, and hence decreased morbidity. In mild AP, if there is absence of vomiting, and if abdominal pain has improved, oral feeds should be started as soon as possible. Oral feeds in mild AP are introduced as a low-fat, low-residue, light diet as the patient improves clinically. Polymeric feeds (feeds containing all major nutrients) are preferred consisting of 25–30 kcal/kg with 1.2–2 gm/kg protein. In mild as well as severe AP, total parenteral nutrition ideally should be avoided as it increases chances of infectious complications and other peripheral or central line-related complications.

Use of nasogastric tube for enteral nutrition appears to be safe; however, the use of nasojejunal tube is typically preferred to avoid gastric phase of pancreatic stimulation. Nasogastric tube placement is far easier compared to the nasojejunal tube (requires fluoroscopic guidance for placement and is expensive), which is advantageous for patients in intensive care unit (ICU) treatment. In patients presenting as severe AP, on initial assessment, should be started on enteral tube feeding as a part of primary therapy. In the late phase of AP (2^{nd}–3^{rd} week) maintaining nutrition is critical, the target should be to provide 1500–2000 kcal diet.

Endoscopic Retrograde Cholangiopancreatography (ERCP)–Role in AP

As per the latest recommendations, patients with concurrent AP and acute cholangitis with high clinical suspicion of choledocholethiasis should undergo ERCP with biliary stenting within 24 hours of admission as a therapeutic procedure. Usually, in patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) rather than ERCP should be used to screen for choledocholithiasis.

Also, ERCP on one hand, it can be a therapeutic modality for biliary pancreatitis, while on the other hand, it can be an important and preventable etiology of AP. The risk of post-ERCP pancreatitis is around 5%. Three methods to reduce the risk of post-ERCP pancreatitis, especially severe AP include:

- Pancreatic duct stents
- Use of guidewire for cannulation
- Rectal NSAIDs (diclofenac suppository) pre-procedure.

Infected Pancreatic Necrosis

The step-up approach is recommended with conservative treatment in ICU 1^{st} followed by percutaneous drainage, which is followed by minimally invasive necrosectomy.[7,8] Primarily conservative management results in mortality comparable to surgery in patients with infected pancreatic necrosis.[9] If necrosectomy is required, endoscopic step-up approach should be preferred.[10,11]

Conclusion

The diagnosis and optimal management of AP requires a systematic approach and multidisciplinary decision-making. Regardless of pancreatitis severity, recommended medical management includes goal-directed intravenous fluid resuscitation, early enteral feeding, avoidance of antibiotics as prophylaxis and urgent ERCP for patients with acute biliary pancreatitis complicated by cholangitis. Hence to conclude the first 24–48 hours are critical, and hence triaging of these patients on first presentation to hospital is an important approach to enable appropriate level of care.

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CHAPTER

127 Functional Gastrointestinal Disorders

Uday C Ghoshal

Abstract

Functional gastrointestinal disorders (FGIDs), common problems in GI practice, are diagnosed by symptom-based criteria, such as the most recent iteration by the Rome Foundation, called Rome IV criteria and limited laboratory investigations. However, in presence of alarm symptoms, which may suggest presence of organic diseases, more thorough investigations may be needed. Different FGIDs may overlap in a single patient. The two common subtypes of FGIDs, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD), are elaborated in this chapter. Treatment of FGIDs would depend on its subtypes, such as diarrhea- or constipation-predominant IBS or epigastric pain and postprandial distress syndrome subtypes of FD. The treatment also depends on severity of the condition, presence of psychological comorbidity, biological factors, etc.

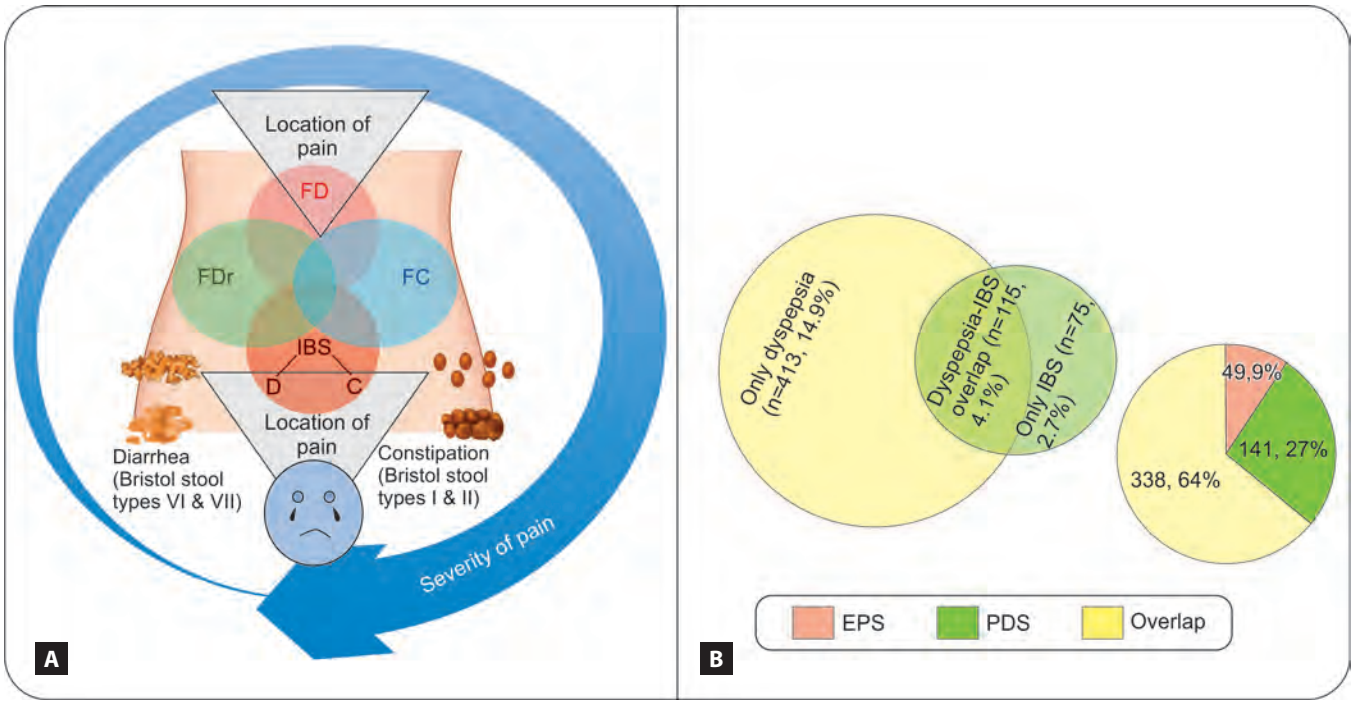
Introduction

Physicians and Gastroenterologists often encounter patients with functional gastrointestinal disorders (FGIDs) in their clinical practice. Patients with FGIDs are diagnosed based on the symptom-based criteria. FGIDs are characterized by the presence of chronic gastrointestinal (GI) symptoms (at least during the last 3 months with onset at least 6 months previously) in the absence of identifiable structural lesions explaining these symptoms on investigations including GI endoscopy.[1] It is, however, noteworthy that though the routine investigations, including GI endoscopy, do not pick-up organic lesions in patients with FGIDs, more sensitive tests may pick-up subtle structural abnormalities and molecular aberrations that may explain their symptoms. Hence, in the recent time, it has been considered that many of these disorders may be "micro-organic" in nature, challenging the concept that these disorders are entirely functional or psychogenic.[1,2] Rome Foundation, which formulates diagnostic and treatment algorithm for FGIDs, released its fourth iteration of Rome criteria in April 2016.[3] Experts of Rome Foundation correctly decided to underscore term "functional" and consider the gut to be more important than brain in the pathogenesis; hence, the new name for these disorders has been "Disorders of Gut-brain Interaction (DGBI)."[3]

FGIDs are chronic disorders that are not fatal but cause considerable impairment of quality of life, work absenteeism, burden to the society, health care, economy, and family. Considering the high frequency of these disorders in the global population, the magnitude of the problem of FGIDs cannot be underestimated. Hence, knowledge about the diagnosis and management of these disorders at primary and secondary care settings are essential issues that need to be deliberated. Accordingly, this chapter will briefly discuss the current classification of FGIDs, and the diagnostic criteria, and management of common forms of FGIDs, for example, irritable bowel syndrome (IBS) and functional dyspepsia (FD). The current classification of FGIDs (Rome IV) is presented in **Table 1**.[1,3]

TABLE 1 Different categories of functional gastrointestinal disorders according to the most recent iteration of Rome Foundation (Rome IV classification)

Esophageal disorders	
• Functional chest pain • Functional heartburn • Reflux hypersensitivity	• Globus • Functional dysphagia
Gastroduodenal disorders	
• Functional dyspepsia – Postprandial distress syndrome (PDS) – Epigastric pain syndrome • Belching disorders – Excessive supragastric belching – Excessive gastric belching	• Nausea and vomiting disorders – Chronic nausea vomiting syndrome (CNVS) – Cyclic vomiting syndrome (CVS) – Cannabinoid hyperemesis syndrome (CHS) • Rumination syndrome
Bowel disorders	
• Irritable bowel syndrome (IBS) – IBS with predominant constipation (IBS-C) – IBS with predominant diarrhea (IBS-D) – IBS with mixed bowel habits (IBS-M) – IBS unclassified (IBS-U)	• Functional constipation • Functional diarrhea • Functional abdominal bloating/distension • Unspecified functional bowel disorder • Opioid-induced constipation
• ***Centrally mediated disorders of gastrointestinal pain***	
• Centrally mediated abdominal pain syndrome (CAPS)	• Narcotic bowel syndrome (NBS)/opioid-induced GI hyperalgesia
Gallbladder and sphincter of oddi (SO) disorders	
• Biliary pain – Functional gallbladder disorder – Functional biliary SO disorder	• Functional pancreatic SO disorder
Anorectal disorders	
• Fecal incontinence • Functional anorectal pain – Levator ani syndrome – Unspecified functional anorectal pain – Proctalgia fugax	• Functional defecation disorders – Inadequate defecatory propulsion – Dyssynergic defecation
Childhood functional GI disorders: Neonate/Toddler	
• Infant regurgitation • Rumination syndrome • Cyclic vomiting syndrome (CVS) • Infant colic	• Functional diarrhea • Infant dyschezia • Functional constipation
Childhood functional GI disorders: Child/Adolescent	
• Functional nausea and vomitting disorders – Cyclic vomiting syndrome (CVS) – Functional nausea and functional vomiting ♦ Functional nausea ♦ Functional vimiting – Rumination syndrome – Aerophagia	• Functional abdominal pain disorders – Functional dyspepsia ♦ Postparandial distress syndrome ♦ Epigastic pain syndrome – Irritable bowel syndrome (IBS) – Abdominal migraine – Functional abdominal pain - NOS • Functional defecation disorders – Functional constipation – Nonretentive fecal incontinence



Figs. 1A and B: (A) Overlap between common functional gastrointestinal disorders (*Source:* Reproduced from Reference 4). (B) Summary of results from in Indian rural community study showing overlap between IBS, dyspepsia and different subtypes of dyspepsia (For the data in details, see Reference 5)
C, constipation-predominant; D, diarrhea-predominant; EPS, epigastric pain syndrome; FC, functional constipation; FD, functional dyspepsia; FDr, functional diarrhea; IBS, irritable bowel syndrome; PDS, postprandial distress syndrome

In the above classification, the different FGIDs are considered as pure disorders. However, in practice, more than two-thirds of patients present overlapping symptoms of multiple FGIDs. The various categories of bowel disorders such as IBS, functional diarrhea, and functional constipation often overlap with upper GI disorders such as FD and gastroesophageal reflux disease **(Fig. 1A)**.[4] In an earlier study on 3,426 adult population of rural northern India, overlap of FD-IBS was commoner (4.1%) than IBS alone (2.7%) though FD was the most common form of FGID (15%; **Fig. 1B**).[5] Overlap disorders often have a more severe illness, may require combination treatment, and may have a worse prognosis.[6] In this chapter, the diagnosis and treatment of two common FGIDs (FD and IBS) are briefly discussed. It is important to note that several management principles of pure FGIDs, such as those of FD and IBS, would apply to overlap disorders. For example, a patient with constipation-predominant IBS and postprandial distress syndrome subtype of FD is expected to benefit from treatment with a pan-GI prokinetic drug such as prucalopride along with fundic relaxant such as acotiamide.

Functional Dyspepsia

"Dyspepsia" is a Greek word that refers to "bad digestion." As per Rome IV criteria, FD is diagnosed using the symptom-based criteria that are listed in **Table 2**.[7] However, if a patient fulfills the symptom-based criteria, he should be considered as having uninvestigated dyspepsia. Subsequently, a few investigations, including upper GI endoscopy, are required before a diagnosis of FD is made. However, in the absence of alarm features discussed later in this chapter, even an empirical trial of drug-treatment may be instituted after due consideration by the physician on a case-to-case basis. A firm diagnosis of FD, however, requires an upper GI endoscopy. Though currently, most international recommendation warrant tests for *Helicobacter pylori* and its eradication, if present, its universal acceptability in the Indian scenario is subject to debate based on the limited available data **(Flowcharts 1A and B)**.[7]

TABLE 2 Rome IV criteria for the diagnosis of functional dyspepsia (FD)[7]

Functional dyspepsia
Diagnostic criteria 1. One or more of the following: a. Bothersome postprandial fullness b. Bothersome early satiation c. Bothersome epigastric pain d. Bothersome epigastric burning
No evidence of structural disese (including at upper endoscopy) that is likely to explain the symptoms

Must fulfill criteira for PDS and/or EPS.
Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) are the two subtypes of FD. In practice, however, patients rarely present with pure EPS or PDS, but most patients have overlapping symptoms. The criteria, as suggested by the Rome IV Committee for diagnosis of EPS and PDS, are presented in **Table 3**.[7]

Management of FD

Management of the patients with dyspepsia as per the Rome IV system is presented in **Flowcharts 1A and B**. One must not forget to look for alarm features (age >45 years, history of GI bleeding, weight loss, family history of gastric cancer, anemia, etc.). Patients with a history of alarm features must undergo thorough investigations including upper GI endoscopy and CT scan of the abdomen (in patients with a family history of gastric cancer and a high degree of clinical suspicion of gastric cancer) before considering dyspepsia to be functional.[7] It is also important to note that the age cut off of 45 years may vary depending on the local epidemiology of gastric cancer. International societies, including experts in the Rome IV committee, suggested that *H. pylori* infection, if present on appropriate testing, should preclude the diagnosis of FD. If eradication of infection improves dyspeptic symptoms, the condition should instead be called *H. pylori*-associated dyspepsia.[7] The applicability of this international guideline in India, however, may be viewed with skepticism. Though Indian literature on this issue is scanty, yet considering the high frequency of *H. pylori* infection in Indian adults, this strategy may not be practicable. Treatment of FD depends on its subtype. Whereas EPS, an uncommon subtype is treated with proton pump inhibitors and when unresponsive, antidepressants, PDS is treated with prokinetics, fundic relaxants, and psychotropic agents. Overlap syndrome is treated with combined therapeutic agents. **Table 4** lists the drugs available currently in the Indian market for the treatment of two subtypes of FD.[7]

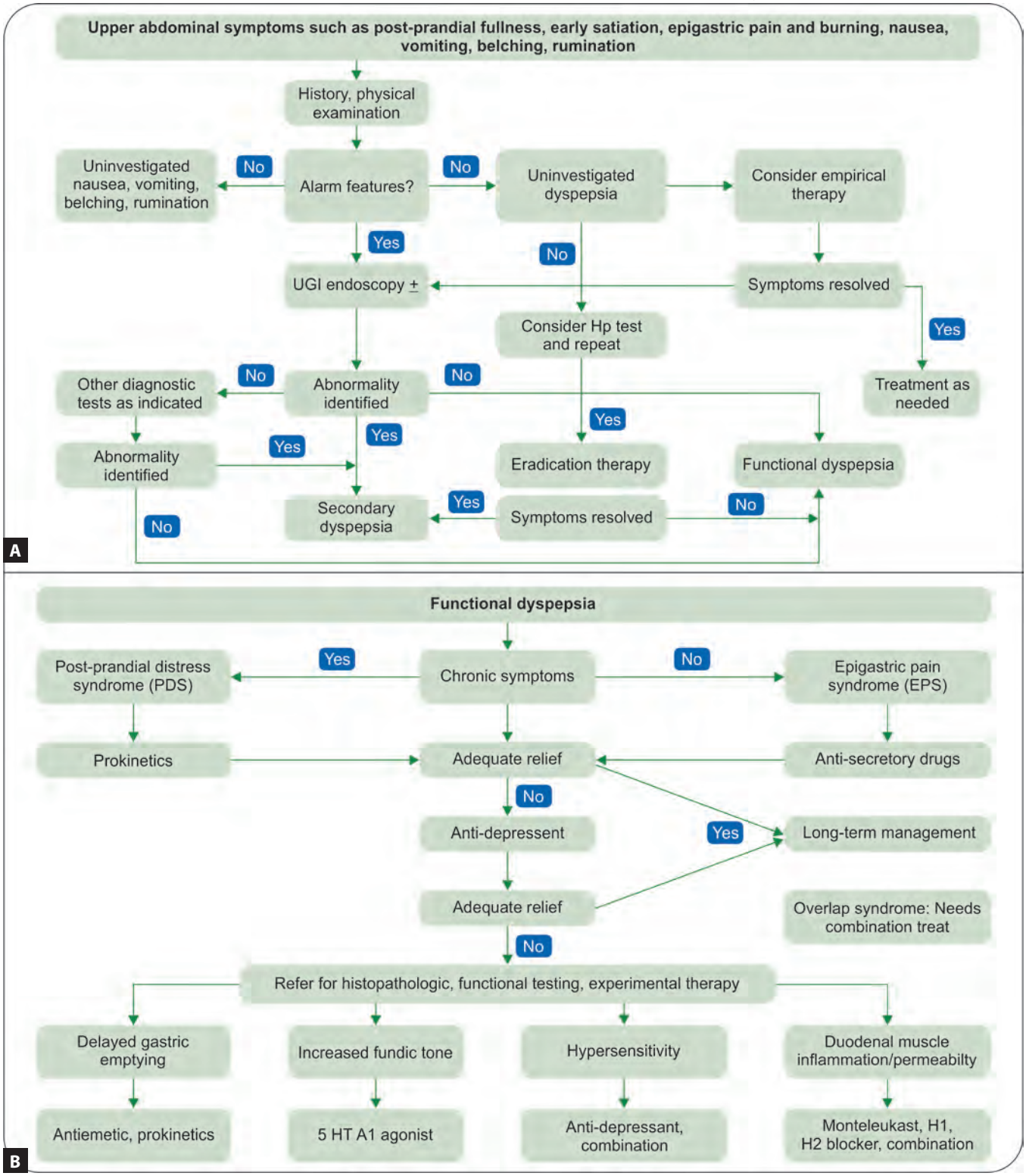
Irritable Bowel Syndrome

Diagnosis of IBS

IBS is one of the common FGIDs seen in clinical practice both by the Gastroenterologists and the Physicians. IBS was variously called earlier, albeit inappropriately, as spastic colitis, chronic amebiasis, etc. In the past, the diagnosis of IBS could only be made once extensive investigations failed to find a cause for the chronic lower GI symptoms. Manning and Thompson, for the first time, introduced the criteria-based diagnosis of IBS in 1978.[8] Since then, the Rome Foundation brought in several iterations of Rome criteria for the diagnosis of IBS. Manning's criteria **(Box 1)** encourage a positive diagnosis of IBS without the need for multiple unnecessary investigations to exclude organic diseases before diagnosing IBS.[8]

However, it is essential to note that in the study by Manning and Thompson, organic disorders excluded were peptic ulcer disease, inflammatory bowel disease, gastroesophageal reflux disease, gallstones, and carcinoma of the colon and not the conditions which closely mimic IBS such as lactose intolerance, celiac disease, microscopic colitis, small intestinal bacterial overgrowth, fecal evacuation disorder, collagenous colitis and microscopic, etc.[2,8] Hence, over-reliance on such symptom-based criteria to exclude every organic disorder (some of which are rather micro-organic) may result in overlooking such conditions. Another limitation of the Manning criteria is the lack of due consideration for the duration of symptoms. As some of the organic disorders are expected to have a short duration of symptoms, the importance of time of illness cannot be overestimated. However, despite these limitations, Manning's criteria remain quite useful and popular in practice not only among Gastroenterologists but also among Physicians. In addition to the higher sensitivity of Manning's criteria as compared to the various iteration of Rome criteria in India,[4] the simplicity of the former is a significant reason for its popularity.

Flowcharts 1A and B: Rome IV algorithm for management of functional dyspepsia



Bx, biopsy; Hp, *helicobacter pylori*; UGI, upper gastrointestinal

TABLE 3 Rome IV criteria for the diagnosis of epigastric pain and postprandial distress syndromes[7]

Postprandial distress syndrome

- *Diagnostic criteria:* Must include one or both of the following at least 3 days per week:
  - Bothersome postprandial fullness (i.e., severe enought to impact on usual activities)
  - Bothersome early satiation (i.e., severe enough to prevent finishing a regular-size meal)
- No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

- Supportive remarks
  - Postprandial epigastic pain or burning, epigastric bloating excessive belching, and nausea can also be present
  - Vomiting warrants consideration of another diorder
  - Heartburn is not a dyspeptic symptom but may often coexist
  - Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
- Other individual digestive symptoms or gourps of symptoms, e.g. from gastroesophageal reflux disease and the irritable bowel syndrome may coexist with PDS

Epigastric pain syndrome

- *Diagnositc criteria:*[a] Must include at least 1 of the following symptoms at least 1 day a week:
  - Bothersome epigastric pain (i.e., severe enough to impact on usual activities)

    AND/OR
  - Bothersome epigastic burning (i.e., severe enought to impact on usual activities)
- No evidence of organic systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

- Supportive remarks
  - Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
  - Postprandial epigastric bloating, belching, and nausea can also be present
  - Persistent vomiting likely suggests another disorder
  - Heartburn is not a dyspeptic symptom but may often coexist
  - The pain does not fulfill biliary pain criteria
  - Symptoms that are relieved by evacuation of feces or gas generally should not be considered as part of dyspepsis
- Other digestive symptoms (such as from gastroesophageal refuls disease and the irritable bowel syndrome) may coexist with EPS

TABLE 4 Drugs available currently in Indian market for treatment of two subtypes of FD

Epigastric pain syndrome	***Postprandial distress syndrome***
• Omeprazole • Pantoprazole • Lansoprazole • Dexlansoprazole • Esomeprazole • Ilaprazole • Rabeprazole • Dexrabeprazole • Potassium competitive acid blocker	*Fundic relaxants* • Acotiamide • Buspirone • Mirtazapine *Prokinetics* • Metoclopramide • Domperidone • Mosapride • Itopride • Levosulpiride • Cinitapride • Prucalopride *Visceral neuromodulators*

TABLE 5 Rome IV criteria for IBS[9]

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

BOX 1 The Manning criteria that suggest a positive diagnosis of irritable bowel syndrome if any four of the listed six symptoms are present[8]

- Onset of pain associated with more frequent bowel movements
- Onset of pain associated with more loose bowel movements
- Relief of pain with defecation
- Abdominal distension
- Sense of incomplete evacuation
- Passage of mucus

Currently, Rome IV criteria **(Table 5)**, developed after several iterations through Rome I, II, and III criteria, are used to diagnose IBS.

Alarm Features

Alarm features also called "red flags," suggest the possible presence of an organic disease warranting investigations

before the diagnosis of IBS is made. Alarm features include the age of onset at or more than 45 years, anemia, blood in the stools, unintended weight loss, nocturnal symptoms, fever, abdominal mass, and a family history of colorectal cancer. As mentioned earlier, the age cut off of 45 years may vary depending on the local epidemiology of gastric cancer.

For clinical trials, all patients should have at least full blood counts, erythrocyte sedimentation rate, C-reactive protein, and limited colonoscopic examination, and other investigations, if indicated.[9]

BOX 2 Multidimensional clinical profile in functional gastrointestinal disorders[10]

- Categorical diagnosis (symptom-based criteria)
- Clinical modifier (e.g., IBS-C, D, M, post-infectious, FODMAP sensitive)
- Impact (mild, moderate, severe)
- Psychosocial modifier
- Physiological dysfunction and biomarker

IBS: irritable bowel syndrome, FODMAP: fermentable oligo- di-monosaccharides and polyols.

Multidimensional Clinical Profile

There has been a significant paradigm shift in the management of FGIDs after the introduction of a multidimensional clinical profile (MDCP) in the Rome IV algorithm in 2016. Currently, experts, including the author, are in the process of generating a plausibility consensus in relation to organic issues on FGIDs. According to MDCP, in addition to assigning the patients to a diagnostic category, it is essential to evaluate the patients as a whole rather than only a diagnostic label. Sir William Osler wrote that it is better to treat the patient who has the disease rather than treating the disease. MDCP necessitate the physician to assess several critical issues in addition to the categorical diagnosis of FGIDs such as IBS **(Box 2)**.[10]

A component of MDCP includes subtyping **(Fig. 2)** of FGIDs; for example, constipation-predominant or diarrhea-predominant IBS (IBS-C, and IBS-D, respectively), EPS or PDS subtypes of FDF, etc. As described in the treatment of these disorders, such subtyping is the cornerstone for the choice of appropriate drugs to treat these disorders.[9] Moreover, those with alternating (change in symptoms over weeks to months) and mixed type is more difficult to treat and may require pathophysiology modifying measures such as an attempt at manipulating gut microbiota.

Table 6 and Figure 3 list the biological factors that may contribute to two subtypes of IBS, namely diarrhea-predominant and constipation-predominant IBS.[4]

Treatment

In addition to pharmacological treatment, dietary modification (low FODMAP diet) and management of psychological issues may help in relieving symptoms and improving the quality of life. To address these issues, dieticians and psychologists are essential members of the team to manage these patients. Treatment would depend on the predominant symptoms: diarrhea, constipation, or pain/gas/bloat **(Figure 3, Table 7)**.[4]

Initial treatment for patients with IBS should include various combinations of antispasmodic, laxative, and antidiarrheal agents as they are quite safe and relatively inexpensive.[12] Antispasmodics, which reduce abdominal pain by reducing muscle spasm, include antimuscarinics, smooth-muscle relaxants, and anticholinergics.[12] Common adverse effects include dry mouth, dizziness, blurred vision, confusion, urinary retention, and constipation, which are associated with anticholinergics. Bulking agents are commonly prescribed drugs, especially for IBS-C.[12] However, bulking agents may even aggravate abdominal pain and bloating.[12] For the control of diarrhea, loperamide has the best quality of evidence but has not been shown to improve abdominal pain or distension.

Several visceral neuromodulators, which also have central nervous system effect, such as tricyclic antidepressants, serotonin reuptake inhibitors (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI), relieve abdominal pain, diarrhea, insomnia, and depression. These drugs are useful in the treatment of IBS even in the absence of psychiatric illness.[12] Another approach to treating IBS is psychotherapy.[12] Aims of psychotherapy include reframing maladaptive beliefs, reduction of over-responsiveness to stress, reduction of maladaptive psychological responsiveness, and modification of maladaptive behaviors. Hypnotherapy is one of the essential tools in psychotherapy. The essence of hypnotherapy is to create a relaxing and calming environment and allowing the patient to refocus away

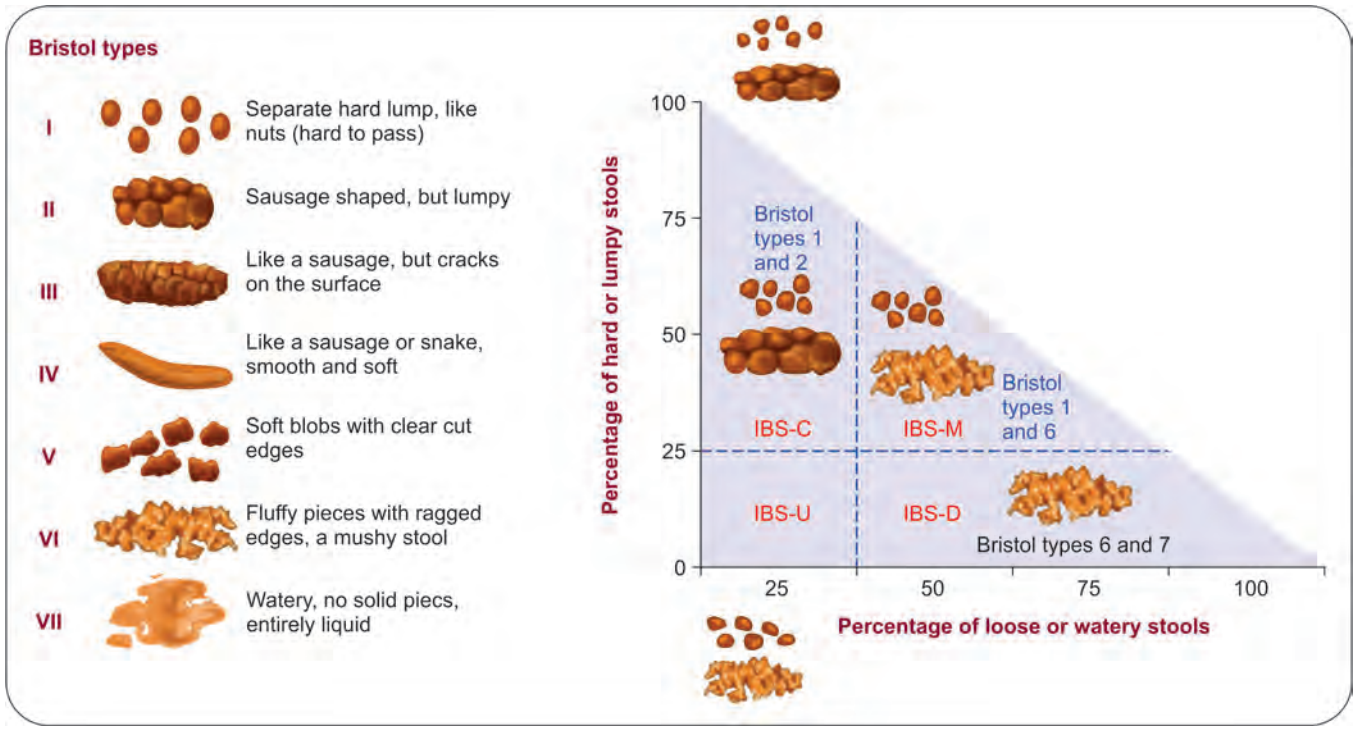


Fig. 2: Bristol stool types and method of sub-typing of IBS according to Rome IV system. IBS subtypes should be established according to stool consistency, using the Bristol stool form scale. Whether 25% of the stools are constipating types (I and II) or 25% of the stools are diarrheal types (VI or VII) determine IBS subtypes according to Rome IV criteria

TABLE 6 Different physiological factors that may cause or exacerbate symptoms of patients with two subtypes of irritable bowel syndrome[4]

Types of IBS	*Contributing physiological dysfunctions*
Constipation-predominant IBS	• Fecal evacuation disorder • Slow transit
Diarrhea-predominant IBS	• FODMAP sensitivity including lactose or fructose intolerance • Bile acid malabsorption • Non-celiac wheat sensitivity • Small intestinal bacterial overgrowth • Post-infectious

IBS: irritable bowel syndrome, FODMAP: fermentable oligo- di-monosaccharides and polyols.

from uncomfortable symptoms and toward a more pleasant perception of his or her current state. There is little evidence for the efficacy of such an approach in IBS. The major drawback of hypnotherapy is the requirement of well-trained mental health professional.

Another novel approach to the treatment of IBS is targeting the gut microbiota dysbiosis and small intestinal bacterial overgrowth (SIBO). Rifaximin, a broad-spectrum poorly absorbed antibiotic, has been found useful in the treatment of non-constipating IBS.[13] Rifaximin works against Gram-negative bacteria, Gram-positive bacteria, and anaerobes and also has anti-inflammatory activity. In the famous TARGET study, a 2-week treatment with rifaximin (550 mg thrice daily) resulted in 41% non-constipating IBS patients reporting improvement as compared to 30% placebo-treated patients.[13] However, symptoms recur in most patients within 2–3 months. This study is essential as it brings a novel concept of treating a "functional disorder," which is now believed to result from altered gut microbiota, with an antibiotic.

Dietary modification is an essential component of the treatment of patients with IBS. Symptoms exacerbation due to intolerance to different nutritional ingredients is not uncommon among patients with FGIDs, including IBS. Worsening of symptoms following intake of curry and

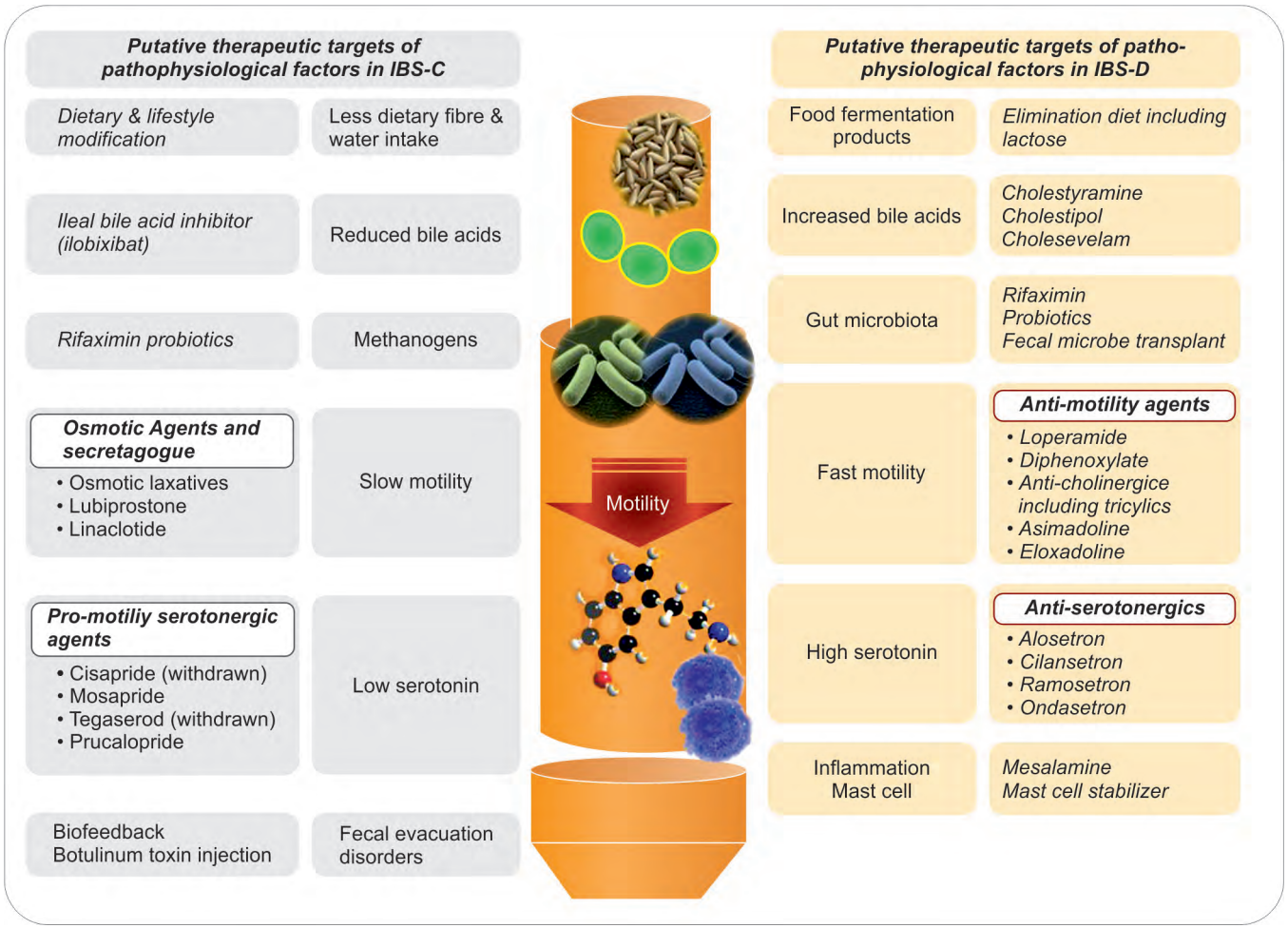


Figure 3: Pathophysiological mechanisms of constipation and diarrhea-predominant irritable bowel syndrome (IBS-C and D) and possible therapeutic agents to target these abnormalities. It is important to note that the therapeutic agents work in functional constipation and IBS-C and functional diarrhea and IBS-D comparably
(*Source:* Reproduced from Reference 4)

TABLE 7 Current symptom-based management of irritable bowel syndrome[11]

Symptom	*First line*	*Second line*	*Future*
Constipation	• Fiber • Osmotic laxative, including polyethylene glycol • Lactulose/Lactitol • Stool softener, e.g., docusate	• Bisacodyl • Sodium picosulfate • Tegaserod (withdrawn) • Lubiprostone • Linaclotide • Prucalopride (5-HT4 agonist)	Elobixibat (ileal bile acid transporter inhibitor)
Diarrhea	• Loperamide • Diphenoxylate	• Alosetron • Ramosetron • Ondansetron • Bile acid sequestrant (cholestyramine, colestipol) • Rifaximin • Clonidine	
Bloating	Treat constipation	• Probiotic • Antibiotic (rifaximin)	
Pain		• Antispasmodics • Anticholinergics • Mebeverine • Pinaverium • Otilonium bromide • Antidepressant – Tricyclic antidepressants – SSRI – RI	

SSRI: serotonin re-uptake inhibitor, RI: reuptake inhibitor

chili is not unusual in Asia.[14,15] Though malabsorption of lactose is as common among patients with IBS as healthy subjects, the patients reported symptoms following the ingestion of this disaccharide than the controls, possibly due to visceral hypersensitivity. Lactose is a component of Fermentable Oligo-, Di-, Monosaccharide, and Polyol (FODMAP) foods. All the high FODMAP foods lead to pathophysiological effects, such as production of osmotically active substances, and gas causing flatulence, distension, and pain, somewhat similar to lactose, among the patients with IBS. Hence, avoidance of high FODMAP foods improves symptoms of IBS.[16] FODMAP diet chart is available from http://spreadhealth.in/New%20Folder/High%20&%20low%20FODMAP%20foods.pdf.

Conclusion

FGIDs, including IBS and FD, are common in medical practice. These disorders have multiple pathophysiological basis. Multimodality treatment directed to the subtypes and underlying pathophysiological factors is often successful in managing these patients.

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CHAPTER

128 Variceal Bleed Management

Srikanth Gopi, Deepak Gunjan

Abstract

Variceal bleed is a clinically significant event in the natural history of cirrhosis, and provides opportunity to treat and correct the underlying cause in the first decompensation. With advancement in critical care, endoscopic variceal band ligation and use of vasoactive agents had improved the management of acute variceal bleed in last few decades. However, refractory variceal bleed is difficult to manage, requires specialized care, and has poorer prognosis. Transjugular intrahepatic portosystemic shunt (TIPS) is reserved for patients with high risk for treatment failure and refractory variceal bleed. Primary and secondary prophylaxis by non-selective beta blocker is another important development in the medical management of esophageal varices and variceal bleed.

Introduction

Upper gastrointestinal bleed (UGIB), one of the common medical emergencies, can be broadly divided into variceal and non-variceal UGIB. Varices are the abnormally dilated submucosal veins in gastrointestinal tract usually developed as a complication of portal hypertension to decompress the portal system. The collaterals gradually increase in size due to various factors and the most important factor is progressive rise in portal pressure and consequent increase in flow through these collaterals.

Approximately half of the patients with cirrhosis have esophageal varices and one-third of all the patients with varices will bleed in their natural course of the disease. In India, the proportion of patients with variceal bleed among all the cases of UGIB presenting to emergency varies widely between 12% and 55% based on region of study.[1] The esophageal varices are the most common source of variceal bleed followed by gastric varices. Cirrhosis is the most common cause of the variceal bleed in >90% of the cases. The overall 6-week rebleeding rate at 6 weeks is 24–30%,[2] whereas 6-week mortality of variceal bleed in cirrhosis is 12–22%.[3] The following sections will be the overview of the management of the esophageal variceal bleed in accordance with the recent guidelines.[4-6] We will not discuss the management of gastric and ectopic varices.

Risk Stratification (Fig. 1)

Cirrhosis can be stratified according to Child-Pugh-Turcotte (CTP) stage or MELD. Higher the score, more severe is the disease. For clinical point of view, it is broadly classified into compensated and decompensated cirrhosis, and later is characterized by variceal bleed, ascites, or hepatic encephalopathy. The higher the number of the decompensation events, the worse is the prognosis.

Hepatic venous pressure gradient (HVPG) ≥10 mm Hg is associated with clinically significant portal hypertension (CSPH), where esophageal varices start to appear; and HVPG >12 mm Hg is associated with bleeding risk. HVPG responders (reduction in HVPG by ≥20% of the baseline value or absolute HVPG <12 mm Hg by NSBBs) are associated with lower risk of rebleed; however, in routine

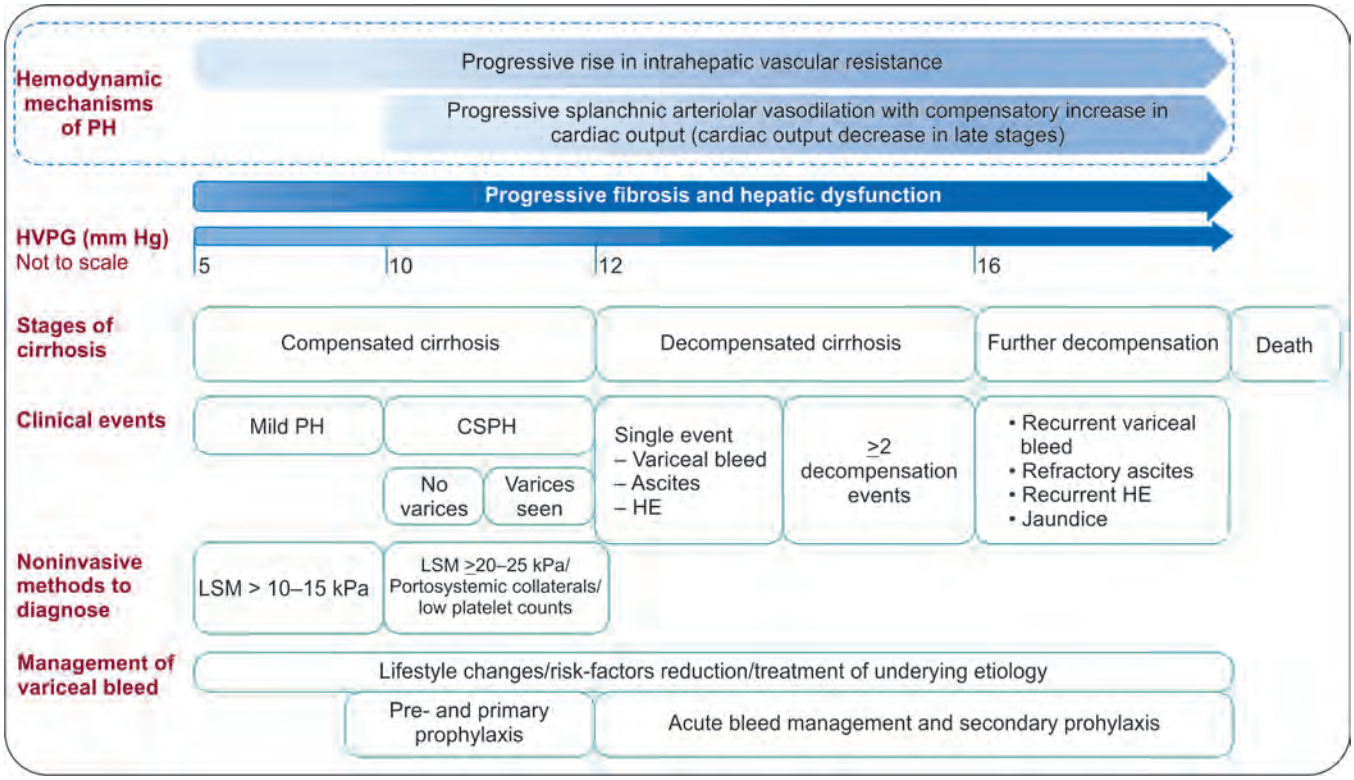


Fig. 1: Stages of cirrhosis, clinical events, and underlying hemodynamics in portal system (modified and adapted from AASLD 2016 Practice Guidance[4])
(CSPH, clinically significant portal hypertension; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; kPa, kilo Pascal; PH, portal hypertension)

clinical practice HVPG measurement is not feasible due to its cost and invasiveness.[4]

Management of Acute Variceal Hemorrhage (Flowchart 1)

Acute variceal hemorrhage (AVH) is to be suspected and treatment should be started immediately in all cases of UGI bleed in known cirrhotics or patient with high-risk of cirrhosis without waiting for the confirmation by endoscopy. The main cause of death in AVH is not uncontrolled bleeding, but due to additional decompensation and complications resulting from acute bleed. The management of AVH will be discussed here.

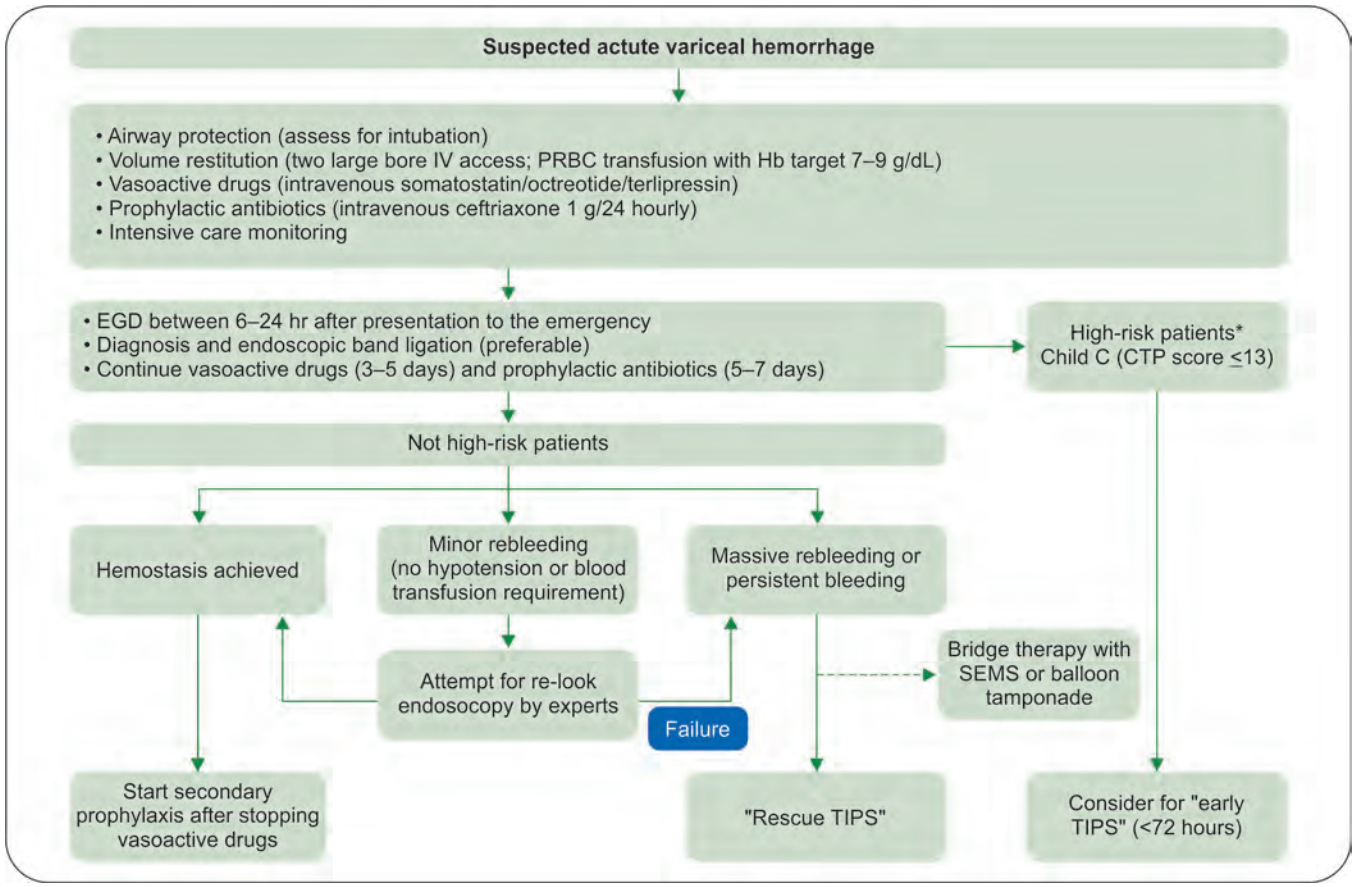
Immediate Management

Assessment of the airway and circulatory function should be done first and orotracheal intubation should be considered in any obtunded patient or in patients with massive hematemesis with high-risk of aspiration. Intravenous access with two large-bore cannula should be secured for careful volume resuscitation. Blood samples should be sent for complete blood counts, liver function test, blood urea and creatinine, and for cross-matching.

The volume resuscitation is done by the crystalloids; and a "restrictive" packed red blood cell (PRBC) transfusion strategy (i.e., target range for the post-transfusion hemoglobin level of 7–9 g/dL), which is associated with significant lower early rebleeding and mortality rates in patients with cirrhosis compared to liberal transfusion strategy.[7] However, cases with cardiovascular comorbidities, ongoing bleeding, and hemodynamic instability require higher hemoglobin target and it should be individualized considering the patient conditions.

In a recent randomized control trial, thromboelastography-guided blood-product transfusion strategy was associated with reduced blood-product transfusion to

Flowchart 1: Algorithm for acute variceal bleed management (adapted and modified from AASLD 2016 Practice Guidance[4])



(CTP, Child-Pugh-Turcotte; EGD, esophagogastroduodenoscopy; SEMS, self-expandable metallic stent; TIPS, transjugular intrahepatic portosystemic shunt)
*Baveno VI consensus and American Association for the Study of Liver Diseases guidelines also consider Child B cirrhosis with active bleed on endoscopy despite vasoactive drugs as high-risk patient.

correct coagulopathy without compromising hemostasis in cirrhotic patients.[2] There is no recommendation for use of platelet transfusion, intravenous vitamin K, or tranexamic acid to halt the acute ongoing variceal bleed. Transfusion of fresh frozen plasma or factor VIIa to correct INR is not recommended.[8]

Any one of the vasoactive drugs **(Table 1)** and antibiotic prophylaxis should be initiated at the earliest prior to esophagogastroduodenoscopy (EGD).[4] These vasoactive drugs cause splanchnic vasoconstriction and reduce the portal pressure. Even in patients on noradrenaline infusion for hypotension, one of the vasoactive drugs should be continued.[9] Intravenous antibiotic prophylaxis (ceftriaxone 1 g/24 hourly) prevent the infectious complications and reduce mortality. A nasogastric tube placement is usually not recommended and prokinetic administration can enhance the gastric mucosa visualization during endoscopy (erythromycin 250 mg IV 30–120 minutes before endoscopy, if no QT prolongation on electrocardiography).

Endoscopic Treatment

There is no need to hurry for EGD to achieve hemostasis. While the first and foremost step is hemodynamic resuscitation and stabilization before sending the patients for endoscopic hemostasis. EGD can be safely performed between 6–24 hours after presentation to the emergency, but it should be individualized if there is evidence of active ongoing bleed despite vasoactive drugs, hemodynamic instability due to blood loss despite resuscitation, actively

TABLE 1 Vasoactive drugs used in acute variceal hemorrhage (adapted from AASLD 2016 Practice Guidance[4])

Drug	*Recommended dose*	*Predominant mechanism of action*	*Significant adverse effects and contraindications*
Somatostatin	Initial IV bolus 250 µg (can be repeated in the first hour if ongoing bleeding) followed by continuous IV infusion of 250–500 µg/hr Duration: 2–5 days	Splanchnic vasoconstriction due to inhibition of vasodilatory hormones	Major adverse events are rare
Octreotide (somatostatin analogue)	Initial IV bolus of 50 µg (can be repeated in first hour if ongoing bleeding) followed by continuous IV infusion of 50 µg/hr Duration: 2–5 days	Similar to somatostatin	Major adverse events are rare. Category B drug in pregnancy
Terlipressin (vasopressin analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding followed by 1 mg IV every 4 hours to prevent rebleeding Duration: 2–5 days	Mesenteric arteriolar vasoconstriction	**Common adverse events:** abdominal pain, hypertension, and hyponatremia **Contraindications:** history of ischemic disease of heart, brain, gut or peripheral limb; and in pregnancy Use with caution in elderly and hypertension

vomiting fresh blood, or persistent fresh blood from nasogastric tube.[10]

Endoscopic variceal obliterative techniques commonly used are endoscopic variceal band ligation (EVL), the preferred technique; and the endoscopic variceal sclerotherapy (EST). Once EVL is done, next session will be planned after 2–4 weeks till complete eradication of varices. Once eradicated, next screening endoscopy will be after 3–6 months and then every 6–12 months.

Role of TIPS

Monitor for rebleed (recurrence of hematemesis/drop in hemoglobin/hypotension due to bleed after endoscopic hemostasis) and assessment for high-risk factors for treatment failure should be done. In patients with high-risk of treatment failure [Child C (with CTP score ≤13) or Child B with active bleeding on endoscopy despite vasoactive drug therapy], evidence showed that the early transjugular intrahepatic portosystemic shunt (TIPS) done within 24–72 hours of presentation after first endoscopy was associated with lower treatment failure and mortality rates compared to standard therapy.[11] So, guidelines recommend "early or pre-emptive TIPS" in acute variceal bleed at high-risk of treatment failure after combined vasoactive drugs and endoscopic therapy.

Post-endoscopic Hemostasis Management

Vasoactive drugs should be continued for 3–5 days and antibiotic prophylaxis should be given for 5–7 days. Assessment for any other decompensation should be done and treated accordingly. Non-selective beta blockers (NSBBs) **(Table 2)** should be started before hospital discharge after the discontinuation of vasoactive agents unless the patient undergoes TIPS.

At our center, in hemodynamically stable patient, we keep the patient fasting for 4–6 hours after endoscopic hemostasis followed by liquid diet for 24–48 hours and then the solid food is allowed. There are some concerns for increase in splanchnic blood flow and increase in portal pressure after enteral nutrition. Some guidelines advocate withholding of enteral nutrition for at least 48–72 hours after an episode of AVH.[12] Avoid placing a nasogastric tube after EVL for first few days to avoid the risk of dislodging the newly placed bands. However, if there is indication for nasogastric tube placement, a tube can be gently placed by an experienced clinician.

Management of Refractory Bleed or Treatment Failure

Treatment failure occurs in 10–15% of the patients with AVH despite treatment and associated with high

TABLE 2 Drugs used in prophylaxis of esophageal variceal bleed (adapted from AASLD 2016 Practice Guidance[4])

Drug	*Recommended dose*	*Predominant mechanism of action*	*Significant adverse effects and contraindications*
Oral non-selective beta blockers (Propranolol or Nadolol)	**Initiation dose:** 20–40 mg BD for propranolol and 10–20 mg OD for nadolol **Dose titration:** Adjust every 2–3 days to achieve maximally tolerated dose or therapy goal achieved **Maximal daily dose:** For propranolol: 320 mg/day if no ascites and 160 mg/day if ascites present For nadolol: 160 mg/day if no ascites and 80 mg/day if ascites present **Therapy goal**: Resting heart rate of 55–60 beats/minute and systolic blood pressure should not be < 90 mm Hg	Reduce portal venous inflow by splanchnic vasoconstriction (by β2-blockade and unopposed α-adrenergic activity) and decrease cardiac output (by β1-blockade)	**Common adverse events:** fatigue, lightheadedness, and shortness of breath **Contraindications:** decompensated heart failure, advanced heart block, severe sinus bradycardia, aortic valve disease, advanced peripheral arterial disease, obstructive pulmonary disease, insulin-dependent diabetes -In spontaneous bacterial peritonitis, refractory ascites, and severe circulatory dysfunction like hyponatremia (Na^+ <130 meq/L) and hepatorenal syndrome, the dose of NSBB should be reduced or withheld temporarily till circulatory dysfunction or sepsis improves
Carvedilol	**Initiation dose:** 3.125 mg OD **Dose titration:** Adjust every 3 days to 6.25 mg BD **Maximal daily dose:** 12.5 mg/day (except in patients with persistent arterial hypertension) **Therapy goal:** Systolic blood pressure should not be <90 mm Hg	Non-selective beta-blocker (reduce portal blood flow) with additional anti-α_1-adrenergic action (reduce intrahepatic resistance)	**Common adverse events:** orthostatic hypotension, dizziness and fatigue **Contraindications:** decompensated heart failure, advanced heart block, obstructive airway disease, and severe bradycardia To be avoided in decompensated cirrhosis as it can worsen ascites and renal dysfunction

mortality.[4] Patient should be referred to higher center for adequate and prompt management. If rebleed is mild (no hemodynamic instability), a re-look endoscopy should be attempted by experienced endoscopists.

Tamponade as Bridge Therapy

If the rebleeding is persisting despite first endoscopy or the rebleed is massive (hemodynamic instability, blood transfusion or 3 g/dL drop in hemoglobin) or the second endoscopic attempt fails, balloon tamponade (Sengstaken–Blakemore tube) or self-expandable metal stent (SEMS) can be used as bridge therapy till definite portal decompressive therapies is available. The balloon tamponade can achieve hemostasis in ~80% cases and should be used for maximum of 24 hours, but it is associated with severe complications such as aspiration and esophageal rupture.[5,13] SEMS is effective and safer alternative than balloon tamponade for control of bleeding and can be left in place for up to 7 days.[14]

Rescue or Salvage TIPS

This can effectively control bleeding in more than 90% of refractory esophageal variceal bleeding cases, but the mortality rate remains high (30–50%) as well as the risk of encephalopathy.[15] So, the patients with high-risk of rebleed are to be identified and offered aggressive strategies (like early TIPS) to prevent treatment failure. Surgical shunts are rarely performed nowadays, may be done in good surgical candidate (child A cirrhosis), when TIPS is not technically feasible.

Patients who Recovered from Recent Variceal Bleed and Secondary Prophylaxis

Untreated patients who recover from first episode of bleed are at high-risk of rebleed (55–67% in first year) and mortality (25–50%).[16] So, initiation of secondary prophylaxis against rebleed is essential before hospital discharge. Patients with indication for liver transplantation should be referred for the same. The patients who underwent TIPS as a part of AVH management do not require additional therapy for rebleed prevention.

All guidelines recommend combination of NSBB (propranolol or nadolol) with EVL as first-line management for secondary prophylaxis. NSBBs **(Table 2)** form the cornerstone of combination therapy; meta-analysis showed an improvement in survival with the addition of NSBBs to EVL, while the addition of EVL to NSBBs has no survival benefit.[17] NSBBs can be used as monotherapy if patients are unable or unwilling to undergo EVL.[5] Currently neither HVPG-guided therapy nor TIPS is recommended for secondary prophylaxis. Unless contraindicated, TIPS is the recommended treatment in patients with recurrent bleed despite combination therapy and also in patients who are intolerant to NSBBs (EVL alone cannot be used as secondary prophylaxis) and especially if patient has ascites also.

Screening and Primary Prophylaxis for Varices

All cirrhotics should undergo variceal screening by endoscopy. However, EGD can be avoided in patients whose liver stiffness on transient elastography (TE) is <20 kPa with platelet count >1,50,000/μL (TE-based criteria); or serum albumin >3.6 g/dL and platelets >1,20,000/mm^3 (platelet-albumin criteria).[6,18]

There is no role of prophylaxis in cirrhosis with no varices or low-risk varices. Primary prophylaxis must be initiated in all cirrhosis with varices at high-risk of rupture. High-risk varices are small varices with red color signs, small varices in CTP C cirrhosis and medium or large varices irrespective of CTP class. The choice between NSBBs **(Table 2)** and EVL depends on variceal size, patient preference, and local resources. A recent network meta-analysis showed that NSBBs are associated with lower mortality compared to EVL.[19]

Conclusion

Acute variceal bleed is an important prognostic event in the natural history of cirrhosis. It is a medical emergency with high mortality and must be managed with resuscitation, vasoactive drugs, prophylactic antibiotics, and endoscopic treatment. Non-selective beta blocker plays a crucial role in the primary and secondary prophylaxis. TIPS has role in refractory bleed and prevention of rebleed in high-risk patients.

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CHAPTER

129 Hepatorenal Syndrome: Current Diagnosis and Management

Shri Krishna Gautam

Abstract

HRS is a life threatening complication of advanced liver disease. It is considered as development of renal failure in patients with pre-existing liver disease but without any underlying renal dysfunction. The term HRS first emerged in the year 1932 in a group of postoperative patients of billiary tract surgery. The Pathophysiology of HRS is poorly understood, three essential components play vital role in Pathophysiology of HRS:

- Arterial vasodilatation in the splanchnic and systemic circulation,
- Renal vasoconstriction, and
- Cardiac dysfunction. Spontaneous bacterial peritonitis is an important risk factor for development of HRS. About one third of patient of spontaneous bacterial peritonitis develop HRS.

Most common presentation of HRS is asymptomatic followed by decrease in urine output. Due to acute kidney injury (AKI), glomerular filtration rate decreases (GFR) and the blood urea nitrogen (BUN) level increases which may result in hepatic encephalopathy as the initial clinical presentation of HRS. Based on clinical features and prognosis HRS is of two types: Type 1 HRS and Type 2 HRS.

HRS requires a very aggressive management considering its poor prognosis. There are three treatment options available for management of HRS:

- Medical therapies are the mainstay of treatment of HRS consisting of vasoconstrictor agents like: Terlipressin, Noradrenaline, and Midodrine plus Octreotide.
- Transjugular intrahepatic portosystemic shunt (TIPS) placement, and
- Liver transplantation.

Therefore, HRS is a life threatening complication of liver cirrhosis. In addition to increased knowledge regarding liver cirrhosis, portal hypertension, ascites as well as HRS, new pharmacological treatments like administration of terlipressin and albumin have proven vital role in improving the short-term outcome of HRS. The other medical treatments using different pharmacological principles such as endothelin antagonists, adenosine-receptor antagonists, and N-acetylcysteine may also help in minimizing renal vasoconstriction and improving renal function, but liver transplant remains to be the mainstay of the treatment.

Introduction

Hepatorenal syndrome (HRS) is a life-threatening complication of advanced liver disease. It is considered as development of renal failure in patients with pre-existing liver disease but without any underlying renal dysfunction.[1]

The term HRS first emerged in the year 1932 in a group of postoperative patients of biliary tract surgery.[2] International ascites club has formulated diagnostic guidelines for HRS in 1994, which were modified in 2007.[3]

Diagnostic Criteria for HRS

See **Box 1**.

BOX 1 Diagnostic criteria of HRS (EASL)

- Cirrhosis with ascites
- Serum creatinine 1.5 mg/dL (133 lmol/L)
- Absence of shock
- Absence of hypovolemia as defined by no sustained improvement of renal function (creatinine decreasing to 133 lmol/L) following at least 2 days of diuretic withdrawal (if on diuretics), and volume expansion with albumin at 1 g/kg/day up to a maximum of 100 g/day
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal renal disease as defined by proteinuria 0.5 g/day, no micro hematuria (50 rbc/high powered field), and normal renal ultrasonography

Pathophysiology

The pathophysiology of HRS is poorly understood, three essential components are:

- Arterial vasodilatation in the splanchnic and systemic circulation,
- Renal vasoconstriction, and
- Cardiac dysfunction.

Several cytokines are involved which alter the renal blood flow and glomerular microvasculature. Important among them are cysteinyl leukotrienes, thromboxane A2, F2-isoprostanes, and endothelin-1. Knowledge about these vasoactive compounds is also important from therapeutic and preventive point of view.

Arterial Vasodilatation in the Splanchnic and Systemic Circulation

Splanchnic vasodilatation is the hallmark of portal hypertension seen in chronic liver disease. Several vasodilators like nitric oxide, glucagon, carbon mono oxide, prostacyclin are released which are responsible for these vasodilatory response.[4-7] In the initial stages, cardiac compensatory mechanism tends to counter the vasodilation.[8]

Renal Vasoconstriction

Due to splanchnic vasodilatation and renal vasoconstriction there is activation of the renin-angiotensin-aldosterone system (RAAS). The clear pathway is not known but cytokines like endothelins, prostaglandins, kallikreins, and F2 isoprostanes are considered to cause renal vasoconstriction.[9-11]

These hemodynamic changes in renal microvasculature and splanchnic vasodilation compromises renal blood flow leading to fall in glomerular filtration rate.[5]

So, HRS is initially a functional renal syndrome, which later progresses to an organic disease.

Cardiac Dysfunction

The development of cirrhotic cardiomyopathy leads to impairment of cardiac function, which may further lead to a relative impairment of the compensatory increase in cardiac output secondary to vasodilatation.

Risk Factors of HRS

Spontaneous bacterial peritonitis is an important risk factor for development of HRS.[12-14]

About one third of patient of SBP develops HRS.[12] The outcome of HRS is very poor. Median survival time of all patients with HRS is approximately 3 months only.[15] High MELD scores and type 1 HRS further worsen the prognosis. Type 1 HRS patients if not treated have very poor outcome with median survival of approximately 1 month.[16]

Clinical Features and Classification of HRS

Most common presentation of HRS is asymptomatic followed by decrease in urine output. Due to acute kidney injury (AKI), glomerular filtration rate (GFR) decreases and the blood urea nitrogen (BUN) level increases which may result in HE as the initial clinical presentation of HRS.

Based on clinical features and prognosis, HRS is of two types (type 1 and type 2).[3]

Type 1 HRS

Type 1 HRS has worse prognosis than type 2 HRS. There is very rapid deterioration in renal function in type 1 HRS. Typically, the leve[0l] of serum creatinine rises to a value higher than 2.5 mg/dL within 2 weeks or less. Most of time type 1 HRS has a triggering event. These triggers interfere with the renal blood flow.[17] Some of the common triggers are bacterial infections,18 GI bleeding, surgery, and acute hepatic injury[3,19]

Among bacterial infections, SBP is the most important trigger event to develop HRS.[20,21] There are certain predisposing factors like high levels of inflammatory markers, severe circulatory depression prior to the onset

of infection, and adrenal insufficiency, which have more chances of development of HRS.

Type 2 HRS

Type 2 HRS is more slowly progress[0i]ve than type 1 HRS, but still carries a median survival of only approximately 6 months. Typically patient presents with pre-existing resistant ascites with mild renal dysfunction (serum creatinine < 2.5 mg/dL). Type 2 HRS patient can progress into type 1 HRS after a triggering event.

Prevention of HRS

HRS has a very poor prognosis and very high mortality rate. So prevention of HRS is an important aspect in management of patients of chronic liver disease. Most important strategy is to prevent depletion of intravascular volume. Important causes of volume depletion are over diuresis, diarrhea due to lactulose, variceal bleed, and large volume paracentesis.

Use of nephrotoxic drugs should be avoided. Beside these prevention of infection and its prompt treatment is also very important for prevention of HRS.[18]

Treatment of HRS

HRS requires a very aggressive management considering its poor prognosis. There are three treatment options available for management of HRS:

- M2 4ed]ical therapies,
- Transjugular intrahep[0a] tic portosystemic shunt (TIPS) placement,
- Liver transplantation.

Aim of medical therapy is to maintain intravascular volume. Vasoconstrictors are used to counter splanchnic vasodilatation. Colloid infusion is done for volume expansion. Aim of the medical therapy is to act as a bridge until definitive treatment of liver disease is done or until the triggering event (SBP, UGI bleed) has subsided.

Medical Therapy

- Non-specific medical therapy:
  - Vitals monitoring and maintaining fluid balance is very important. Monitoring of blood pressure, central venous pressure, urine output helps in maintaining fluid balance.
  - Infection control: prophylactic antibiotic therapy should be given if indicated for prevention of SBP. Sepsis should be identified early using culture of blood, urine, and ascetic fluid. There is no role of antibiotic without proven infection.
  - Diuretic has to be stopped to prevent depletion of intravascular volume.
- *Specific therapies:*

  Vasoconstrictors: Aim is to reverse the splanchnic vasodilatation to maintain the renal blood flow vasopressin analogues are most commonly used for vasoconstriction. Terlipressin has been studied extensively in HRS patients.[15,22]

  Terlipressin improves renal function in about 40–50% patients of HRS[15,23] The dose of terlipressin is 1 mg every 4–6 hours. It can be increased up to 2 mg every 4–6 hours after 3 days if there is no improvement in renal function (fall in serum creatinine by at least 25% of baseline). Terlipressin is discontinued if serum creatinine comes below 1.5 mg/dL[22] with improvement in renal function there is increase in urine volume, blood pressure, and serum sodium concentration. Improvement is slow and can take up to 14 days for renal function to become normal. Duration is shorter with lower serum creatinine at the time of starting terlipressin.[24]

  Better response is observed in patients with baseline serum bilirubin less than 10 mg/dL.[24] Also patients who show reduction in mean arterial pressure of more than 5 mm Hg after 3 days of medical therapy have favorable response to medical therapy.[24] Reoccurrence after stopping terlipressin is rare. Terlipressin is effective in reoccurrence.

  Common side effects of terlipressin include cardiovascular and ischemic complications. So terlipressin is avoided in patients with known cardiovascular and ischemic conditions. Patients of HRS are given albumin along with terlipressin to maintain intravascular volume. Albumin is given in a dose of 1 g/kg body weight.

  Terlipressin shows improvement in renal function in patients of type 2 HRS also,[25] but there are limited studies in patients of type 2 HRS.

  There are other vasopressors that are used in type 1 HRS:

  - Midodrine plus octreotide
  - Noradrenaline

Midodrine is an alpha adrenergic receptor agonist. It is an oral drug started at a dose of 2.5 mg tds and can be increased up to 12.5 mg. Octreotide is started with a dose of 100 microgram tds and can be increased up to 200 microgram tds. There are only few studies with midodrine and octreotide.[26]

Noradrenaline (0.5–3 mg/h) is a vasopressor drug. Increased arterial pressure helps to maintain adequate blood flow to kidneys.[27] comparative studies between noradrenaline and other vasoconstrictors drugs are the area of research. Noradrenaline is given as continuous infusion with an aim to keep systolic blood pressure above 110 mm Hg.

There have been few studies on prevention of HRS. Short-term treatment (4 week) with pentoxifylline (400 mg three times a day) in a randomized double-blind st[u8]dy was shown to prevent the development of HRS in patients with severe alcoholic hepatitis. In a recent study, long-term treatment with pentoxifylline was not associated with an improved survival but with reduced frequency of some complications of cirrhosis, including renal failure, yet this 7w as not the primary endpoint of the study. Finally, norfloxacin (400 mg/day) reduced the incidence of HRS in advanced cirrhosis.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS has been used for treatment of portal hypertension associated with cirrhosis.[28] TIPS helps to control ascites along with improvement in renal function in patients of HRS.

Renal replacement therapy: Hemodialysis is used in patients of HRS. Indication of hemodialysis is similar to any cause of acute renal failure.[29,30] There are no separate studies to see results of hemodialysis in HRS patients. Comparison of renal replacement therapy and medical therapy for HRS is an area of further evaluation.

Liver Transplantation

Treatment of choice for both types of HRS is liver transplantation.[31] Liver transplantation success rate is about 65% in patients of type 1 HRS.[31] Renal failure subsides after liver transplantation. Patients who remain on renal support therapy for more than 12 weeks should be considered for combined liver kidney transplantation.

Conclusion

Therefore, HRS is a life-threatening complication of liver cirrhosis. In addition to increased knowledge regarding liver cirrhosis, portal hypertension, ascites as well as HRS, new pharmacological treatments like administration of terlipressin and albumin have proven vital role in improving the short-term outcome of HRS. The other medical treatments using different pharmacological principles such as endothelin antagonists, adenosine-receptor antagonists and N-acetylcysteine may also help in minimizing renal vasoconstriction and improving renal function,[32,33] but liver transplant remains to be the mainstay of the treatment. The multiple aspects in the pathophysiological process will likely be targeted by the future treatment of HRS.

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CHAPTER

130 Hepatic Encephalopathy: Management

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Abstract

Hepatic encephalopathy is defined as brain dysfunction caused by liver insufficiency and/or portosystemic shunting; its clinical manifestations include spectrum of neurological or psychiatric dysfunction ranging from subclinical alterations to deep coma. The development of hepatic encephalopathy correlates with the severity of liver disease. Hepatic encephalopathy is classified into overt hepatic encephalopathy, which is characterized by neurologic and neuropsychiatric dysfunctions detected by clinical examination and bedside tests or minimal hepatic encephalopathy, characterized by normal mental status and normal neurologic examination but abnormalities on psychometric testing. Early detection and rectification of precipitating factors is most important in the management. The first-line therapy is still lactulose which is effective in minimal, overt and recurrent hepatic encephalopathy. Rifaximin is equally effective to lactulose and is better tolerated. Branch chain amino acids have a beneficial effect on hepatic encephalopathy in protein intolerant patients. Probiotics and L-ornithine L-aspartate are also useful in the management of hepatic encephalopathy. Combinations of rifaximin and lactulose have shown promising results in the treatment of overt and recurrent hepatic encephalopathy. Embolization of large portosystemic shunts and liver transplantation are effective treatment in few and highly selected patients. Nutritional therapy and fecal microbiota transplantation are emerging treatment options but data is limited.

Introduction

Hepatic encephalopathy (HE) is identified by indiscriminate neurological and psychiatric manifestations, which adversely impacts the life of patients and their family members. The requirement of multiple hospital admissions due to HE is a matter of great concern for the health-care sector. HE has been categorized based on preexisting liver disorder, gravity of the clinical features, the trends over time, and triggering/precipitating factors **(Table 1)**.[1,2] Type A HE is a consequence of acute liver failure, type B of large portosystemic shunts (PSS), and type C of liver cirrhosis.[3] Type C is the most common. The scope of HE scales from not easily observable clinical features characterized as minimal hepatic encephalopathy (MHE), overt neuropsychiatric features characterized as overt hepatic encephalopathy (OHE) to comatose state. Overt HE is observed in 10–14% of cirrhotic patients at the time of diagnosis. Forty percent of patients with cirrhosis encounter at least one outbreak and many encounter frequent outbreaks of HE. In cirrhotic patients the prevalence of MHE is 20–80%.[3-5] In patients with cirrhosis HE is a marker of poor prognosis, with up to 85% 1-year mortality.[4] The available literature on pathogenesis suggest that an increase in ammonia concentration is implicated and a role for inhibitory neurotransmission through gamma aminobutyric acid (GABA) receptors in the central nervous system along with changes in central neurotransmitters and circulating amino acids.

TABLE 1 Classification of hepatic encephalopathy

According to WHC severity	*According to ISHEN*	*Based on underlying disease*	*Based on time course*	*Based on precipitating factors*
MHE	Covert	A	Episodic	Spontaneous
Grade I				
Grade II	Overt	B	Recurrent	Precipitated
Grade III				
Grade IV		C	Persistent	

ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; WHC, West Haven Criteria

TABLE 2 West Haven Criteria for severity of hepatic encephalopathy

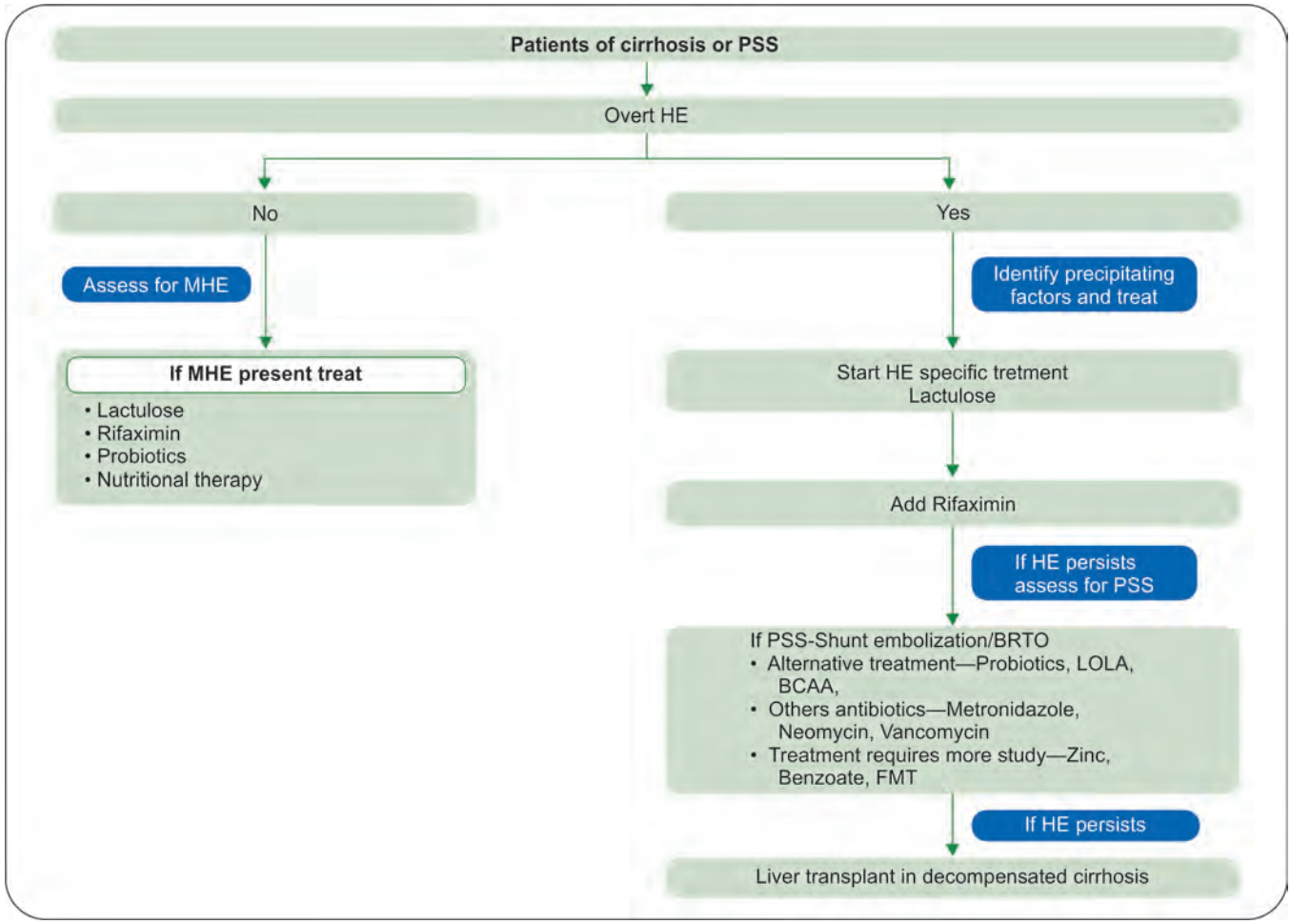
Grade of HE	*Minimal*	*Grade I*	*Grade II*	*Grade III*	*Grade IV*
Clinical features	No clinical manifestations	Short attention span, Altered sleep rhythm, Impairment of addition or subtraction, Minimal lack of awareness, Anxiety	Lethargy, Disorientation for time, Personality changes, Inappropriate behavior, Flapping tremors	Gross disorientation, Confusion, Somnolence to semi stupor, Bizarre behavior, Involuntary passage of urine and feces	Coma

HE, hepatic encephalopathy

Overt Hepatic Encephalopathy Management

Management of OHE includes finding and resolving any triggering factor, to reduce blood ammonia level with lactulose or rifaximin and the proper setup for its treatment. The severity of OHE is graded from I to IV, based on the clinical features **(Table 2)**. The treatment depends on the severity of OHE. Patients with grade I HE may be managed on outpatient basis, if caregivers are available to look for signs of worsening and to bring the patient to the hospital if required. Hospital admission of a patient with grade II HE depends on the degree of lethargy and confusion. If the patient is not able to take the treatment or if caregivers are not available for monitoring the patient, the patient needs to be admitted to the hospital. Patients with more severe HE (grades III and IV) require hospital admission for management, ideally in the intensive care unit and intubation should be considered for airway protection. All patients with HE should receive supportive care, which includes balanced nutrition, avoiding dehydration and electrolyte abnormalities, and providing a safe environment. Disoriented and agitated patients need extra care to prevent falls. Judicious use of restraints is a safe option than sedative drugs, as patients with advanced cirrhosis and HE are vulnerable to over sedation with drugs. If at all medications are required, haloperidol is a better and safe option than benzodiazepine.[6] Nutritional support includes 35–40 kcal/kg energy with 1.2–1.5 g/kg protein per day. Cirrhotic patients are usually malnourished and restriction of protein can increase mortality, so patients with HE should not restrict their protein intake.[7,8] Grades I and II HE patients can take their diet orally, but patients with severe HE are usually unable to receive oral nutrition. These patients should be fed through Ryle's tube along with necessary medications. All HE patients are advised to take small portions at regular intervals with a late-night snack of complex carbohydrates, as fasting further promotes the production of glucose from amino acids, which leads to ammonia production.[9] Vegetable proteins are preferred as they improve nitrogen balance and mental status. Addition of branched-chain amino acids (BCAA) to a low-protein diet should be considered for patients intolerant to protein. Usually patients with transjugular intrahepatic portosystemic shunt (TIPS) or surgical PSS have severe HE and use of vegetable protein or protein restriction with BCAA supplementation is beneficial in these patients. The algorithm for management of HE has been shown in **Flowchart 1**.

Flowchart 1: Algorithm for management of hepatic encephalopathy



BCCA, branch-chain amino acids; BRTO, balloon occluded retrograde transvenous obliteration; FMT, fecal microbiota transplantation; HE, hepatic encephalopathy; LOLA, L-ornithine L-aspartate; MHE, minimal hepatic encephalopathy; PSS, portosystemic shunts.

Acute Episode of Overt Hepatic Encephalopathy Management

The treatment of acute HE starts with finding and management of triggering factors and the reduction of blood ammonia level. Treatment of precipitating factors combined with standard ammonia lowering therapy is associated with a rapid reversal of HE. Common precipitating factors are constipation, gastrointestinal bleeding, infections (including spontaneous bacterial peritonitis, urinary tract infection, and respiratory tract infection), renal failure, hypokalemia, metabolic alkalosis, hypovolemia, hypoxia, hypoglycemia, and use of sedatives. Blood ammonia concentration is reduced with lactulose, lactitol, rifaximin, and other ammonia lowering agents. Lactulose is administered in the dose of 30–45 mL (20–30 gm) two to four times per day and it should be adjusted so that it results in two to three soft stools per day. Lactitol powder of 67–100 gm diluted in 100 mL of water represents an equivalent dose. It is recommended to administer lactulose or lactitol enemas (1–3 L of a 20% solution) in patients who cannot take it orally. For patients who have not improved within 48 hours or who are unable to take lactulose or lactitol, rifaximin is the next option. The recommended dose of rifaximin is 400 mg orally thrice daily or 550 mg twice daily. Both the doses are equally effective. The safety and tolerability of rifaximin has been proved for up to 2 years. As a rule, antibiotics

are added rather than substituted to nonabsorbable disaccharides. In a study, complete reversal of HE was observed more with combination of lactulose and rifaximin compared to lactulose alone (76% vs. 50.8%, p=0.004) along with decreased mortality (23.8% vs. 49.1%, P < 0.05).[10] Hence, combination therapy is recommended in the management of HE. If the precipitating factor has been resolved and there is no recurrence of HE for next 3 months, the rifaximin can be discontinued. Neomycin, vancomycin, and metronidazole are other alternatives of rifaximin but rifaximin is preferred as it has less side effects. L-ornithine L-aspartate (LOLA) and branch-chain amino acids (BCCA) are the next in consideration for patients who do not respond to conventional therapy.[11,12]

Hepatic Encephalopathy—Primary and Secondary Prophylaxis

Lactulose and rifaximin are proved to be equally effective in patients with acute variceal bleed for primary prophylaxis of HE. In a study, HE developed in a smaller number of cirrhotic patients with variceal bleed in lactulose group compared to placebo group (14% vs. 40%, p=0.03).[13] In another study, lactulose and rifaximin were equally effective.[14] Secondary prophylaxis of HE is defined as preventing another episode of HE in patients who had a previous episode of HE. In secondary prophylaxis chronic therapy with lactulose or lactitol is indicated and if HE recurs on lactulose therapy, combination therapy including lactulose and rifaximin should be considered.[10,15,16] A published study revealed the efficacy of lactulose in prevention of HE recurrence compared to placebo (19.6% vs. 46.8%, p=0.001).[16] Recurrence of HE can also be prevented with the help of probiotics, glycerol phenylbutyrate (PB), BCAA, and LOLA.[15-20] Patients with refractory HE may have large spontaneous PSS. Refractory HE in these patients can be prevented by PSS embolization and balloon occluded retrograde transvenous obliteration (BRTO) of large spontaneous splenorenal shunts.[21,22] Fecal microbiota transplantation (FMT) also prevents recurrence of HE, improve cognition and dysbiosis without major side effects in patients with cirrhosis.[23] Liver transplant is the last resort in patients with decompensated cirrhosis who present with recurrent HE despite of being on above therapy.

Management of Minimal Hepatic Encephalopathy

Patients with MHE have poor quality of life, increased risk of OHE, require frequent hospitalization, and have high mortality. The available treatment options for MHE are disaccharides (lactulose, lactitol), rifaximin, probiotics, and nutritional support.[24-28] In a study that compared a nutritional therapy of 30–35 kcal/kg and 1.0–1.5 g vegetable protein/kg with no dietary intervention in 120 cirrhotic patients with MHE, the rate of reversal of MHE was higher in those receiving nutritional therapy (71.1% vs. 28.8%, p=0.001). Prevention of OHE and improvement in quality of life was also observed with nutritional therapy.[28]

Drugs Used in Management of Hepatic Encephalopathy

Nonabsorbable Disaccharides

Lactulose and lactitol are nonabsorbable disaccharides used as first-line treatment for HE. Lactulose reduces formation and absorption of ammonia from the gut by altering the microbiota, increases nitrogen excretion in the feces and reduces production of toxic short chain fatty acids. It works as an osmotic purgative, prebiotic, and also leads to gut acidification.[29] A Cochrane data base review proved the efficacy of lactulose in HE management compared to placebo or no intervention. Efficacy of lactulose has been seen in the management of MHE, OHE, and recurrent HE. It is also effective in reducing the risk of variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, liver failure, and mortality.[30] Lactulose is well tolerated, and the main side effects include abdominal cramps, diarrhea, and flatulence. About 70–80% patients of HE responds to lactulose.[31] Lactitol is as effective as lactulose, is more palatable, and have less side effects.[32,33]

Nonabsorbable Antibiotics

Ammonia lowering effect has been observed with use of antibiotics such as metronidazole, vancomycin, neomycin, paromomycin, and rifaximin as they have activity against urease-producing gut bacteria. As rifaximin has minimal systemic absorption, broad spectrum, and less adverse events, it is most commonly used. Rifaximin effectively

prevented the recurrence of HE when used as an add-on therapy for refractory HE, despite on appropriate lactulose therapy.[11] Rifaximin is effective in recovery from HE, secondary prophylaxis, and in reducing the mortality as shown in a meta-analysis.[34] It also enhances the performance and health-related quality of life in patients with MHE.[35,36] Rifaximin had similar efficacy to nonabsorbable disaccharides for acute and chronic HE, and somewhat better tolerated. Although neomycin and metronidazole have been used for the management of HE, data are very old and inadequate.[37-39] These antibiotics also have serious adverse events, like neomycin can cause nephrotoxicity, ototoxicity, malabsorption, and metronidazole can lead to peripheral neurotoxicity.

Branch Chain Amino Acids

Cirrhotic patients show reduce blood level of BCCA (leucine, isoleucine, valine). The BCCA have a role in skeletal muscle protein synthesis and detoxification of ammonia. High ammonia level decreases protein synthesis by diminishing the mTOR signaling in cirrhotic patients, this effect is prevented by BCAAs. A Cochrane data base review showed that BCAAs have a favorable effect on HE in cirrhotic patients.[40] Both oral and intravenous preparations are effective. The BCCA helps in muscle building in all cirrhotic patients with sarcopenia along with favorable effects on HE which lead to improvement in quality of life. There is no benefit of BCAA supplementation in protein-tolerant patients. A recent randomized trial on 116 patients who had an episode of HE in the past, found no benefit of BCAA on the prevention of recurrent HE, although supplementation appeared to improve MHE and muscle mass.[20] Based on these results, dietary BCAA supplementation is indicated only in severely protein-intolerant patients.

L-Ornithine L-Aspartate

LOLA promotes ammonia detoxification as it works as metabolic substrates for urea cycle in liver and glutamine synthesis in skeletal muscle thus reduces blood ammonia levels. There was improvement in HE, reduction in venous ammonia level, recovery time and duration of hospital stay with use of intravenous LOLA along with lactulose.[17] A Cochrane data base review revealed favorable effect of LOLA on HE in cirrhotic patients and reduced mortality.[41] This effect was observed with both oral and intravenous preparations.[42] Prophylactic LOLA infusion proved to be effective in decreasing venous ammonia concentration in patients who underwent TIPS placement.[43] LOLA is ineffective in patients acute liver failure.

Probiotics

Prebiotics and probiotics reduce blood ammonia concentrations by promoting colonization of acid-resistant, non-urease producing bacteria. The most efficacious species for HE appears to be Lactobacilli and Bifidobacterium. Use of probiotics improves recovery in HE, but when compared with lactulose they failed to show a benefit in significant outcomes as shown in a meta-analysis.[44] Probiotics are effective in MHE, OHE, and prevention of recurrent HE.[27]

Other Therapies

Large Spontaneous Portosystemic Shunts Embolization

Improvement in OHE and recurrence of HE has been observed with embolization of these shunts and BRTO of splenorenal shunt without deteriorating ascites, variceal bleed, and portal hypertensive gastropathy.[21,22]

Polyethylene Glycol

Polyethylene glycol (PEG) solution results in increase excretion of ammonia in the stool by its purgative action thus it helps in HE management. Although the efficacy of PEG has been proved in a study, more such studies are required for the same.[45]

Acarbose

Acarbose enhances the growth of gut saccharolytic bacterial flora and diminishes proteolytic flora that produces ammonia, mercaptans, and benzodiazepine-like substances. Improvement in HE and reduction in ammonia level has been observed with use of acarbose.[46]

Ammonia Lowering Agents

Ammonia lowering agents like PB, ornithine phenylacetate (OPA), and benzoate binds to ammonia and leads to excretion of nitrogen by urinary non-urea excretion. To date there is no definite evidence for OPA and PB for the management of HE. Sodium benzoate had similar efficacy

to lactulose in the management of HE in a small study.[47] Further studies are required to prove their efficacy.

Flumazenil

Use of flumazenil shows reduction in the GABA/benzodiazepine receptor complex activity thus reversing the neurological inhibition in HE. The short-term (minutes) favorable effect of flumazenil on HE has been proved in a meta-analysis but it does not have any effect on recovery, mortality, and quality of life.[48] Flumazenil may be useful, in patients who received benzodiazepines.

Zinc

Zinc has a role in few patients with recurrent HE, but more studies are required to prove its efficacy.

Newer Therapies

Fecal Microbiota Transplant

In cirrhotic patients there is reduced level of favorable bacterial families like Lachnospiraceae and Ruminococcaceae and rise of the pathogenic Enterobacteriaceae, Streptococcaceae. Fecal microbiota transplant prevents HE recurrence, improves cognitive function, and decreases frequent hospitalization as shown in a randomized pilot trial.[23]

Albumin

Albumin has anti-inflammatory properties; it binds and clears many toxic substances, which accumulate in liver failure. Lactulose with albumin has been proved to be more effective than lactulose alone in treatment of HE (75% vs. 53.3%, p=0.03).[49]

Other Experimental Therapy

Glutamine synthetase replacement, Liposome supported peritoneal dialysis, Melatonin, L-carnitine, Glutamatergic antagonist, serotonin antagonist, opioid antagonist, and spherical carbon (AST-120).

Conclusion

Early detection and correction of precipitating factors is utmost important in the management of HE. The most commonly used therapy is still lactulose, which is effective in MHE, OHE, and recurrent HE. Efficacy of rifaximin is similar to lactulose in the treatment of HE with less side effects. In protein intolerant patients, BCCA have a favorable effect on HE. Probiotics and LOLA also have favorable effects in the treatment of HE. Nutritional therapy and FMT are emerging therapies for HE treatment but the data are limited. Combination of rifaximin and lactulose is more effective in the management of overt and recurrent HE. Liver transplant, embolization of large PSS, and BRTO of splenorenal shunts are effective management options in highly selected patients.

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CHAPTER

131 The Healthy Indian Gut Microbiota

Rupjyoti Talukdar

Abstract

This chapter discusses the current understanding of the gut microbiome in Indian population. It also highlights the differences of the Indian gut microbiome from other populations. Most of the earlier studies involved small to relative moderate sample size from specific geographic locations of India. An ideal study to evaluate the core gut microbiota of healthy Indians should involve a large homogeneous population across the country and use the same technology and data analytics tools. The LogMPIE (Landscape of gut microbiome-Pan India Exploration) is such a study. This study confirmed the most predominant organisms in the Indian gut are Prevotella copri and Faecalibacterium prausnitzii.

Introduction

The microbial ecosystem within the human body has established a symbiotic relationship that results in mutually beneficial metabolic and protective functions. Depending on the mode of delivery, the human gut gets colonized earliest from the maternal vaginal or skin flora.[1] Even though organisms had been demonstrated in amniotic fluid, studies have even raised the possibility of colonization even before birth as organisms have been demonstrated in the first meconium. However, this observation is currently under scrutiny.[2-4] Recent studies have also reported similarity between the ancient microbiome to the modern human gut microbiome, especially with modern rural population.[5] It is now known that the gut microbiome is shaped throughout life in a dynamic manner by factors such as mode of delivery, diet patterns (vegan, fiber-rich, or meat-based), use of food preservatives and emulsifiers, environmental antimicrobial peptides, lifestyle behavior, such as alcohol intake, use of antibiotics and probiotics[1,6,7] host genetics, and surrounding biodiversity.

The Indian subcontinent, which has a rich biodiversity, is undergoing a transition in the sociodemographic profile.[8] Therefore, the India gut microbiota has evolved to be an interesting area to be studied. In this chapter, we review the published data on the gut microbiota in healthy Indian individuals.

Indian Gut Microbiota and Its Determinants

Mode of Delivery and Early Diet

It was shown by Pandey et al. that the fecal microbiota of vaginally born infants was dominated by *Acinetobacter* sp., *Bifidobacterium* sp., and *Staphylococcus* sp.[9] On the contrary, the infants born by cesarean delivery conspicuously lacked *Bifidobacterium*, which is a crucial organism required for milk digestion. In a subsequent study, Kabeerdoss et al.[10] reported a dynamic evolution of organisms in the infant gut, with the most dominant being *Lactobacilli* and *Enterobacteriaceae*. This was significantly higher than in infants born by cesarean delivery on the first day of life but equaled thereafter. After 3 months

of birth, an abundance of *Bifidobacterium* was higher in stools of the vaginally born infants while there was a progressive increase in abundance of the *Bacteroides-Prevotella* group in these infants from birth to 3 months of life. Meanwhile, exclusively breast-fed infants had a higher abundance of *Enterobacteriaceae* compared to those who were additionally fed with supplemental cow's milk.[10]

Age

Balamurugan et al. reported the first Indian study on 130 children and adolescents that demonstrated a dynamic change in the gut bacterial composition.[11] The study cohort was fairly homogeneous and predominantly consumed a lactovegetarian diet with infrequent meat intake. *Bifidobacterium longum* showed predominance from the age of 2–3 years but declined rapidly after reaching adulthood. Similarly, *Lactobacillus acidophilus* was predominant in the 2–3 years age group but progressively declined as age progressed toward adulthood. On the other hand, the *Bacteroides-Prevotella-Porphyromonas* group which was low in early childhood constituted the major organisms in later childhood and adolescence. The study by Marathe et al. also suggested a change in the gut microbiota with progressing age.[12]

Habitat and Geography

A multicenter study[13] from urban and adjacent rural Delhi and Pune reported *Prevotella*, *Megasphaera*, *Faecalibacterium*, *Lactobacillus*, *Ruminococcus*, and *Roseburia* as the most dominant organisms. Interestingly, the gut microbiota in these individuals could be divided into two groups on the basis of the absolute counts of *Prevotella* and *Megasphaera*. The microbial diversity was significantly higher among the urban individuals.

Another subsequent study[14] *that evaluated the gut microbiota in rural and urban Ballabgarh (sea level) and Ladakh (11,500 ft above sea level) demonstrated region-specific differences in bacterial diversity. The genus and species level diversity were least in the rural Ladakh region while in individuals from urban Ballabgarh had* high alpha and beta diversity, while individuals from the rural region had high alpha but low beta diversity.[14] The genus *Parabacteroides*, *Blautia*, *Brevundimonas*, *Pelomonas*, and *Megamonas* were significantly higher in the Ballabgarh rural cohort. On the other hand, while *Lactobacillus* was abundant in the Ballabgarh urban cohort, *Bacteroides*, *Vibrio*, *Eggerthella*, and *Pseudomonas* were high in both the Ballabgarh cohorts.

The region-specific variation in the gut microbiota in this study was also associated with enrichment of xenobiotic metabolizing pathways in the Ballabgarh rural and urban cohorts compared to the Ladakh population, implying higher exposure to industrial chemical and drugs in the Ballabgarh populations.

Another recent study[15] that evaluated the gut microbiota in Bhopal (Central India) and Kerala (South India) identified two distinct clusters of organisms. Cluster 1 was enriched in organisms from the genera *Prevotella* while Cluster 2 was enriched with species from the genus *Bifidobacterium*, *Ruminococcus*, *Clostridium*, and *Faecalibacterium*. Location-wise distribution revealed *Prevotella* and *Megasphaera* to be predominant in Central Indian cohort while the others including *Bacteroides* were more abundant in the South Indian cohort. Moreover, the authors also reported three characteristics fecal metabolomic clusters among the study cohorts. The Central Indian cohort abounded in metabolites such as palmitic acid, stearic acid, and valeric acid, while in the South Indian cohort, there was a significant enrichment of BCAAs (especially isoleucine), cadaverine, propionate, and lauric acid.

Ethnicity

Since tribal populations are closely attached to nature and their lifestyle is largely determined by agriculture, fishing, hunting, tribe specific dietary patterns, culture, and traditions, they are likely to harbor an evolutionarily conserved gut microbiota. India harbors the largest tribal population in the world and thus constitutes the ideal for evaluation of the "normal" gut microbiota. In the first and so far, the largest study on the Indian tribal gut microbiota,[16] we evaluated healthy tribal volunteers belonging to 15 tribes of Mongoloid or Proto-Australoid decent dispersed over different geographic locations across Northeast and Southern India. The genus *Prevotella* contributed to 40% of the genus across all tribes. The other genera that constituted the core microbiota irrespective of geography and ethnicity included *Faecalibacterium*, *Eubacterium*, *Clostridium*, *Blautia*, *Collinsella*, *Ruminococcus*, and *Roseburia*. In addition to these genera, *Bacteroides*, *Dialster*, and *Veillonella* were found to abound the tribes from Manipur while *Bacteroides*, *Dialster*, *Bifidobacterium,* and

Lactobacillus abounded in the tribes from Sikkim. Tribes from Manipur had the least abundance of *Bifidobacterium*. Correlational analyses within the core microbiota revealed that *Prevotella* had a negative correlation with *Bacteroides, Faecalibacterium,* and *Clostridium* in the Telangana tribes, with *Faecalibacterium*, *Bacteroides,* and *Roseburia* in the Manipur tribes, and with *Bacteroides*, *Clostridium*, *Ruminococcus*, and *Blautia* in the tribes from Sikkim. Tribes from Sikkim had a significantly lower abundance of *Enterobacter* compared to tribes from Assam, Telangana, and Manipur.

Dietary Factors

Diet has been established as a major factor that shapes the human gut microbiota. In the foregoing sections of this review, even though there were variations in the gut microbiota according to geography and habitat, a closer look actually converges these variations to dietary patterns. Overall, *Prevotella,* which is responsible for complex plant-derived polysaccharide degradation, was dominant in a majority of the study populations implicating this as a signature genus in Indians.[13,15-17]

The study from Ballabgarh and Ladakh[14] also suggested that cooking oil and ghee could impact the Indian gut microbial composition. For instance, individuals from Ladakh consumed predominantly sunflower oil, which has a high concentration of linoleic acid that is known to be degraded by *Roseburia*. Similarly, *Sporobacter* was also abundant in individuals consuming sunflower oil; while *Collinsella* was specifically predominant in individuals who consumed clarified butter (ghee).

In the tribal study by Dehingya et al.,[16] the gut microbiota was similar between tribes from Assam and Telangana despite the geographic and ethnic differences. Therefore, it appears likely that the carbohydrate and dietary fiber-rich diet (including rice, whole grain, vegetables, fruits, legumes, tubers) determines the core microbiota, which is predominant in *Prevotellaceae*, *Ruminococcaceae*, *Lachnospiraceae,* and *Eubacteriaceae*, which are enriched in carbohydrate metabolizing enzymes. In the Lepcha, Nepali, and Bhutia tribes from Sikkim the abundance of *Bifidobacterium* and *Lactobacillus* can be explained by the higher consumption of milk products and fermented food. Among the Malayali tribes from Tamil Nadu, the higher abundance of *Bacteroidetes* and *Clostridium* could be explained by their daily intake of a moderate amount of pork meat, and non-intake of milk, and milk products due to their religious beliefs.[17]

Comparison of Indian Gut Microbiota with Worldwide Data

It has now been consistently shown that the Indian gut microbiota differs significantly from that of other regions of the world. In our study,[16] we observed two distinct clusters, the first involving the Hadza, Italian, and Americans individuals that abounded in *Faecalibacterium*. The rest of the tribal groups, including Indians, constituted the other group with a higher abundance of *Prevotella*. Interestingly, within this group there was close similarity of the Indian tribal microbiome to the Mongolian tribal microbiota. Of note, the origins of the Nepali and Tai-Phake tribes from India can be mapped to Mongolians.

In the study by Bhute et al.,[13] comparison of gut microbiota of Western and North Indian cohorts with Americans revealed 76 OTUs, out of which six, including *Prevotella*, *Lactobacillus*, *Lachnococcus,* and *Roseburia*, specifically belonged to the Indians. In this study, it was also observed that Indians shared 25 OTUs with the Bangladeshi cohort (majority belonging to families *Lachnospiraceae*, *Ruminococcaceae,* and *Enterobacteriaceae*, and genus *Prevotella*). Other than differences at the overall genera and species level OTUs, differences were also noticed between Indian and European cohorts even within the same genus.[13]

Finally, a metagenome wide meta-analyses (MGWAS) by Dhakan et al., which included datasets from India, China, USA, and Denmark demonstrated completely separate species level clustering of the Indian gut microbiome compared to the American, Danish, and Chinese microbiome.[15] *Prevotellaceae* emerged as the most highly abundant bacterial family in the Indian individuals. In addition, the Indian gut microbiota was found to be enriched in functions that corroborate with a carbohydrate-rich diet.

Conclusion

Results of gut microbiota studies can be influenced by several technical factors such as sample size, sample collection and storage, sequencing technique, reference database, and depth of statistical and bioinformatics analyses.

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In this review, we discussed the gut microbiota in healthy Indians based on the individual studies that involved small to medium sample size and different techniques to evaluate the microbiome. The ideal way to evaluate the true core Indian gut microbiota would be to include a large homogeneous population across the entire country and use the same methods of sample processing, sequencing, and data analyses. The LogMPIE (Landscape of gut microbiome-Pan India Exploration) is such a study that was recently published.[18] This study evaluated 1,004 individuals from 14 centers across India (4 from north, 3 from east, 4 from west, and 3 from south) and bacterial metagenomic sequencing was performed in the Ion oneTouch 2 system. There were 390 microorganisms that were common in all the geographic locations, while 36 were unique to north, 149 to south, 95 to west, and 62 to east India. The most predominant organisms emerged to be *Prevotella copri* and *Faecalibacterium prausnitzii*, thereby qualifying *Prevotella* and *Faecalibacterium*.

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CHAPTER

132 Celiac Disease: Who to Screen and How to Screen?

Ashish Agarwal, Archita Makharia, Govind K Makharia

Abstract

Traditionally celiac disease (CeD) has been defined as a disease involving the proximal small intestine with a presentation with diarrhea, loose stools, malabsorption, weight loss, failure to thrive, and growth retardation in children. This presentation which has long been portrayed as "classical" for CeD, allows us to diagnose only the patients with most severe gastrointestinal involvement and thus miss out those with milder or no GI manifestations. However, it is being increasingly recognized that celiac disease is a multisystem disease with a myriad of presentation including asymptomatic. Even though studies have indicated around 1% population prevalence of celiac disease, most of these patients however remain undiagnosed and hence untreated. There is thus a need for increased awareness of these varied presentations of celiac disease so that the patients can be diagnosed and treated with gluten-free diet thus preventing complications. In this chapter we have discussed the indications for screening for celiac disease and the strategy for screening these individuals.

Introduction

Celiac disease (CeD) is a chronic immune-mediated enteropathy which is triggered on consumption of gluten protein present in cereals like wheat, barley, and rye in genetically predisposed individuals. Although initially believed to be an uncommon disease and limited to the western countries, CeD has now become a global disease and it is now reported from almost all the continents.

Global Burden of CeD

In a systematic review and meta-analysis, we have recently shown that the global pooled seroprevalence (proportion of people having a positive celiac specific serological test in a population) is 1.4% (that means, 1 in 70 people is seropositive for CeD) and the prevalence of biopsy-confirmed CeD (proportion of patients having a combination of positive serological tests and villous abnormalities on duodenal biopsies) is 0.7% (means 1 in 140 individuals globally has CeD).[1] With a global population of 7.2 billion people, approximately 40–60 million people around the world are likely to have CeD.

Burden of CeD in India

Although reported since 1960s in India, an increase in number of patients with CeD in the last 2 decades has been reported from many states, predominantly Northern and Western States of India. Two population-based studies from Northern part of India have shown that the population prevalence of CeD is 1.04% (1 in 96) and 0.33% (1 in 330), respectively.[2,3] Because of predominance of reporting of CeD from the Northern states, people believe that CeD is seen only in the Northern part of India. To explore the question "is there a regional variation in the prevalence of CeD in India," we conducted a multi-site population-based study recruiting 23,331 healthy individuals from three different regions of India including Northern (Haryana),

Southern (Vellore), and Northeastern (Guwahati) regions of India. The combined pan-India prevalence of CeD is 0.67% (1 in 140). Indeed, there is a regional variation in the prevalence of CeD at this point of time, the highest being in Northern India (1.23%), lowest in Southern India (0.1%) and in between in the Northeastern region of India (0.87%).[4] This difference is likely related to the different eating patterns, with rice being staple diet in Southern India and wheat in Northern India. However, with increase in the consumption of products made from wheat in rice eating regions, it is very likely that CeD will emerge in such populations also. With the Indian population of 120 crores, it is estimated that approximately 60–80 lakhs of Indians have CeD. Of this large estimated numbers of people having CeD, only a minority have been diagnosed and a large proportion of them (85–95%) exists in the population but currently remain undiagnosed.

Where are They?

If there are so many patients with CeD both worldwide and in India, then where are they? Why are we not able to pick them up? There are multiple reasons:

- The lack of awareness amongst physicians about changing epidemiology of this disease is the most important reason. We do not think about this diagnosis in appropriate clinical setting.
- It was believed that CeD affects only children, but now it is known that CeD can affect people of all age groups. Although not well established, it is however believed that the pathophysiological changes in CeD starts since early part of life. The clinical manifestations may appear at different ages of life depending upon the severity of the disease.
- While some patients have fully expressed disease with obvious symptoms and manifests in childhood or during adolescence, in others, the disease is expressed in milder form, and hence may not come to clinical attention till late. CeD is diagnosed nowadays more often in adulthood and even in the elderly.
- The classical manifestations, as portrayed in the older textbooks, draw our attention to mainly the more classical form of disease (emaciated child with diarrhea and anemia), which are present in those having a more advanced disease. In early stages of the disease, patients may not have any symptoms or have only mild symptoms.
- While CeD is thought to be mainly a disease of the intestine and recognized in those having gastrointestinal symptoms, only half of the patients however present with predominant gastrointestinal manifestations. The GI symptoms (*Classical CeD*) include chronic diarrhea, malabsorption, failure to thrive, abdominal distension, and weight loss **(Fig. 1)**.
- Approximately half of all the patients with CeD present to a clinician with predominant non-GI symptoms such as short stature, liver abnormalities, infertility, endocrinopathies, etc. in the absence of or with minimal GI symptoms. The diagnosis of CeD is often not suspected in such patients, since most physicians believe that patients with CeD should have GI manifestations **(Fig. 1)**.

Therefore, patients with CeD can present to an internist/gastroenterologists with symptoms of chronic diarrhea, anemia, fatigability, to a pediatrician with irritability, diarrhea, failure to thrive and anemia, to a hematologist with anemia refractory or unresponsive to iron supplementation, to an endocrinologist with type 1 diabetes, hypothyroidism, or growth failure, to a dermatologist with dermatitis herpetiformis, to a neurologist with ataxia, peripheral neuropathy, and to a gynecologist with menstrual abnormalities or infertility.

Thus, there is an increased need for increasing awareness amongst primary care physicians, internists, gastroenterologists, hematologists, endocrinologists, and neurologists about a wide and varied spectrum of manifestations of CeD so that these patients are diagnosed early. An early diagnosis and initiation of gluten-free diet in them can control and the symptoms, and prevent consequences of malabsorption and nutritional deficiencies and prevent adverse health consequences.[5]

Therefore, CeD should be suspected in the patients even in the absence of typical gastrointestinal manifestations. We have summarized below the diseases or symptoms where screening for CeD should be done.

Who should be Screened for CeD (Table 1)

Patients having Diseases and Symptoms Secondary to CeD

Chronic Diarrhea with Features of Malabsorption

Patients having intermittent or chronic diarrhea with features of malabsorption, such as anemia, growth

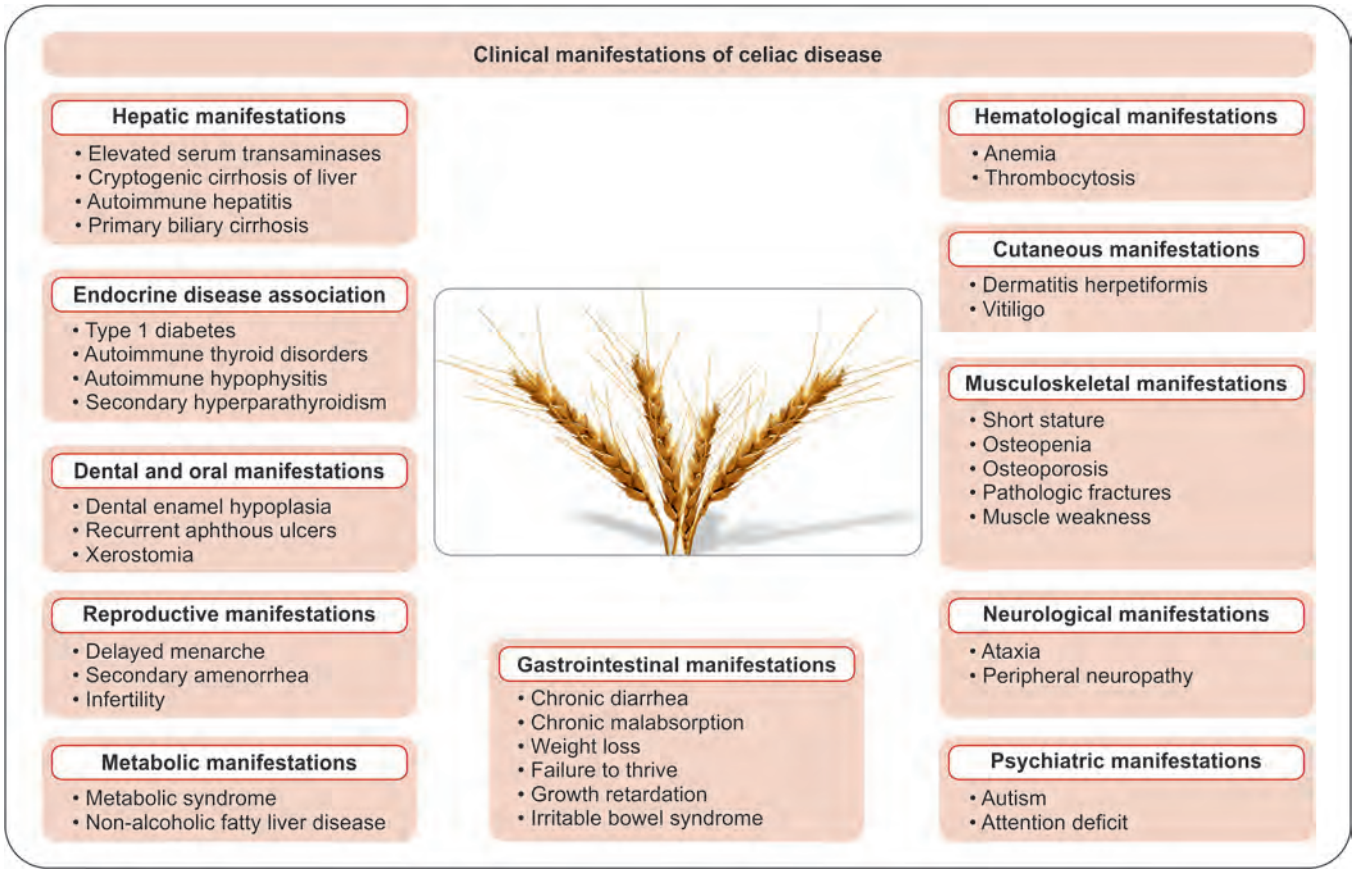


Fig. 1: Clinical manifestations of celiac disease

TABLE 1 Indications for screening for celiac disease

Gastrointestinal manifestations	*Extraintestinal manifestations*	*Associated conditions*
Chronic diarrhea	Cryptogenic hypertransaminasemia	First-degree relatives
Malabsorption	Cryptogenic cirrhosis	Type I diabetes
Growth retardation/Short stature	Infertility	Hypothyroidism
Failure to thrive	Idiopathic cerebellar ataxia	Other autoimmune diseases
Iron deficiency anemia	Dermatitis herpetiformis	Down's syndrome
IBS (IBS-D, IBS-M)		

retardation, poor weight gain, easy fatigability, should be screened for CeD. CeD is now the most common cause of malabsorption syndrome, unlike tropical sprue being the most common cause some times back.

Functional Gastrointestinal Disorders

Some of the patients with CeD may have mild GI manifestations such as altered bowel activity, abdominal pain/discomfort, and bloating. With such a symptom complex, they are likely to be diagnosed as having functional gastrointestinal diseases including irritable bowel syndrome. In fact, in a meta-analysis of 7 studies including 3,383 patients with CeD, it was shown that 38% patients with CeD had IBS-like symptoms.[6] In yet another meta-analysis of 22 eligible studies including 6,991 patients with irritable bowel syndrome, it was found that

3.3% of them had CeD more so in those having mainly IBS-diarrhea predominant and IBS-mixed subtypes.[7]

Iron Deficiency Anemia

Between 50–80% of patients with CeD have anemia and that occurs most commonly because of iron deficiency. Anemia secondary to B12 and folate deficiency in addition to iron deficiency has also been described.

On the other hand, it has been observed that 3.2% (95% CI 2.6–3.9%) of all patients with iron deficiency anemia, when screened for CeD, are found to have CeD.[8] That would mean than 1 of every 31 patients with iron deficiency anemia has CeD. In a study from India, almost 1 in 10 with iron deficiency anemia had CeD. Thus, all patients with iron deficiency anemia should be screened for CeD.

Short Stature/Growth Failure

Almost one third of the adult patients and half of the adolescent patients with CeD have short stature. Since height can increase only till 18 years of age, it is really important to make a diagnosis of CeD much before that age. A timely treatment of CeD can lead to catch up growth and attainment of a normal height.

On that other hand, of the patients presenting for the evaluation of short stature, 6.6% (approximately 1 in 15) have been found to have CeD. The proportion of patients having CeD is still higher (13.4%; 1 in 8) in those having idiopathic short stature, when all known causes have been excluded. The prediction of having CeD in these patients is higher if they also have associated GI manifestations or anemia. Nevertheless, all patients with short stature at any age, with or even without associated GI manifestations, should be screened for CeD.

Dermatitis Herpetiformis

Dermatitis herpetiformis (DH) is characterized by clusters of papules and vesicles associated with intense pruritus. The typical sites for DH lesions include extensor surfaces of upper and lower extremities, elbows, knees, scalp, and buttocks. The extent of skin lesions may vary from small area to more diffuse involving multiple sites at one time. DH shows an excellent response to GFD with complete resolution of skin lesions. Thus, all patients with DH must be screened for CeD.

Infertility

Menstrual abnormalities including delayed menarche and secondary amenorrhea are quite frequent in patients with CeD. Furthermore, patients with CeD have been found to have a low rate of fertility. Patients with CeD are at three-times higher risk for infertility than the general population. On the other hand, 2.3% of patients with infertility have been found to have CeD.[9] As CeD is one of the few treatable causes of infertility, all women patients with infertility should be screened for CeD.

Liver Abnormalities

Almost one-fourth patients with CeD have asymptomatic elevation of serum transaminases at the time of diagnosis which normalize within 1 year of GFD in majority. If this liver injury is not recognized and remains untreated, it can lead to cirrhosis of the liver. In fact, CeD has been found to be one of the causes of cryptogenic cirrhosis. Furthermore, approximately 7% of all those who have hypertransaminasemia and 5% of those having cryptogenic liver disease have been found to have CeD.[10,11] Treatment of CeD in these patients has been shown to lead to an improvement in the liver disease. Therefore, all patients with cryptogenic hypertransaminasemia and cryptogenic cirrhosis of liver should be screened for CeD. As discussed below, as anti-tissue transglutaminase antibody may be falsely positive in those with cirrhosis; therefore, a more reliable screening test in this setting is anti-endomysial antibody.

Neurological Disorders

Some of the patients with cerebellar ataxia, especially those having idiopathic ataxia, have been found to have gluten-related disorders and CeD. The treatment of CeD has also been shown to lead to some improvement in ataxia. Therefore, patients with idiopathic ataxia should be screened for gluten-related disorders. In such patients both anti-gliadin antibody and anti-tissue transglutaminase antibodies should be used for screening.

First-degree Relatives of Patients with CeD

As we know, genes play a major role in the pathogenesis of CeD. The first-degree relatives of index patients with CeD are at much higher risk of developing CeD. A recent

meta-analysis including 10,252 FDRs of patients with CeD has shown that 7.5% of first-degree relatives of CeD have CeD.[12] Furthermore, the sisters (1 in 7) and daughters (1 in 8) of the index patients with CeD are at the highest risks. Thus, all the first-degree relatives of index patients with CeD should be screened for CeD.

Type I Diabetes

CeD has been found to be strongly associated with type I diabetes and a recent meta-analysis has shown that 6% of all patients with type I diabetes have CeD.[13] It means that of 16 patients with type I diabetes, one will have associated CeD. Many of them may have symptoms because of CeD, but these symptoms are often considered to be due to diabetes, and hence they are not specifically investigated for CeD. Therefore, all patients with type I diabetes should be screened for CeD.

Autoimmune Thyroid Disease

An association has been shown between CeD and autoimmune thyroid disorders. Between 10–15% patients with CeD have coexistent clinical hypo/hyperthyroidism. In fact, a recent study showed that of 6,024 patients with autoimmune thyroid disorders screened for CeD, 1.4% patients had CeD.[14] Thus, all patients with autoimmune thyroid disorders should be screened for CeD.

Down's Syndrome

Approximately 1%–19% patients with Down's syndrome have been reported to have CeD. A recent meta-analysis of 31 studies and including 4,383 patients with Down's syndrome has reported that 5.8% of them have CeD, which is much higher than that in the general population.[15] Therefore, all patients with Down's syndrome should be screened for CeD.

Other Conditions

A higher prevalence of CeD has also been observed in certain other conditions including patients having dental enamel defects, other autoimmune disorders like systemic lupus erythematosus, juvenile rheumatoid arthritis, and autoimmune liver diseases, etc.; however, there is a lack of robust data suggesting the utility of routine screening for CeD in these patients.

How do we Screen for CeD?

Once we suspect a patient to have CeD, the first-line screening tests are the CeD specific serological tests. Immunoglobulin subclass A (IgA) anti-tissue transglutaminase, (IgA anti-tTG Ab), anti-endomysial antibody (IgA EMA), and deamidated glutamine dipeptide (IgA anti-DGP Ab) are the currently available assays for screening for CeD. Of these, IgA anti-tTG is the most commonly used test for the screening and diagnosis of CeD because of the ease of detection and a high accuracy with a sensitivity of 92.8% and specificity of 97.9%[16] (Table 2). While IgA EMA testing has a high specificity of 99%, recent systematic review has reported a lower sensitivity of 73%. Detection of anti-EMA requires indirect immunofluorescence and it is not widely available. IgA anti-DGP assay have a pooled sensitivity of 87.8% (95% CI, 85.6–89.9%), and specificity 94.1% (95% CI, 92.5–95.5%) and thus have an inferior performance than anti-tTG Ab **(Table 2)**. Since all these antibodies are IgA based, hence they may be falsely negative in patients having IgA deficiency. In such situations, IgG based tests such as IgG anti-DGP or IgG anti-tTG Ab should be done.[17]

ELISA kits for anti-tTG antibody are manufactured by many companies and their performance varies significantly. Furthermore, there are differences in the cut-off values of the anti-tTG antibody amongst ethnically different population. Hence, a clinician should be aware about these limitations.[18]

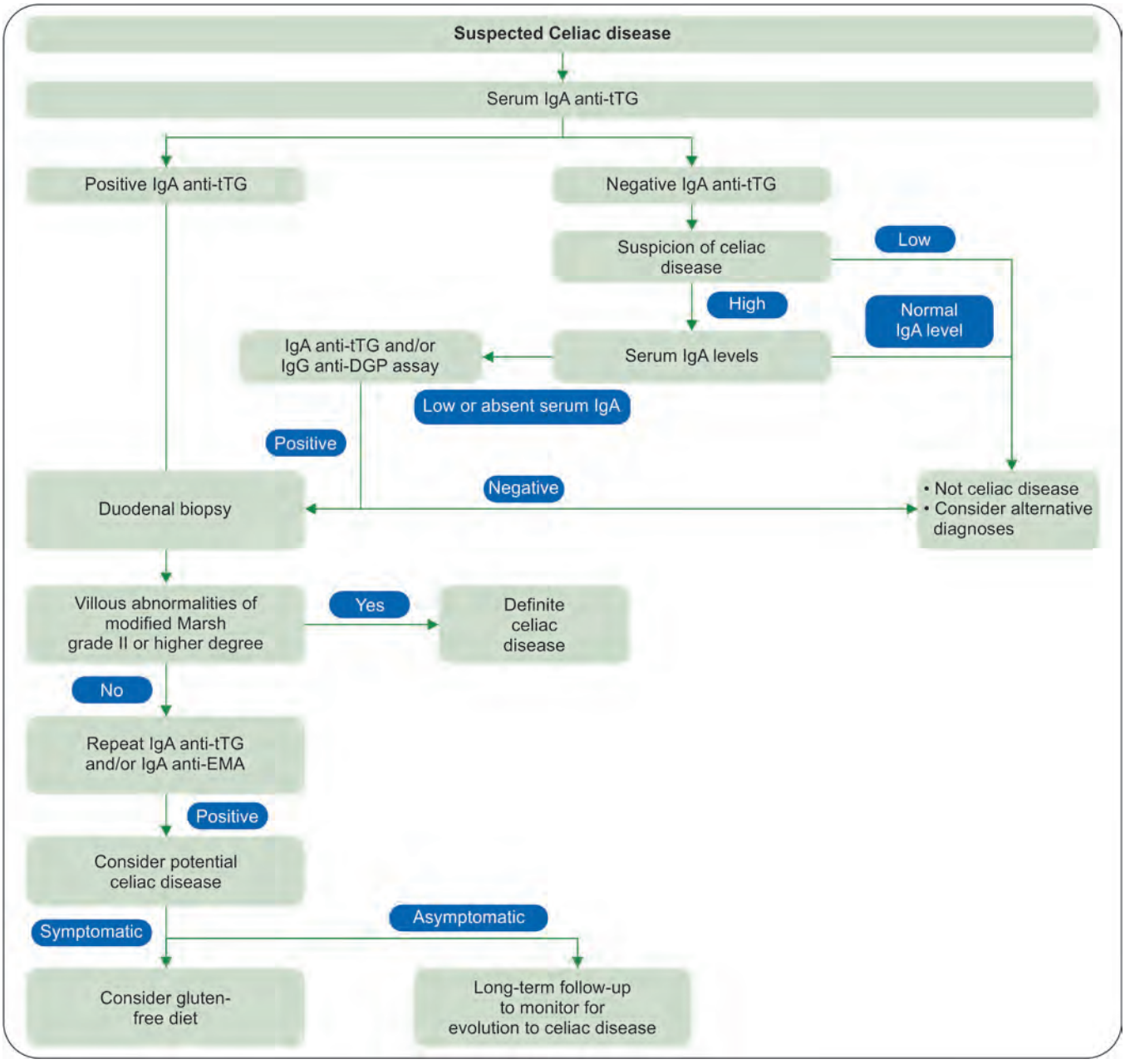
Diagnosis of Celiac Disease (Flowchart 1)

If a patient screened for CeD is detected to have a positive celiac specific serological assays, the diagnosis needs to be confirmed by demonstration of villous abnormalities in the intestinal mucosa, which is still the gold standard

TABLE 2 Diagnostic performance of various serological assays for the diagnosis of celiac disease

	Sensitivity	*Specificity*
IgA anti-tTG	92.8% (95% CI, 90.3–94.8)	97.9% (95% CI, 96.4–98.8)
EMA	73.0% (95% CI, 61.0–83.0)	99.0% (95% CI, 98.0–99.0)
IgA anti-DGP	87.8% (95% CI, 85.6–89.9)	94.1% (95% CI, 92.5–95.5)

Flowchart 1: Algorithm for the diagnosis of celiac disease



for the diagnosis of CeD. Multiple biopsy specimens from the second part of duodenum and at least one biopsy specimen from the first part of the duodenum should be taken for adequate histopathological assessment.[19-21] Modified Marsh classification system is currently used to grade the severity of villous abnormalities based on identification of increased intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy. A diagnosis of CeD is made in patients with villous abnormalities of modified Marsh grade II or more.

The gold standard diagnostic criteria of CeD is based on a combination of clinical manifestations, a positive celiac specific serology and demonstration of villous abnormalities of modified Marsh grade II or more. The

European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN 2019) has suggested a *Non-Biopsy Approach* for making of a diagnosis of CeD.[20] This is based on the evidences that suggest a high degree of prediction of presence of villous abnormalities if anti-tTG Ab titers are more than tenfolds higher above the cut-off value. The ESPGHAN 2019 guidelines suggest that a non-biopsy approach may be considered in children if their anti-tTG Ab titer is more than tenfolds and there is a positive anti-endomysial antibody in a second blood samples. Otherwise, duodenal biopsies should be performed, if anti-tTG titer is less than tenfolds. For adults patients, most of the guidelines, including Indian, recommend a confirmation of diagnosis of CeD with small intestinal biopsy in patients having a positive serological test.[19,21,22]

More often around the world, the ESPGHAN guidelines are misinterpreted and the diagnosis of CeD is made even when anti-tTG Ab titer is less than tenfolds. A hurried diagnosis based on incomplete evidence leads to problems during follow-up. All efforts should be made for the confirmation of the diagnosis before advising GFD. One should realize that anti-tTG Ab, especially at low titer could be falsely positive and the enteropathic changes are not specific for CeD and they could be caused by many other conditions.

Conclusion

CeD has now become a global public health problem and it affects approximately 1% of the world's population. The spectrum of clinical manifestations of CeD is wide include both gastrointestinal and extra-intestinal manifestations. Many patients with CeD do not have GI manifestations but present solely with non-gastrointestinal manifestations. All patients with high-risk of CeD should be screened using IgA anti-tTG antibody.

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CHAPTER

133 Differentiating Crohn's Disease from Intestinal Tuberculosis: A Diagnostic Challenge

Pabitra Sahu, Saurabh Kedia, Vineet Ahuja

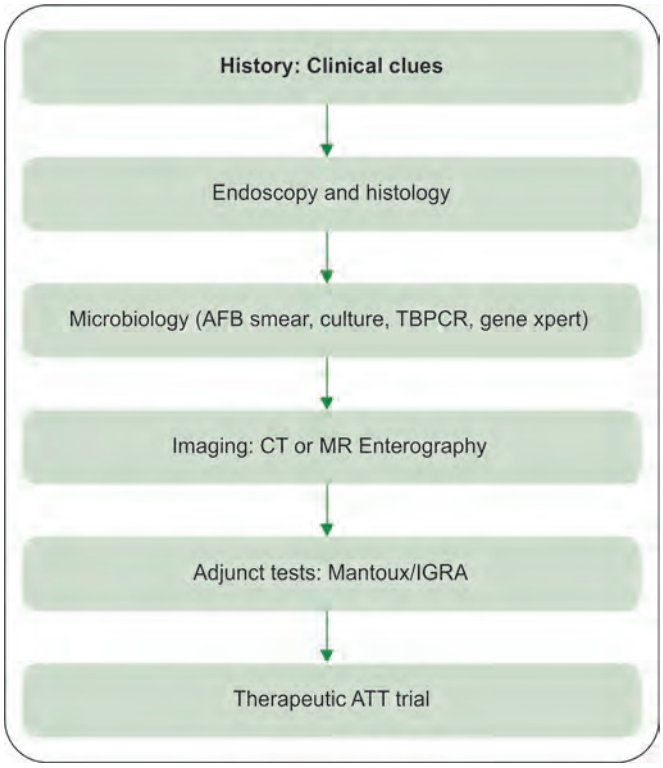
Abstract

Diagnosing intestinal tuberculosis (ITB) and Crohn's disease (CD) has always been a challenge in countries like India where TB is endemic and incidence of inflammatory bowel disease (IBD) is increasing rapidly. Definitive diagnosis of tuberculosis requires demonstrating AFB in smear or culture, caseation necrosis in biopsy or necrotic lymph node in cross sectional imaging. But all these are limited by poor sensitivity. There are certain clinical (diarrhea, hematochezia, perianal disease common in CD; fever, night sweats common in ITB), endoscopic (longitudinal, aphthous ulcers common in CD; transverse ulcers/patulous ileocecal valve common in ITB), histologic (caseating confluent large granuloma common in ITB; microgranuloma common in CD) and radiologic (long segment involvement, comb sign, skip lesions common in CD; necrotic lymph node, contiguous ileocecal involvement common in ITB) differences between CD and ITB. Despite all these differentiating features, in more than 1/3rd of cases a definitive diagnosis cannot be made without a therapeutic ATT trial. Recent advances in this field like newer biomarkers (enumeration of peripheral blood T-regulatory cells) and CT based predictive models (quantification of visceral and subcutaneous fat) can help in difficult cases. As a clinician we need to assess all these clinical and investigational parameters meticulously to solve this diagnostic conundrum.

Introduction

Intestinal tuberculosis (ITB) and Crohn's disease (CD), a sub-type of inflammatory bowel disease (IBD), are both chronic granulomatous disorders of the intestine with different etiologies, but similar presentations.[1,2] Due to globalization and industrialization Southeast Asian countries like India, which are endemic for TB, are in a state of socio-epidemiologic transition with a rising incidence of CD and other non-communicable disorders (Crohn's disease and the "white plague" hypothesis).[3,4] Despite growing number of literature, conclusive diagnosis of ITB and CD still remains a clinical conundrum. There have been reports of misdiagnosing ITB as CD for as long as 7 years before the correct diagnosis was reached.[5] Misdiagnosing these two clinical conditions can have disastrous implications like drug toxicity of anti-tubercular therapy (ATT), delay in CD-specific therapy leading to disease progression along with impaired quality-of-life, and flare up of TB on immunosuppressive therapy for CD.[6,7] For definitive diagnosis of ITB, we need to demonstrate mycobacterium tuberculosis (MTB) in smear or culture, or caseating granuloma in biopsy or a complete symptomatic and endoscopic response to ATT; but all these methods have unsatisfactorily low sensitivity.[8,9] So in clinical practice, most often we gather diagnostic clues from conglomerate of laboratory tests and investigations.[10] In this review, we will discuss the overlapping and discriminative features of both the diseases and try to elucidate a proper approach to solve the diagnostic dilemma. Evaluation of any patient suspected of ITB or CD runs through the following steps **(Flowchart 1)**:

Flowchart 1: Diagnostic algorithm



Clinical Features

Both the diseases present with some common clinical features like abdominal pain, diarrhea, partial bowel obstruction, fever, weight loss and extra intestinal manifestation (EIM) like arthralgia, skin rash, or ocular symptoms. But some of the symptoms are more frequently seen in either of two diseases. Despite some heterogeneity most studies reported diarrhea, hematochezia, perianal disease, and EIMs as being more common in CD whereas partial bowel obstruction, night sweat, and ascites predominate in ITB **(Table 1)**.[10-13] Longer disease duration also supports the diagnosis of CD over ITB, but a specific cut off for duration is not available.[12] A recent meta-analysis reported that diarrhea, hematochezia, perianal disease, and EIMs favored the diagnosis of CD, while fever, night sweats, lung involvement, and ascites favored the diagnosis of ITB.[14]

Endoscopic Appearance

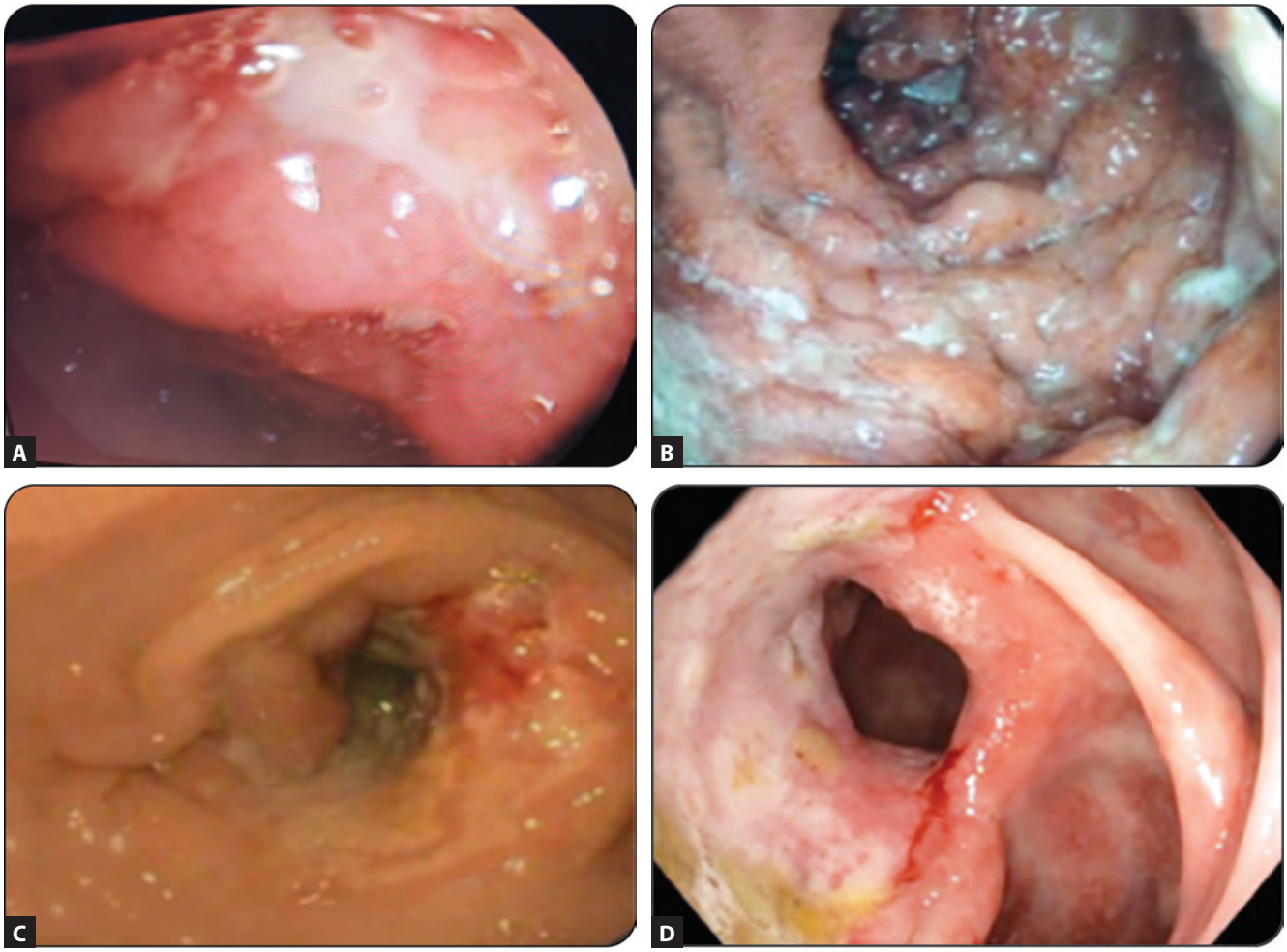
Endoscopic features in CD and ITB have been well described. Albeit some overlap, left colonic involvement, presence of longitudinal ulcers, aphthous ulcers, cobblestoning, and skip lesions are more common in CD whereas presence of transverse ulcers and patulous ileocecal valve are more common in ITB **(Table 1 and Figs. 1A to D)**.[10,11,13,14] Lee et al. described a predictive model based on four common endoscopic findings in CD (anorectal lesion, longitudinal ulcers, aphthous ulcers, and cobblestone appearance) and ITB (less than 4 segment involvement, patulous IC valve, transverse ulcers, and pseudopolyps). A score of +1 and –1 was assigned for each parameter of CD and ITB respectively. Total score >0 indicated the diagnosis of CD with a PPV of 94.9% and score <0 indicated diagnosis of ITB with a PPV of 88.9%.[15]

TABLE 1 Features differentiating CD and ITB

	Favoring Crohn's disease	*Favoring ITB*
Clinical features	• Chronic diarrhea • Hematochezia • Perianal disease • Longer duration of symptoms	• Ascites
EIM	• Peripheral arthropathy • Aphthous ulcers • Any/multiple EIMs	
Endoscopic features	• Left as well as right colonic involvement • Longitudinal ulcers • Aphthous ulcers • Cobblestoning	• Transverse ulcers • Ileocecal valve involvement
Histology (minimum 6–8 biopsies from the ulcerated and inflamed area)	• Microgranuloma	• Large caseating confluent granuloma
Radiology	• Long segment involvement • ≥3 segments involvement • Comb sign • VF/SF >0.63 • Pseudosacculation	• Ileocecal involvement • Lymph node >1 cm • Necrotic lymph node • <3 segment involvement • Short segment involvement

Histopathology

Both these diseases are chronic granulomatous disease of the GI tract and share many histopathological features



Figs. 1A to D: Endoscopic images. (A) Deep longitudinal jejunal ulcer in a patient with Crohn's disease. (B) Cobblestoning in a patient with Crohn's disease. (C) Ulcerated stricture in a patient with ITB. (D) Strictured IC valve with gaping in a patient with healed ITB

like architectural abnormalities (crypt distortion, crypt branching, or crypt loss), chronic inflammation (chronic inflammatory infiltrate, increased IEL, basal plasmacytosis) and granulomas.[10,16,17] But there are subtle differences which can be helpful to discriminate these two pathologies. As reported by Pulimood et al., granulomas are more common in tuberculosis than CD and tubercular granulomas are usually multiple (>5–10/HPF), large (>200 μm), confluent, located more in submucosa and with central caseation which is almost pathognomic for ITB while the granulomas in CD are sparse, small and poorly organized (microgranuloma).[17,18] Apart from granuloma, ulcers lined by epitheloid histiocytes and disproportionate submucosal inflammation favors the diagnosis of ITB, on the other hand focally enhanced colitis is characteristic of CD. A recent meta-analysis also echoed similar findings.[19] One of the major limitations of HPE is that more often we do not find granuloma in biopsy specimens to characterize it. Minimum 6–8 biopsies must be taken from the ulcerated and inflamed area to mitigate this problem.

Microbiology

One of the major challenges of diagnosing ITB is the poor sensitivity of microbiological tests to detect the bacilli **(Table 2)**. ITB is a paucibacillary disease, so demonstrating the organism is difficult. Acid fast bacillus (AFB) staining in a biopsy specimen has a sensitivity of 2.7–37.5% as reported in different studies.[20-22] Although culture of intestinal biopsy in Lowenstein Jensen medium is the

TABLE 2 Sensitivity of different microbiological tests for ITB

Diagnostic tests	*Sensitivity*
AFB smear[20-22]	(2.7–37.5)%
Culture (LJ/BACTEC)[21-23]	(19–50)%
TB-PCR[24]	47%
Gene-Xpert MTB/RIF[20,25]	(8.1–32)%

gold standard, it has been replaced largely by BACTEC culture which is less time consuming. Most of the studies have reported less than 50% culture positivity rate in biopsy from ITB patients.[8,21-23] Polymerase chain reaction targeted against IS6110 (TB-PCR) as a stand-alone test is not diagnostic for ITB but can help in diagnosis. Jin et al. in his meta-analysis reported a pooled sensitivity of 47% and specificity of 95% for TB-PCR in intestinal biopsy.[24] Gene-Xpert MTB/RIF in the intestinal biopsies has not been well studied in patients with ITB. In a study of 37 ITB patients it showed sensitivity of 8.1% and specificity of 100%.[20] Another study by Bellam et al. reported sensitivity of 32% and specificity of 100%.[25]

Radiology

CT/MR enterography are the preferred imaging modalities for evaluating and differentiating between patients with ITB and CD. Along with access to whole of the GI tract, cross sectional imaging has additional advantage as it can detect other significant findings like peritoneal or omental involvement and mesenteric or intra-abdominal lymphadenopathy. CT findings commonly seen in patients with CD are left colonic involvement, multifocal (>3 segments) or long-segment involvement, comb sign, and pseudosacculation. On the other hand, involvement of ileocecal area, short segment involvement (<3 cm), and presence of lymph nodes larger than 1 cm are more common in ITB.[26,27] A predictive model based on three characteristics [long segment (>3 cm) involvement, >1 cm lymph node, ileocecal involvement] had a specificity of 90% in differentiating CD from ITB.[27] A meta-analysis involving six studies concluded that necrotic lymph nodes had the highest diagnostic accuracy (sensitivity 23%, specificity 100%) for ITB diagnosis, and comb sign (sensitivity 82%, specificity 81%) followed by skip lesions (sensitivity 86%, specificity 74%) had the highest diagnostic accuracy for CD diagnosis[28] **(Figs. 2A to D)**.

Patients with ITB may also have evidence of concomitant pulmonary involvement. 3–25% of ITB patients show evidence of healed or active pulmonary TB on chest X-ray.[29] Data from our centre (not published) indicates addition of CT chest (in place of chest X-ray) with CT enterography can significantly increase the sensitivity of diagnosing ITB.

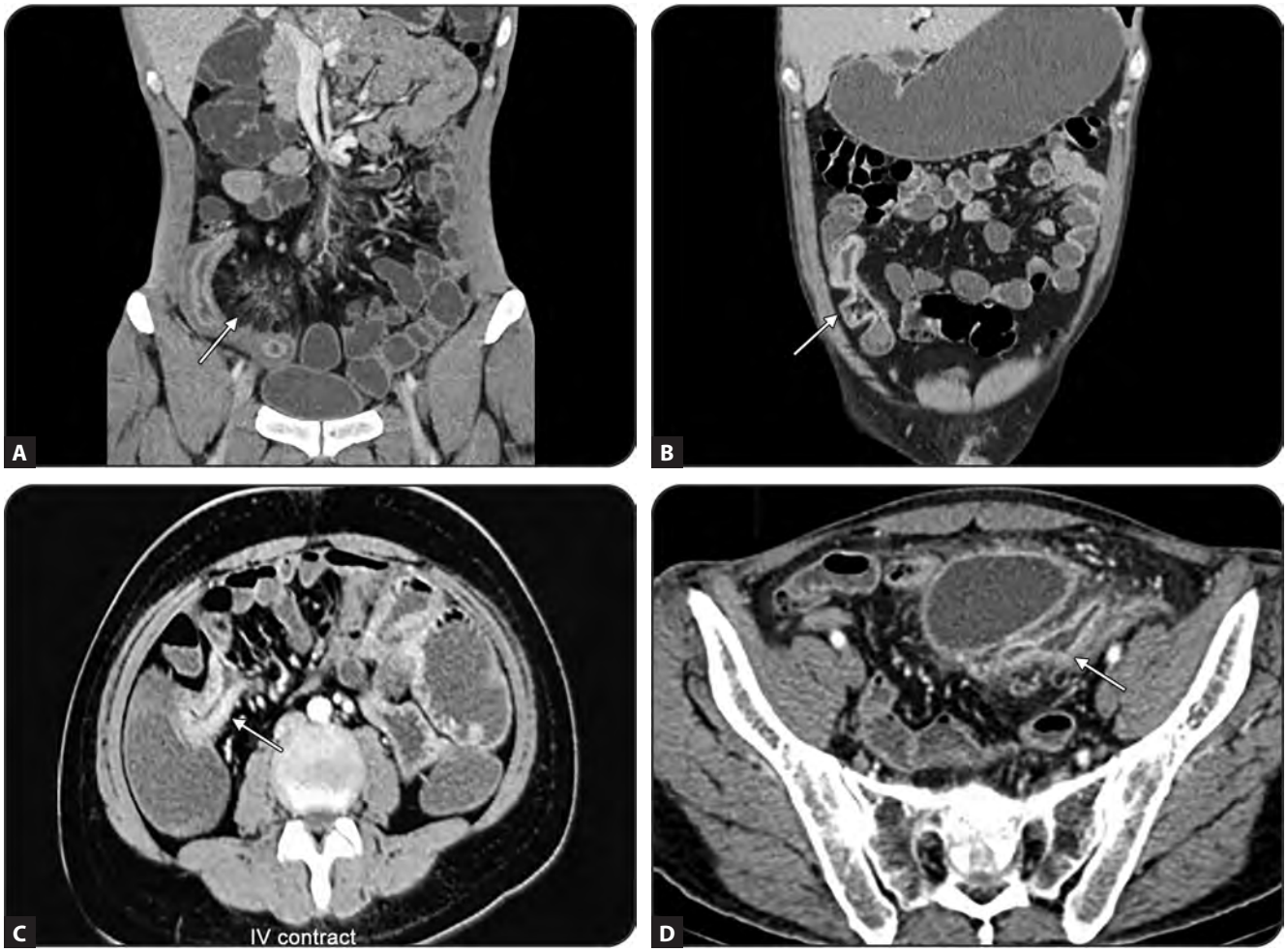
Adjunct Tests

Both interferon gamma release assays (IGRA) and Mantoux are predictive of latent TB rather than active TB; hence, a positive or a negative IGRA will neither rule in nor rule out the diagnosis of ITB. Positive Mantoux has been reported in 50–100% patients with ITB patients whereas meta-analysis on IGRA reported a pooled sensitivity of 74% and specificity of 87% in differentiating ITB from CD.[30,31] Both these tests provide supporting evidence but are not diagnostic.

Another serological test, anti-saccharomyces cerevisiae antibody (ASCA), has been investigated for this purpose but one study from India and a recent meta-analysis denied any significant role.[32,33]

Therapeutic ATT Trial

As we have discussed above, all these investigations have limited diagnostic accuracies and despite all these tests, in some cases it is nearly impossible to conclusively diagnose ITB or CD. Treating with steroid in such cases can be disastrous if the patient has underlying ITB, so trial of ATT is almost imperative for further management of such a case. A recent retrospective study from Korea reported that 17.9% CD patients were misdiagnosed as ITB and 10.8% patients of ITB were misdiagnosed as CD before the correct diagnosis being made. Forty-eight percent of ITB patients required therapeutic ATT trial for the final diagnosis.[34] Asia-Pacific consensus statements for CD have also advocated ATT trial in a patient with CD/ITB dilemma, and the diagnosis of CD should be considered in a patient who does not respond to ATT, and subsequently responds to CD-specific therapy.[35] But the big question is the timeline of ATT trial, when to say a patient as non-responder and how to assess response. A recent study from our centre compared the response between two groups (CD patients who received ATT as therapeutic trial and ITB patients). By 3 months more than 90% of patients with



Figs. 2A to D: Radiologic images (CT enterography). (A) Stricture with comb sign in a patient with CD. (B) Pseudosacculation in a patient with CD. (C) Thickening of terminal ileum with IC valve involvement in a patient with ITB. (D) Long segment stricture with enhancement and proximal dilatation in a patient with CD

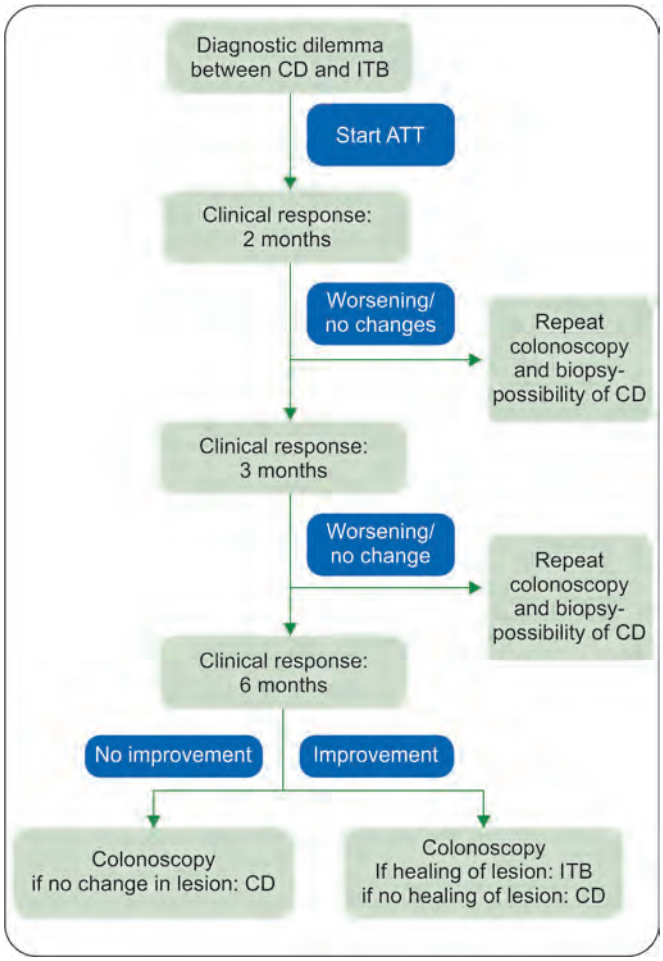
ITB, and up to 1/3rd patients with CD responded to ATT but response was ill-sustained in patients with CD, and up to 80% of them worsened on follow-up. Moreover, repeat colonoscopy at 6 months of treatment showed mucosal healing in 100% patients with ITB, whereas less than 5% of patients with CD had an endoscopic response.[36] Based on this study following algorithm has been proposed which is now a routine practice **(Flowchart 2)**.

Pitfalls of the Strategy

One of the major concerns is that should we consider possibility of MDR-TB while designating a case as CD on the basis of non response to ATT trial. There is not much data on prevalence of MDR-TB in gastrointestinal tuberculosis. Lin et al. reported MDR-TB rate of 13% among patients with lower gastrointestinal TB.[37] But an Indian study reported a prevalence of only 5.4% among patients with abdominal TB and another study from our center found no cases of MDR-TB among patients with ITB.[20,38] Moreover ITB being a paucibacillary disease is expected to have a low rate of drug resistance.

Although most ITB patients respond well to ATT, study from our centre showed that only one-fourth of patients with ITB related stricture had resolution of stricture after ATT and majority had symptoms pertaining to stricture even after ATT.[39] This observation should also be kept in mind during assessment of response to ATT.

Flowchart 2: Algorithm for follow-up of a patient with CD/ITB dilemma who has been initiated on a therapeutic ATT trial



Predictive Models

Due to limitation in accuracy and sensitivity of any single characteristic, several multiparametric predictive models incorporating more than one feature across single or multiple diagnostic modalities have been described. A multicentre study from India described hematochezia, weight loss, sigmoid colon involvement, and focal enhanced colitis as independent predictors for diagnosis of CD/ITB, and a score based on these variables had an AUC of 0.91 in differentiating CD from ITB.[10] Another Korean study included age, gender, diarrhea, transverse ulcer, longitudinal ulcer, sigmoid colon involvement, and suspicion of pulmonary TB in their predictive models. The AUC for differentiating CD and ITB was 0.98, and on validation in a separate cohort, the accuracy was similar with an AUC of 0.92.[40] But most of these predictive models have their own limitations in terms of application in clinical practice and these have not been widely validated across other population.

Recent Advances in this Field

There have been many recent advances in the field regarding newer biomarker or other investigational parameters to differentiate these two diseases.

Mesenteric fat proliferation and creeping fat have long been associated with active CD.[41,42] A Korean study described increased visceral fat (VF) in patients with CD and ratio of VF and subcutaneous fat (SF) can help in differentiating CD from ITB.[41] Yadav et al. in his study established a cut off value for VF and SF ratio. At a cut off value of 0.63, VF/SF ratio was found to have a sensitivity of 82% and specificity of 81% in differentiating CD from ITB. It showed equally good diagnostic accuracy when applied to the validation cohort.[42] Another study from our centre combined VF/SF ratio with other features on CT scan and showed that combination of VF/SF >0.63 and long segment involvement was almost exclusive for diagnosing CD.[43]

T-regulatory cells (CD4+CD25+FOXP3+) are regulators of inflammation and these are increased in peripheral blood and at the site of infection in patients with pulmonary TB. In a preliminary study, it was shown that FOXP3 mRNA expression was upregulated in the colonic mucosa of patients with ITB as compared to CD.[44] We further showed higher frequency of FOXP3+ T regulatory cells in peripheral blood of patients with ITB compared with CD. A value of more than 32.5% for FOXP3+ cells in peripheral blood could differentiate ITB and CD with 75% sensitivity and 90.6% specificity.[45] This has also been validated in a separate cohort of 73 patients.[46] VF/SF ratio and circulating FOXP3+ cells in peripheral blood are specially helpful where differentiation between CD and ITB is not possible on the basis of routine radiological, histological, and microbiological evidence.

One recent study reported that immune-histochemistry (IHC) for CD-73 in biopsies could differentiate granulomas of CD and ITB with high diagnostic specificity but it has not been replicated in other studies.[47]

He et al. developed a nomogram based on seven parameters that were significant on regression analysis including age, transverse ulcer, rectum involvement,

skipped small bowel involvement, target sign, comb sign, and IGRA (for model 1) or Mantoux test (for model 2), respectively. Nomogram 1 showed a sensitivity of 86.8% and specificity of 90.9% while nomogram 2 showed 84.2% sensitivity and 100% specificity for differentiating CD from ITB in the validation cohort.[48]

One of the most significant findings was described recently from our centre. It described that patients who received ATT before an eventual diagnosis of CD have higher chance of progressing to stricturing or fistulizing disease compared to patients who are ATT naive (OR: 11.05; 95% CI 3.17–38.56, p <0.001) and they also have higher risk of surgery than ATT naive patients (HR: 3.22; 95% CI, 1.46–7.12, p = 0.004) on long-term follow-up.[49] This finding can challenge our practice of therapeutic ATT trial in cases with diagnostic dilemma. This also highlights the importance of accurate discrimination between these two diseases right at the outset and the importance of close follow-up and early assessment in suspected cases.

TB on CD: The New Challenge

As more and more patients of CD are now being treated with anti-TNF therapy in developing countries like India, a new challenge is setting in. Agarwal et al. reported that 11.6% IBD patients on infliximab therapy developed reactivation of tuberculosis despite that all these patients were screened for latent TB before the initiation of therapy and most of them developed it within 1st year of therapy.[50] Similar findings have also been reported in other studies.[51] A recent meta-analysis compiled 128 studies (130,114 IBD patients) and reported a pooled prevalence of 0.08% for developing TB on anti-TNF therapy. The risk increased with increasing TB burden, pooled prevalence being 0.02%, 0.21%, and 1.59% for low, intermediate, and high TB burden countries, respectively. Seventy-three percent of patients who developed TB had no evidence of latent TB on screening. Apart from therapeutic challenge, this tubercular reactivation poses a new set of diagnostic dilemma, as to decide whether it was ITB to start with or it is only tubercular reactivation on immunosuppression.[52]

Conclusion

Since time long the deceptive similarities between CD and ITB has been a matter of debate among clinical practitioners. With scientific advances and availability of newer radiological tools and biomarkers, we have made significant progress in solving the clinical dilemma. But it needs careful interpretation of all diagnostic evidence and clinical judgment on case to case basis. And with newer challenges like "TB on CD" or ATT complicating disease course of CD patients, we need to be more accurate, more precise, and more vigilant in diagnosing and managing patients with ITB and CD.

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CHAPTER

134 Acute Liver Failure and Acute-on-Chronic-Liver Failure in India: How They Are Different from West?

Subrat Kumar Acharya

Abstract

Acute liver failure (ALF) and acute-on-chronic-liver failure (ACLF) are severest forms of liver failure with high short-term mortality. Their definition and diagnosis depend upon the clinical phenotypic presentation and global consensus on each of these entities are lacking due to differences in regional etiologies of liver injury which is considered to be important determinants of the natural course and clinical manifestations of such liver failures. These differences have been discussed in the present chapter. While hepatitis virus(es) are the major causes of ALF and to some extent in ACLF India, etiologies of ALF in West is heterogenous with Paracetamol overdose as the major causes. Pregnant females in India are more prone to contact hepatitis virus(es), particularly hepatitis E virus and develop more severe hepatitis leading to more frequent ALF than similar patients in males and non-pregnant females. Such events in west is infrequent. Cerebral edema and infections are major complications in ALF leading to high mortality. Prognostic models in ALF are important to identify patients for liver transplant which is associated with significant improved survival in those who are likely to die with expectant therapy. The prognostic models in ALF described from west have been found to perform less efficiently than the recently described ALF-Early Dynamic model (ALF-ED) from India. The differences and controversies in definition of ACLF in Asia Pacific region including India and West (EASL-AASLD) have been discussed in the present chapter. At present Alcohol has emerged as a major cause of ACLF globally. Hepatitis virus(es), drugs, complementary alternative medicines induced acute hepatic insult over pre-existing chronic liver disease are other major causes of ACLF in India while infection, variceal bleed, and alcohol are the major causes of ACLF in west. Occurrence of sever systemic inflammatory response in such patients leading to multiorgan dysfunction results in high short-term mortality. Within 3–7 days of onset of ACLF the prognostic models described both from Asian Pacific region and west predicts mortality assisting in providing to liver transplant to such patients.

Introduction

In health, the liver has multiple functions, and liver failure usually denotes loss of these functions, often threatening life.[1] The concept of liver failure is getting clarified over time and have several phenotypes. The most frequent form of liver failure encountered in clinical practice is the chronic liver failure as in cirrhosis of the liver. In such patients, development of varices, ascites, variceal bleed, encephalopathy, renal failure, and infections gradually sets in over a long period, in many months to many year.[2] In contrast to the above sequential events in cirrhosis, some of them do present with rapid and sudden deterioration in their liver function and liver reserve resulting in features of acute decompensation (AD) (sudden and rapid development of ascites, encephalopathy, variceal bleed), often with occurrence of jaundice, prolonged International Normalized Ratio (INR) with or without kidney failure and infrequently with involvement of other extrahepatic organ dysfunction or failure over few days or weeks. Such rapid AD usually ensues subsequent to an

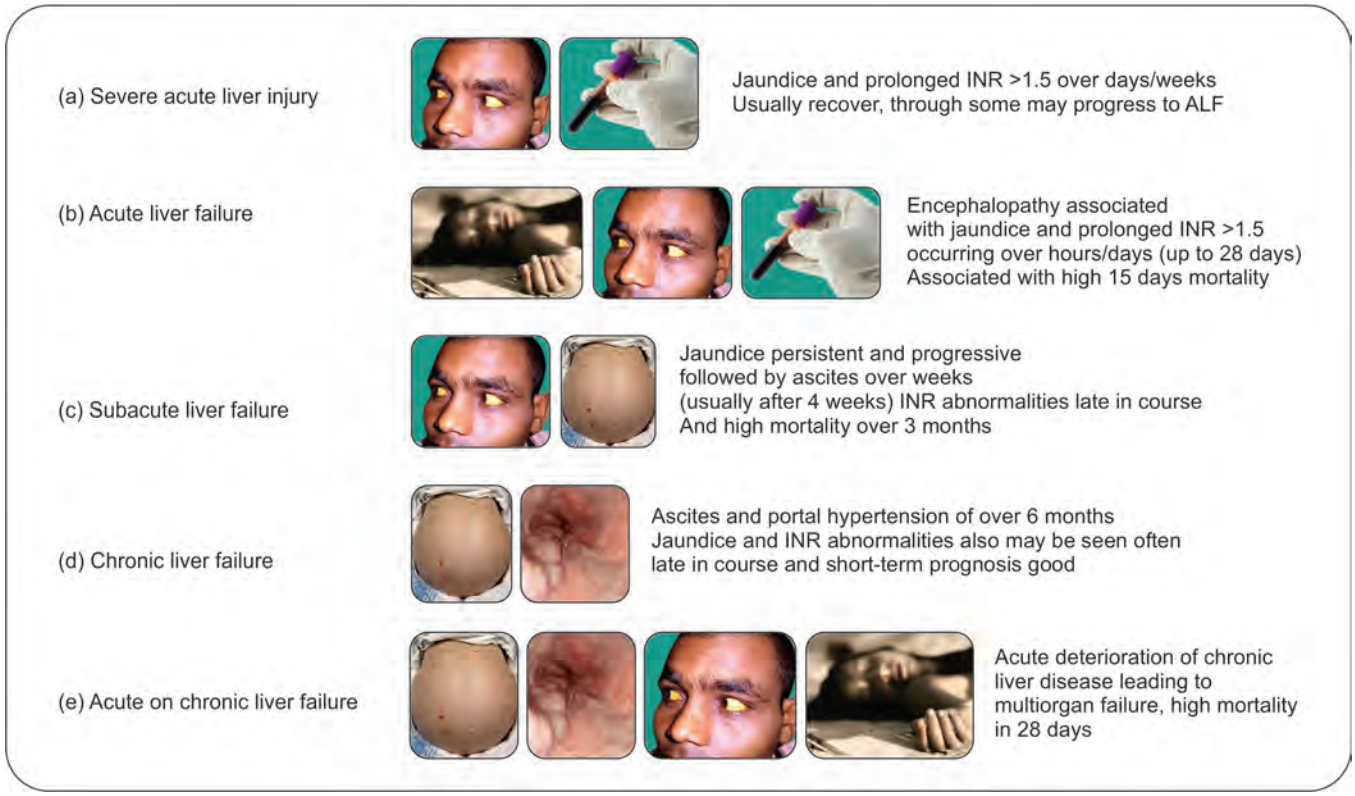


Fig. 1: Five phenotypes of liver failure. In (a), (b), and (c), there is no previous known liver disease. However, it unclear if presence of a subclinical mild liver disease will change presentation, course and outcome, e.g., in patients with non-alcoholic fatty liver, silent autoimmune hepatitis, Wilson's disease, or inactive hepatitis B carrier state. Since classification is based on clinical presentation, phenotype concept helps to classify patient for planning management

acute precipitating event like acute hepatic insult (drugs, super infection of another hepatitis virus or reactivation of underlying etiology of existing chronic liver disease), or a sequel of cirrhosis like a variceal bleed, infection thus causing, rapid loss of hepatocyte reserve in an already compromised liver.

These later patients die quickly and a 28 days mortality of around 50% (high short-term mortality) have been documented in many reports.[3-5] This is in contrast to those patients with cirrhosis who gradually decompensate over years in whom the annual mortality depending upon the decompensating event is much lower.[2] Therefore, the former patients are identified as a distinct group with liver failure and named as "Acute-on-Chronic Liver Failure (ACLF)," albeit, there is no universally accepted consensus definition of this entity.[3-5]

However, various hepatotoxic agents like drugs, hepatitis viruses, and ischemia may cause acute hepatitis in individuals with naïve liver. Patients with acute hepatitis may also have variable degree of liver injury with variable clinical manifestation and natural course such as: conventional acute hepatitis with high spontaneous recovery, severe acute liver injury (sALI), acute liver failure (ALF), or subacute hepatic failure (SHF).[6] The later two forms are associated with high short-term mortality. So the presentations of liver failure in a naïve liver could be acute or subacute. **Figure 1** depicts various forms of Liver Failure.[7]

Patients with acute hepatitis having persistent or progressive jaundice for several weeks with coagulopathy (INR >1.5), but without encephalopathy, are recognized as sALI.[6] Appearance of encephalopathy in such a patient with in few hours to days or weeks is termed as ALF **(Fig. 2)**.[7] Whereas, some with acute hepatitis, in whom the jaundice is prolonged or increases for over a month followed by appearance of ascites (as the manifestation

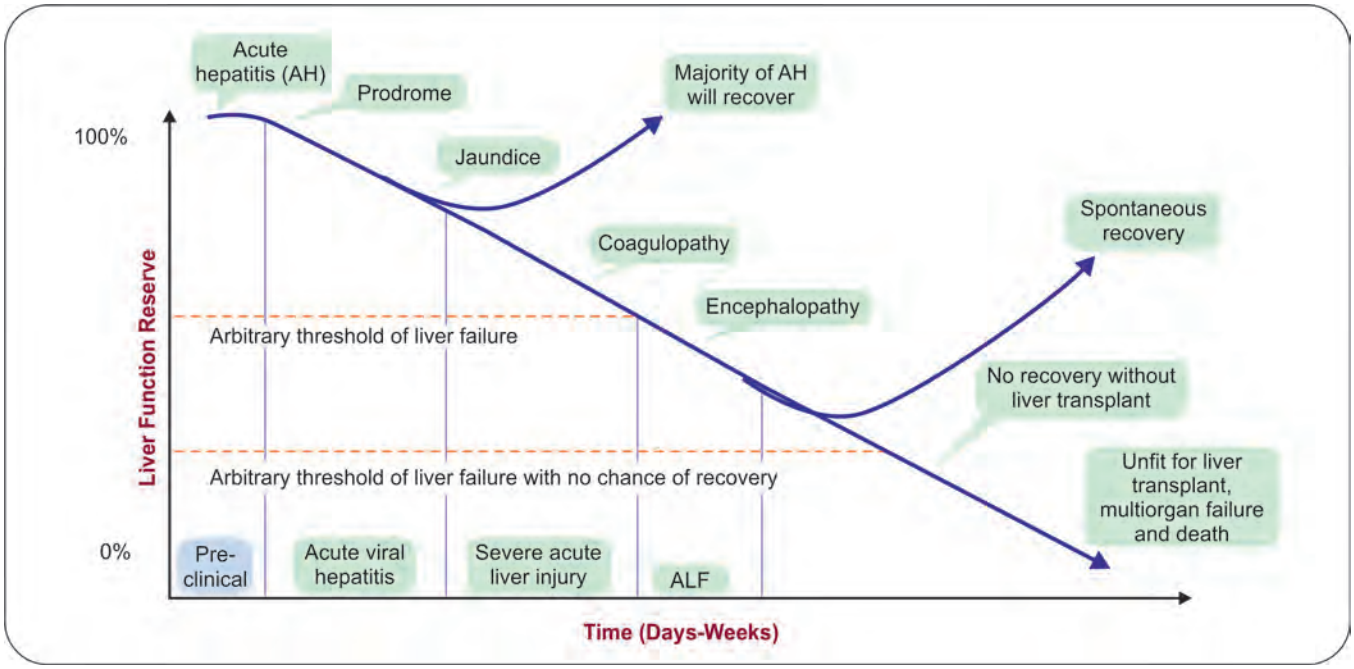


Fig. 2: Clinical course of acute liver failure as seen in Indian subcontinent after infection with a hepatitis virus or drugs or Complementary Alternative Medicine (CAM). As liver dysfunction proceeds rapidly, patient may slide from stage of acute hepatitis to severe acute liver injury and then to (or often directly to) acute liver failure. Deterioration may be seen over a few hours, days, or less often weeks

of liver failure), are identified as patients with SHF.[7] These entities of ALF, SHF, and ACLF are associated with high short-term mortality but the former two occur over a naïve liver, whereas the later ensues over a pre-existing chronic liver diseases either known or diagnosed previously or unknown carrying a silent underlying chronic liver disease[3-5,7] Their diagnosis is based on their characteristic phenotypic presentation with absence of any evidence of presence of chronic liver disease in the former two and with direct or indirect evidence of clinical/endoscopic/imaging or histologic evidence of chronic liver disease in the later. The characteristic differences between these three forms of liver failure have been depicted in **Table 1**.

The present chapter is not intended to include the management of ALF and ACLF or any other form of liver failure and they need a complete chapter by themselves.

Acute Liver Failure

Definition

Trey and Davidson in 1969 first defined ALF "as appearance of encephalopathy within 8 weeks of the onset of acute hepatitic illness, in an individual without pre-existing liver disease." However, over the ensuing time, regional difference in etiology, natural course, complication, and some demographic features in ALF were reported, resulting in variable definition of ALF.[8] Each definition included encephalopathy as an essential criteria but some centers additionally included prolonged INR (>1.5) or prothrombin time (PT) prolongation by more than 15 seconds over control or prothrombin activity (<40%) as an additional criteria to define ALF.[8] The essential difference in various definitions of ALF was "the interval between onset of acute hepatitis illness and subsequent encephalopathy and varied from 2 to 26 weeks.[9] In India, hepatitis virus(es) are the most frequent cause of ALF and encephalopathy occurred in all patients within 4 weeks of onset of jaundice.[10,11] The American Association for the Study of Liver Diseases (AASLD), however defines ALF if encephalopathy ensues within 26 weeks of onset of acute hepatitis symptoms.[9] Indian National Association for the Study of Liver (INASL) consensus statement on ALF published recently defines ALF "A clinical syndrome characterized by encephalopathy, jaundice, and prolonged PT (INR >1.5) developing in a patient without pre-existing liver disease within 4 weeks of the

TABLE 1 Clinical differentiation between acute liver failure (ALF), subacute hepatic failure (SHF), and acute on chronic liver failure (ACLF)[7]

Criteria	*ALF*	*SHF*	*ACLF*
Previous liver status	Naïve – No h/o of previous liver disease	Naïve-No history of previos liver disease	Presence of underlying liver disease either in history or by evidences accrued at presentation
Clinical			
Presentation:			
• Encephalopathy	Present (Definition)	Absent at presentation	Usually absent at presentation
• Jaundice	Usually present	Always present	Always present
• Overt features of Cerebral edema	In 50–80%	Usually absent	Usually absent—occurs as terminal event
• Ascites	Invariably absent	Always present	Always present
• Liver size	Small—not palapable—Liver span reduced markedly	Usually not small—Liver span normal or increased	Not small—may be palpable, span is not reduced in most
• Precipitting factors	Not identified—primay cause of liver damage causes liver failure	Not identified—Primary cause with impaired regeneration cause liver failure	Usally present—Sepsis, variceal bleed, super infection, Superadded DILI, alcoholic binge, flare of underlying cause of chronic liver disease, idiopathic
Laboratory Parameter			
Transaminases	Markedly raised 15–30 times ULN	Moderately raised—5–10 times ULN	Minimally or moderately raised depending upon Precipitating factors—3–5 times ULN
INR	>1.5	Usualy prolonged variably	Prolonged (>1.5 as per APASL definition)
Bilirubin	Markedly raised	Markedly raised	Moderately raised
Albumin	Usually normal—may be decreased in Pregnant females	Initially normal—reduces over time	Usually low than normal
Arterial Ammonia	Markedly raised (100 micromoles/L	Not raised or moderately raised	Mildly raised—may be raised in flares or super added liver injury (usually less than 100 micromoles)
Natural Course			
Duration of disease course	Usually 2–7 days	Months—4 week to 6 months	4 weeks to 1 year
Imaging	Naïve small liver	Regenerating nodules—resulting in humps on liver surface	Evidence of chronic liver disease with or without porto-systemic collaterals
Endoscopy	No varices (but not usually done)	In 30% small varices may present	More than half ususlly have varices
Histology	Features of acute hepatitis with sub massive necrosis of liver	Acute hepatitis with bridging necrosis	Features of Chronic liver disease with or without super added acute liver damage
Etiology	Mostly hepatitis viruses, ATT drug	Hepatitis viruses, drugs	Alcohol, hepatitis virus, NAFLD, other cause of CLD, Precipitating factors in preexisting CLD

APASL, Asian Pacific Association for the Study of Liver; CLD, chronic liver disease; INR, international normalized ratio; NAFLD, non-alcoholic fatty liver disease; ULN, upper limit of normal

onset of symptoms. A few patients presenting with sALI mostly due to DILI may develop encephalopathy later than 4 weeks up to 8 weeks."[7] Further, because the etiology of ALF is heterogenous in the West, all patients clinically do not have similar natural course and subclassification of ALF depending upon the interval between onset of acute hepatitic illness and encephalopathy has been suggested by British and French.[7-9] The French subclassification categorizes ALF in to:

- Fulminant Liver failure (encephalopathy occurring within 2 weeks of onset of jaundice) and
- Subfulminant (encephalopathy occurring between 2 and 12 weeks of jaundice).

The British subcategorizes them to three groups:

- Hyperacute liver failure (encephalopathy within 7 days of onset of jaundice
- ALF (encephalopathy between 7 days and 4 week)
- Subacute hepatic failure (SHF) (encephalopathy within 5–24 weeks of onset of jaundice).[11]

These regions noticed that those presenting with hyperacute or fulminant liver failure had better survival than the other ones and therefore subcategorized them and such events do influence on deciding high risk patients for liver transplantation. However, in India, large series have reported that rapidity of onset of encephalopathy (hyperacute) and the others had similar outcome probably due to homogeneous etiology. Therefore, in India, most patients are either hyperacute or acute without any difference in outcome and practically do not need any subcategorization.[11]

Etiology

The differences in etiology of ALF among the adults across the world are striking **(Tables 2 and 3)**.[7,9] In India, viral etiology predominates, which is responsible for

TABLE 2 Etiological profile in ALF across various centers in India[7,9,11]

Center/Year	*Number*	*HAV*	*HBV*	*HEV*	*Cryptogenic/ Non-A-Non-E*	*Drugs*	*Miscellaneous*
Delhi, 1986–2015 (AIIMS)	1462	2%	8.8%	28.7%	36.0%	ATT- 7.0%	Dual infection (4%), chronic markers (9%), No serology report (4%)
Delhi (ILBS), 2011–2016 Pediatric Population	109	39.4%	0	1.8%	14.6%	11%, n=12 ATT- 4, antibiotics 3, CAM 2, acetaminophen 2, valproate 1	Metabolic liver disease 13.2% Parvovirus-2.7%, EBV 0.9%, VZV 0.9%, Others-15.5%
Assam, 2207–15	255	29.8%	3.1%	13.3%	43.9%	0	Amatoxin 6.2%, AIH 0.7%, combined viruses 2.7%
Bangalore, 1997–2017 Only drug induced ALF	128	-	-	-	-	ATT-72.4%, anti-epileptic 10%, dapsone 5.5%, other drugs 13%	-
Kashmir, 1989–1996	180	2.2%	13.9%	43.9%	31.1%	1	HDV 1.1%, HCV 7.2%
Kolkata, 2005–2007	45	20%	8.8%	13.3%	22.2%	2.2%	Wilsons 2.2%, malaria 2.2%, dual viral 15.5%
Lucknow, 2003–2010	52	23%	12%	23%	15%	15% All ATT	Dual infections 48%, no serology 4%
New Delhi (ILBS) 2011–2018	61	13.1%	11.4%	13.1%	27.8%	14.7% All ATT	Others 19.6%
Chandigarh, 1998	204	Viral hepatitis 91.1%		7.4% All ATT	Others 1.5%		

TABLE 3 Etiologies of ALF in other countries[7,9,11]

UK (1999–2008)	422	2%	5%	1%	17%	Paracetamol 57%, Other drugs 11%	7%
USA	1696	2%	7%		13%	Paracetamol 46%, Antimicrobial agents: ATT, antibiotics, antifungals, antiepileptics, NSAIDs and antimetabolites 12%	Autoimmune 6.5% Ischemic 5%, Wilsons 1% Budd-Chiari 1% Pregnancy 1% Other causes 5%.
France (1986–2006)	363	5%	28%		18%	Paracetamol 7%, Other drugs 21%	21%
Germany (2008–2009)	109	4%	10%	4%	24%	32% (most importantly Phenprocoumon: 23% of non acetaminophen cases) Valproate, NSAIDs, sertraline, clindamycin	Autoimmune 3% Wilsons 3% Budd-Chiari 2% Malignancy 3% Pregnancy 3% Amanita 2% Others 4%
Australia (1988–2001)	80	4%	10%		34% (Non-A Non-B)	Paracetamol 36%, Other drugs 6% (Nitrofurantoin Sodium valproate Isoflurane and ketorolac)	Wilsons 7% Budd-Chiari 3%
Japan (1998–2006)	856	6%	42%	1%	3%	10% (ATT, Acetaminophen), anti-cancer agents, allopurinol and Acarbose	Autoimmune 7% Unknown 30%

90% of ALF cases. The various viral etiologies in order of frequencies those reported in published studies include, non-A to non-E in about 40%, HEV in approximately one third, whereas HBV and HAV causing ALF is less frequent.[7,10,11] Among other causes of ALF, drugs—especially antituberculosis drugs—account for 6% of the cases of ALF. Whereas in the West, where safe drinking water is available, feco-orally transmitted viruses (HEV and HAV) are not seen; drugs and toxins are major causes of ALF and acetaminophen overdose is the most common factor responsible. **Tables 2 and 3** highlight the different etiologies of ALF across the world.[7,9]

Complications of ALF

Patients with ALF may develop various life-threatening complication but their magnitude varies regionally.

- *Renal failure:* In the western reports renal failure in ALF was documented in 40–80% of ALF. NSAIDs and acetaminophen are the dominant cause of ALF in the West and these agents are well-known nephrotoxic agents. In contrast, hepatitis virus(es) being the most common cause of ALF in India do not cause direct nephrotoxicity and therefore renal failure have been reported in about 10% of the patients.[7,9,11] The other causes associated with increased incidence of renal failure include amanita poisoning and trimethoprim-sulfamethoxazole toxicity.
- *GI bleed:* Gastrointestinal bleed has been reported less frequently from all the part of the world, despite associated coagulation abnormality in these patients. The usual reported frequency of gastrointestinal bleed in most series varied between 7% and 20%.[9]
- *Cerebral edema:* Frequency of overt cerebral edema in ALF have been reported to be present in 58% of the Indian patients at hospitalization.[12] Eighty-two percent patients of these with cerebral edema died in comparison to 44% mortality in those without it.[11,12] Cerebral edema irrespective of the region was reported to be one of the main causes of death in ALF. Both from the east as well from the West, cerebral edema has been reported more frequently as the encephalopathy grade worsens.[7,9,11,12] Intracranial pressure estimation assesses the intracranial hypertension subsequent to cerebral edema. With the wide availability of such

methods, presence of intracranial hypertension due to cerebral edema has been documented in all patients with ALF irrespective of the grades of encephalopathy.[9] However, in the West, over the years, improvement in awareness about ALF, early referral to tertiary care center and improved intensive unit care, frequency of cerebral edema in the West is being reported to be less frequent than in former years.[9]

- *Sepsis:* Infection in ALF is frequent and reported from both West and India.[9] ALF is a condition associated with innate immune system compromise occurring rapidly.[7] Therefore infection in them occur very early in the course of the disease.[9,12] The incidence of infection in the authors' experience, from a single center in India is around 55%, the most common site of infection is respiratory tract and the commonest organisms are Gram-negative bacilli.[9,11] Quarter of the patient in the series reported by the author had also fungal infections.[11] From the UK, the report on ALF in early series, identified that about 90% of their patients develop infection, which included bacterial sepsis in 80% and 32% had fungal infection.[9] In more recent reports the predominant organisms reported from the West are Gram-negative but the initial reports from the UK the gram positive organisms were isolated more frequently.[13]

Key points: Complications

- Renal failure in ALF is frequent in the West, because the bulk of the patients are due to drugs (Acetaminophen is associated with direct nephrotoxicity)
- Renal failure in ALF is infrequent in India because of predominant viral etiology
- Sepsis is frequent in ALF. In the West and the bacterial species are mixed between Gram-positive and Gram-negative whereas Gram-negative organisms are common in India. In about quarter of Indian patients' fungal infection has also been documented

Gender, Pregnancy, and Acute Liver Failure

All over the globe, in ALF females predominates except in Japan where the sex distribution is even between the two genders. Despite the fact that the etiology across the region are distinct, the predilection of female sex to develop ALF remains unclear. In India as described earlier, hepatitis virus(es) are the major etiological agent particularly HEV. Various epidemiological as well as sporadic studies reveal that pregnant females are more prone than nonpregnant females and males to contact HEV infection and also develop severe liver diseases than similar male and nonpregnant females patients.[7,9] Further, it is believed that pregnant women with ALF than the ALF in nonpregnant women and males are more sick with higher complication rates and mortality. However, the later conjecture was not evidence based and a large study on pregnant ALF due to viral hepatitis from India disproved this conjecture indicating that in India pregnant females with ALF (except in Acute Fatty Liver of Pregnancy or severe pre-eclamptic toxemia induce ALF) do not benefit from the termination of pregnancy.[14] A summary of studies reporting pregnancy and ALF is shown in **Table 4**.[7,9]

The number of pregnant patients developing ALF is relatively small in the West and therefore do not constitute a major problem in management. In India, about 60% of the females with ALF in the child bearing age are pregnant whereas, the fertility rate among similar population in general is 2.9%.[9,14] It is believed that pregnancy is a immunocompromised state with predilection to contact various infections and manifest usually in more severe form. Multiple epidemics of HEV infection have been documented in India.[7] During such epidemics, pregnant females had more frequent infection (12–20%) than the men and nonpregnant women (2–4%) for unclear reasons.[9,15] The frequency of ALF among the pregnant females was also higher (10–22%) than similar men and nonpregnant women (1–2%).[7,9] This observation indicate that pregnant females are more prone as well develop more severe liver disease subsequent to HEV infection, which is the major cause of viral hepatitis as well as ALF in India. Therefore, the mortality was significantly higher among pregnant women with epidemic hepatitis (10–39%) than in the general population affected with similar hepatitis (0.06–12%).[9,11] In the sporadic setting, HEV is one of the most important etiology of ALF in India accounting for about 30–45% of patients hospitalized with ALF **(Table 2)**. However, the mortality in pregnant females has been found to be similar to that of nonpregnant females and males and is independent of the cause or trimester.[14] The reason for predilection of pregnant females to contact HEV and severe liver disease remains unclear. To elucidate this, viral and host factors in HEV-ALF were evaluated in one study.[15] The study reported more frequent progesterone receptor (PR) gene mutations (PROGINS) associated with reduced expression of PR and progesterone induced blocking factor (PIBF), a

TABLE 4 Studies reporting female predominance and role of pregnancy in ALF[7,9]

Country	No. of cases (N)	Number of females overall (%)	Pregnancy	Percentage of female patients with pregnancy associated liver failure	Etiology of ALF	Overall mortality (pregnant females)
USA	1696	1173 (69%)	16	1.5%		
UK	422	257 (61%)				
Germany	109	69 (63%)	3			33%
Australia	80	64 (80%)	-			
India	1015	590 (58%)	249	38.5%	59.4% (HEV)	54%
India	180	111 (62%)	49/83	59%	96% (HEV)	66%
France	363			2%		
Japan	856	423 (49%)	-			

higher IL-12/IL-10 ratio, and a high viral load. The author associated these changes to the poor outcome in HEV-ALF in pregnant females. Pregnancy as a predisposition to ALF in India could be due to: (1) large number of pregnant population (3%); (2) unavailability of clean drinking water; (3) predilection of pregnant females to contact HEV infection. Hepatitis E virus has been identified as a very important cause of severe liver disease in areas of world where more than 70% of the global population resides. The Global Disease Burden study by World Health Organization identified that, approximately 3.7 million people are infected by HEV annually and 70,000 of them die due to HEV induced severe liver disease of whom a large proportion are pregnant.[16]

Acute fatty liver of pregnancy (AFLP) on the other hand is more frequent in the West than in India.[7] Termination of pregnancy is required for improving prognosis in AFLP. However, termination of pregnancy may not be appropriate in pregnant females with HEV-ALF, because:

- ALF-HEV, in comparison to other causes of ALF, has lowest mortality,[17]
- the mortality in ALF-HEV with pregnancy, ALF-HEV in females without pregnancy and males with ALF-HEV are similar and not higher, indicating that in the pregnancy once ALF develops does not influence the natural course.[14]

Genotypes 1 and 2 of hepatitis E virus are prevalent in hyperendemic regions where the reservoir for HEV seems to be human, and cause outbreaks, sporadic acute hepatitis, ALF, and ACLF.[18] Genotypes 3 and 4 are more prevalent in the USA, Europe, and Japan, where the reservoir seems to be represented by pigs, and the zoonotic transmission is considered to be the cause of infection of human beings, leading to autochthonous acute HEV. Genotypes 3 and 4 have not been reported to be associated with severe liver disease and the majority of cases appear to represent subclinical infection.[19]

Key Points: ALF in Pregnancy

- West and Europe: Pregnant females account for 1–3% of cases
- India: 40–60% of females of child-bearing age with ALF are pregnant and HEV is the most frequent cause in them
- Mortality is not increased in pregnant ALF than the others
- Termination of pregnancy not indicated in such patients
- AFLP: Genetic predisposition, termination of pregnancy improves prognosis

Outcome

The etiology of ALF, which is regionally varied, influences outcome, particularly in the West where the etiology is heterogeneous. Paracetamol is the major cause of ALF in the West. Paracetamol induced ALF presents rapidly (hyperacute) with a spontaneous survival rate of 64% which is significantly higher than similar outcome due to other causes such as ALF due to idiosyncratic drug toxicity (spontaneous survival in 20% cases).[9,11] However, paracetamol induced ALF may progress very rapidly in some. The paracetamol being the frequent etiology in the West constitutes the bulk of all ALF patients in these regions and therefore the total number of deaths due to paracetamol toxicity exceeds all other diagnoses. Nearly one third of these patients who develop encephalopathy die. Paracetamol overdose whether suicidal or unintentional presenting with ALF has similar outcomes.[20]

In the India, acetaminophen overdose induced ALF is infrequent. The drug induced ALF are due to antituberculosis therapy (ATT).[21] The mortality in ATT-ALF has been reported to be 70%.[21] In India, about 90–95% of ALF are due to hepatitis viruses (homogeneous etiology).[7,9,11,12] ATT induced ALF constitutes about 6–7% of all ALFs.[21] Therefore, etiology could not be identified as an independent predictor of mortality.[9,12,21] However, when HEV as a separate group was compared with each individual other etiologies, such as ATT induced ALF and non-A non-E–ALF, etc. the survival frequency among HEV was reported to be significantly superior to other etiologies.[18,21] These survival frequencies reported are transplant-free survivals. Liver transplantation is established therapy in all end stage liver disease and with transplantation, overall survival exceeds 75%.[7,9]

Key points: Outcome
- West: Etiology affects the outcome, because etiology is heterogeneous
- India: Etiology in general does not influence the outcome, because etiology is almost due to hepatitis virus(es)
- Among hepatitis virus induced ALF, HEV has a better prognosis
- Commonest cause of drug induced ALF in India is antitubercular drugs and have high mortality

Prognostic Models[7,9,12]

Liver transplantation has been well established as a curative option in ALF.[9,11] Prognostic models are therefore necessary to identify patients who will need transplantation or should continue on medical therapy. Many prognostic models from all around the globe have been described.[7,9] Each of the prognostic models in summary have highlighted the following important facts. Age and etiology in most reports are important variables influencing survival. HAV, HEV, acetaminophen toxicity, and acute fatty liver of pregnancy induced ALF, survive more frequently.[7,9,12] Patients with drug induced, autoimmune, HBV, and cryptogenic ALF all have spontaneous survival of less than 30%.[7,9,18,21,22] Wilson's disease with ALF survive rarely.[7] Among the dynamic variables, the degree of encephalopathy was documented to influence survival—Patients with encephalopathy grade of III or more in comparison to less advanced encephalopathy (I & II) die more frequently.[7,9,21,22]

Among the prognostic models, King's College Hospital Criteria (KCC) for liver transplantation were proposed by O'Grady, and have been widely used.[22] Although these criteria are specific, they are not very sensitive in predicting cases that will need transplantation. Unfortunately, none of the currently available models have consistently demonstrated reliable accuracy in predicting outcome.[23]

Multiple prognostic models have been reported from India.[7,9,12] A report from North India, the following variables present at admission were identified as independent predictors for poor outcome:
- age 40 years or more;
- bilirubin 15 mg/dL or more;
- PT prolongation 25 seconds or more; and
- clinical features of overt cerebral edema.[21] With increasing number of above risk factors, mortality increased; with three or more factors it was 93%.[11,12,24]

In another study from India, clinical prognostic indicators (CPI) included age 50 years or more, jaundice encephalopathy interval (JEI) more than 7 days, grade 3 or 4 encephalopathy, presence of cerebral edema, PT ≥35 seconds, and creatinine ≥1.5 mg/dL. Presence of any 3 of 6 CPIs was superior to model for end stage liver disease (MELD) or King's College hospital (KCH) criteria in identifying survivors and nonsurvivors.[9]

ALF is a dynamic process in which variables determining prognosis at admission change over time, and thus the clinical course varies accordingly. A new prognostic model, ALF early dynamic (ALFED) model was reported which included four variables: arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy more than grade II, which were identified as the independent predictor of outcome at admission.[7,24] This model evaluated the dynamicity of these four variables over 3 days and documented that the prediction of outcome using these variables on day 3 was markedly superior to the prediction based on admission parameters. Recently, the INASL recommended the ALFED prognostic model to be more appropriate for the Indian subcontinent because it was derived from the cohort of Indian patients who had predominantly viral etiology unlike in the West where viral etiology as a cause of ALF is infrequent.[7]

This is one of the first dynamic models to assess and stratify ALF patients dynamically over a period of 3 days rather than considering variables at baseline. ALFED model study identified four prognostically significant variables: arterial ammonia, serum bilirubin, INR, and hepatic encephalopathy more than grade II. This ALFED

TABLE 5 ALFED Score[7,24]

Variables over 3 days	*Score assigned*
Hepatic encephalopathy (Persistent or progressed to grade >2)	2
INR (Persistent or increased to ≥5)	1
Arterial ammonia (Persistent or increased to ≥123 µmol/L)	2
Serum bilirubin (Persistent or increased to ≥15 mg/dL)	1

Each of the variables above on the day 3 of hospitalization carries a score determined on the strength of the beta integer of the odd's ratio identified in multivariate analysis to predict mortality. Each of the above variables were independent predictors of mortality. On day 3 a score of 4 is associated with 90% mortality where as score 1 is associated with about 5% mortality. With increasing score mortality increases

TABLE 6 Principles in the management of ALF

Aggressive supportive therapy:
Intensive care unit, organ support system, nutrition, electrolyte correction, hypoglycemia prevention, monitoring, hydration
Identification and removal of precipitating factors:
Control of GI bleed, sepsis, hyponatremia, renal failure, constipation, psycho-active drugs.
Reduction of nitrogenous load from the Gut:
Lactulose (not used), antibiotics, enema
Manipulation of neurotransmitters:
Flumazenil, branched chain amino acids (not used)
Cerebral edema:
IV Mannitol, thiopentone, hypertonic saline, hypothermia (not used), IV phenytoin (not used)
Ammonia lowering therapy:
L-ornithine L-aspartate (LOLA- not used), L-ornithine phenyl acetate (LOPA), sodium benzoate, hypothermia (not used), CRRT, plasma exchange
Novel therapies:
Molecular adsorption various bioartificial support system, recirculating system (MARS, promethus), probiotics with increased capacity to consume ammonia (not found beneficial)
Liver
Transplantation: LDLT (living donor liver transplant), DDLT (deceased donor liver transplant), auxiliary LT, split LT

model had an AUROC of 0.91 in the derivation cohort and of 0.92 in the validation cohort. The model showed similar increase in mortality with increasing risk scores from 0 to 6 **(Table 5)**. The performance of the ALFED model was found to be superior to the KCH and the MELD score, even when their 3-day serial values were considered. An ALFED score of ≥4 had a high PPV (85%) and NPV (87%) in the validation cohort. Further, in each patient the model could stratify the risk of dying or surviving on day 3 (score 1 through 6) of hospitalization. Those with score of 1–3 had a survival frequency of about 80% or more and those with ≥4 had a mortality risk of more than 80%.[7,24] These parameters at baseline were also independent predictors of mortality, but the dynamic assessment made these parameter as also model for survival. In India ALF etiology is hepatitis virus and usually individuals without any underlying chronic liver pathology develop ALF. In ALF along with hepatic necrosis, the liver regeneration simultaneously kicks off. Therefore, with liver regeneration, these predictive parameters change, and hence dynamic assessment are important to identify the outcome more accurately. The management and pathogenesis in ALF need another chapter and particularly the therapeutic approach against specific drivers of pathogenesis need special mention **(Table 6)**.

Summary

- ALF in India and the West have different etiology and natural course, and therefore the prognostic models are different. In India, the etiology is homogenous in contrast to the West where it is heterogeneous
- In the West: Drug induced ALF and in the East: Viral etiology is the most common
- Outcome of viral (HAV, HEV) and Drug (paracetamol) are better than other etiologies, but antitubercular drug-ALF has high mortality
- In India, pregnant females are more prone for ALF but not so in the West
- Prognostic models described across the world; dynamic models have been described recently from India and are appropriate for Indian patients
- Management: conservative, organ support and liver transplantation in select group

Acute-on-Chronic-Liver Failure

Introduction

In the early sections of the present chapter the concept of liver failure in general and ALF, ACLF, and chronic liver

failure as well as SHF in particular has been highlighted. **Table 1** depicts the essential phenotypic difference between ALF, SHF, and ACLF.

Patients with decompensated cirrhosis clinically presents with heterogeneity with variable prognosis. AD in cirrhosis usually denotes appearance of ascites, encephalopathy, variceal bleeding or combination of any later three.[4,5] Since liver transplantation in such patients is probably is the only curative option, there short-term survival prediction (usually in 2 years) has been used at many centers.[2] Three states with increasing risk of death have been proposed for decompensated cirrhosis defined by the occurrence of a first variceal bleeding alone (without other decompensating events—mortality 20%), any first non-bleeding decompensating event alone (80% ascites—mortality 24%), or any second decompensating event (mortality—50–78%).[25] However, recent reports indicate that, a more advanced rapid AD state do occur with a very high short-term 28 days mortality of around 20–90% depending upon degree and extent of associated extrahepatic organ failure.[25] These are patients, who developed systemic inflammatory response through proinflammatory precipitating factors (sepsis, excessive alcohol consumption, sudden reactivation of previous chronic liver disease inducing further acute hepatic necrosis) who are usually jaundiced with prolonged INR and develop various organ failures (OF) probably because of cytokine storm effecting extrahepatic organs resulting from the proinflammatory precipitating events. These are patients with ACLF.

Definitions and Concept

The term ACLF was first introduced to identify the above mentioned often observed but not categorized entity in 2002.[26] The first consensus definition on ACLF was provided by APASL (Asian Pacific Association for the Study of Liver) as "an acute hepatic insult manifesting as jaundice (total bilirubin ≥5 mg/dL) and coagulopathy (INR ≥1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with chronic liver disease."[3] However, it was slightly modified in 2014 in which chronic liver disease was modified to "with previously diagnosed or undiagnosed chronic liver disease/cirrhosis" and a "high 28 days mortality" was added.[27] With this APASL criteria, 28 days mortality was reported by the APASL between 25–34%.[27] However, certain patients with AD having above criteria with OF had markedly higher mortality than those without. Therefore, the EASL-AASLD (European Association for the Study of Liver-American Association for the Study of Liver) defined ACLF as "Acute deterioration of pre-existing, chronic liver disease, usually related to a precipitating event and associated with increased mortality at 28 days due to multisystem organ failure." Some report suggested and documented that severity of OF assessed by sequential organ failure assessment (SOFA) scores could differentiate patients with various prognosis (58% with OF vs. 8% without OF).[31]

The first prospective, observational, multicentric European study known as CANONIC study documented the distinction between AD without OF and AD with OF (which according to Western concept was ACLF). Among patients with known cirrhosis admitted with AD (ascites, variceal bleed, encephalopathy, infection; n=1,343), the 28 days and 90 days mortality in those with OF versus those without OF were 34% and 51% versus 5% and 14%, respectively. Thus, this study provided the documentation that patients with AD who were hospitalized with or developed OF after hospitalization were distinct and were named as—ACLF and justified their definition (EASL-CLIF—European Association for the Study of Liver-Chronic Liver Failure definition).[28] North American Consortium for the Study of End-Stage Liver Disease (NACSELD) defined ACLF by the presence of at least two very severe extrahepatic OFs (shock, grade III/IV HE, renal replacement therapy, or mechanical ventilation), which are much more stringent criteria than those of the EASL-CLIF consortium or the APASL. The NACSELD-defined ACLF is associated with a 30-day mortality rate of 41% compared to 7% for patients without ACLF. Accordingly, by definition, the main difference between traditional AD and ACLF is the short- and medium-term prognosis. To unify the definition on ACLF the WGO (World Gastroenterology Association) suggested that "ACLF is a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis, which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the INR) and one or more extrahepatic organ failures that is associated with increased mortality within a period of 28 days and up to 3 months from onset"**(Fig. 3)**.[4]

Components of ACLF

All the above definitions and concept irrespective in their disagreement and region of origin elucidated that there should be five components in ACLF:

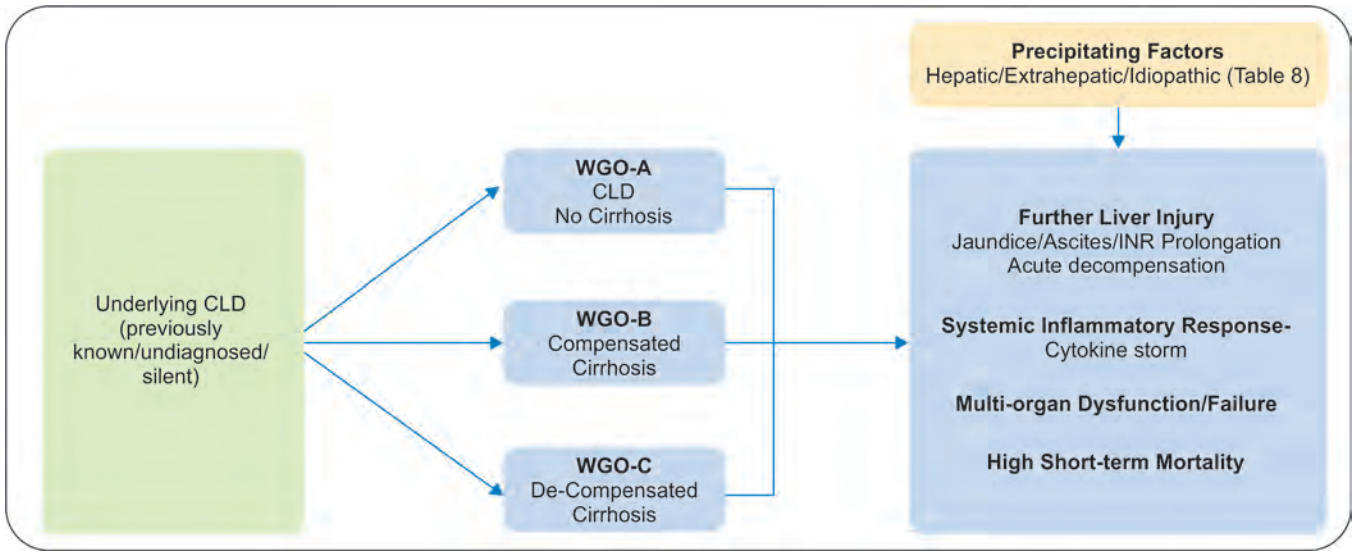


Fig. 3: World Gastroenterology Definition of ACLF[4]
AD, acute decompensation; ACLF, acute on chronic liver failure; CLD-A, chronic liver disease (non-cirrhotics) CLD-B (cirrhosis compensated), CLD-C (cirrhosis with previous history of decompensation)

- There should be pre-existing chronic liver disease (APASL excluded known decompensated liver disease and emphasized that only non-cirrhotics or compensated cirrhosis of any etiology should be included as underlying silent liver disease, which may have been diagnosed or undiagnosed previously; however, the EASL-CANONIC study as described earlier did not exclude patients with chronic liver disease with previous history of decompensation and WGO in an effort to unify these categorized underlying Chronic liver Disease to A-CLD without cirrhosis, B-compensated Cirrhosis and C-Cirrhosis with previous history of decompensation—**Fig. 3**).
- There should be a precipitating factor causing acute hepatic insult with systemic inflammatory response which were different regionally (described below) which should result in overt acute deterioration of hepatic function as well as reserve, resulting in features overt liver failure (CANONIC study defined them as AD and included both hepatic and extrahepatic insult but APASL excluded extrahepatic insults like variceal bleed and sepsis and emphasized on only acute hepatic insult to be further qualified by presence of conjugated hyperbilirubinemia of more than 5 mg/dL with INR more than 1.5 accompanied with development AD in the form of ascites and/or encephalopathy; there by quantifying the severity of the hepatic insult resulting in AD).
- The above-mentioned acute deteriorations should occur within a short period of time (APASL defined it to be within 4 weeks).
- The presence or development of hepatic failure should be associated with extrahepatic organ failure like encephalopathy, respiratory failure, renal failure, coagulation abnormality, circulatory compromise in form of hemodynamic instability as per the EASL-AASLD and NASCLED definition but APASL did not include it and suggested that only with liver failure the mortality exceeded 30% and should be enough to define ACLF and extrahepatic organ failures are the sequels of ACLF. However, the INASL consortium experiences documented that indeed occurrence of the extrahepatic organ failure imparts high short-term mortality.[29-31]
- As has been elucidated earlier, these patients with CLD are distinct from AD and should be categorized as another form of liver failure and to be termed as ACLF. By now both APASL and Western group agree that they have high 28 days mortality (various reports from different region describe it to a tune of around 50%).[1,5] The mortality, however, linearly increases with increases in number of extrahepatic OF (20% with one OF to 90% with ≥4 extrahepatic OF) **(Table 7)**.[28,31]

TABLE 7 European Association for the Study of Liver Consortium for Liver Failure Sequential Organ Failure Assessment Score (EASL-CLIF-SOFA Score- Panel A) and ACLF Grades (Panel B)[28,31]

Panel A				
Parameter for organs		***Score 1***	***Score 2***	***Score 3***
Liver—Serum Bilirubin (mg/dL)		< 6	6-11.9	≥12
Kidney—Serum Creatinine (mg/dL)		<2	2-3.4	≥3.5
Brain—Encephalopathy (West-Haven Criteria)		Grade 0	Grade 1–2	Grade 3–4
Coagulation (INR)		<2	2-2.4	≥2.5
Circulation (MAP in mm Hg)		≥70	<70	Vaso pressure requirement
Respiration	(PaO_2/Fio_2) or SPO_2/FiO_2	>300 >357	≤300–>200 ≤357–>214	≤200 ≤214
Score 1: Absence of OD or OF. Score 2: Organ Dysfunction (OD). Score 3: Organ Failure (OF) INR: International Normalized Ratio; MAP: mean arterial pressure				

Panel B		
AD group	***Mortality***	***ACLF grade***
No OF	4%	**NO ACLF**
One OF + No BD/KD	6.3%	
Single KF	18.6%	**ACLF Grade 1**
Single non kidney OF + KD/BD	27.6%	
Two OF	32%	**ACLF Grade 2**
Three OF	68%	**ACLF Grade 3**
4-6 OF	89%	

TABLE 8 Precipitating factors causing ACLF[27-32]

Acute hepatic Insult	Acute Extra hepatic Insult		Idiopathic Other non-identifiable cause of hepatic insult like Complementary and Alternative medicines (CAM)
	Environmental	Non-environmental	
• HBV Reactivation • HAV super infection • HEV Super infection • Hepatotoxic drug injury • Autoimmune hepatitis flare • Wilson's disease flare • Surgery/liver resection/Transarterial chemoembolization for liver cancer	• Bacterial infection • Alcohol excessive continuous consumption within last 3 months	Variceal bleeding	In various series on ACLF 30–50% patients with ACLF did not have identifiable precipitating factors and in India CAM may be a possibility of hepatic insult

Precipitating Factors Causing ACLF

Varieties of acute insults causing rapid deterioration in liver functions (clinical, biochemical, coagulation parameters) needing hospitalization have been documented and they vary regionally. In brief they can be categorized as follows in **Table 8**.[4,5,26,28-32]

Acute hepatic insult as mentioned in the above table are more often documented as the cause of ACLF in Asian Countries whereas they are less frequent in Europe and America. The hepatitis virus(es) are endemic in Asia as well as antitubercular therapy.[30,31] In the West the common causes were variceal bleed, infection, and idiopathic.[31] However, in recent time Asian region as well as in India the major cause of ACLF has been reported because of continuous excess alcohol consumption, which causes chronic liver disease as well as acute insult on the liver resulting in rapid AD (severe alcoholic hepatitis) and ACLF.[29,30]

Categorization/Types of ACLF and Prediction/ Prognostic Models in ACLF

Depending upon the pre-existing hepatic reserve due to underlying CLD and further loss of hepatic functional capacity due to acute hepatic insult and its regenerative capacity, severity of the systemic inflammatory response due to the cytokine storm and their effect on extrahepatic

organs, the course in ACLF is dynamic and usually unfolds over subsequent few days usually between 3–7 days.[33,34]

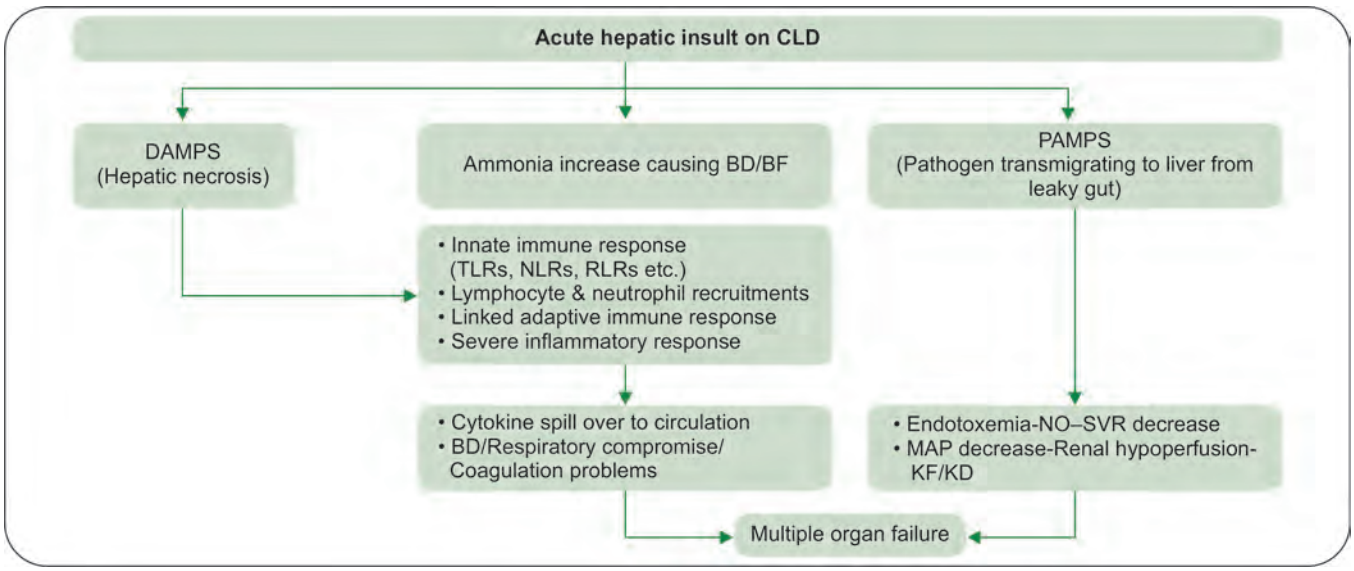
Types/Categorization of ACLF

The canonic study first tried to identify and qualify the extrahepatic organ failure by quantifying the change in the sequential organ failure assessment (SOFA).[28,31] The study included six organs to be evaluated for SOFA score (Liver, Kidney, Brain, Coagulation, Circulation, and Respiration) and graded their dysfunction based on values of serum bilirubin, creatinine, INR, mean arterial pressure (MAP), and ratio between PaO_2/FiO_2 or SpO_2/FiO_2, respectively and allocated 1–3 point scores to these values. Patients with score 2 for each parameter were considered as organ dysfunction (OD) like liver dysfunction (LD), kidney dysfunction (KD), brain dysfunction (BD), circulatory dysfunction (CD), coagulation dysfunction or respiratory dysfunction (RD) and patients with score 3 were defined as individual organ failure. This score was named as EASL, CLIF, SOFA score and depending on these scores as mentioned above. No OD and OF were defined for each of the six organs and then the ACLF in patients with AD were graded as No ACLF, ACLF grade 1–3 depending upon presence or subsequent development of number of OD/OF. With increasing grade, the 28 days mortality increased **(Table 7)**. Since OF were not included in APASL definition, the ACLF was not categorized or typed in APASL cohorts collated subsequently. However, in APASL cohort and many other reports on ACLF which included large cohorts of patients with ACLF reported that occurrence of OF was major determinant of outcome and prognosis.[32] Further the admission grading or status of organs were dynamic and the outcome prediction based on the OF on day 3–7 were more accurate predictors of outcome. Both EASL-CLIF (CLIF-C-ACLF) score and APASL groups have defined their dynamic prognostic scores, which simply reflect the dynamic changes of variable organ parameters.[3,33]

Pathogenesis (Flowchart 1)[26,31]

Pathogenesis in ACLF is unclear. However, the severe cytokine storm in ACLF has been documented to be more pronounced (documented by enhanced C-reactive protein response, neutrophilic leukocytosis, tumor necrosis α, IL18) than in patient with AD as well as in patients with compensated cirrhosis without AD.[31] The ammonia levels also have been recently identified to be markedly increased in such patients than in the other groups.[32] The Cause of Cytokine Storm has been briefly explained in the **Flowchart 1**. The DAMP (damage associated molecular pathogen) due to liver cell damage in diseases causing

Flowchart 1: Pathogenesis in ACLF



BD, brain dysfunction; BF, brain failure; DAMP, damage associated molecular pattern; KD, kidney dysfunction; KF, kidney failure; NLRs, nod like receptors; NO, nitric oxide; PAMP, pathogen associated molecular pattern; RLRs, rig like receptors; TLR, toll like receptors

TABLE 9 Principles in management of ACLF

- Intensive care unit, organ support system, nutrition, electrolyte
- Treatment of infection with appropriate antibiotics with monitoring of renal function and maintenance of serum albumin values with albumin replacement preventing volume overload
- Treatment of precipitating factors:
  - antivirals in HBV reactivation
  - steroid in alcoholic ACLF after ruling out infection
  - specific management for acute variceal bleeding if occurs, d) withdrawal of hepatotoxic drug, CAM
- Specific organ failure management:
  - For RF/RD—CRRT
  - Noradrenaline if needed to maintain MAP>70 mm Hg
  - Treatment for encephalopathy if occurs
  - Adrenal insufficiency (may occurs in some)-IV hydrocortisone
- Treating systemic inflammatory response:
  - Molecular Adsorbtion Recirculating System(MARS)—till date no evidence that it improves survival
  - plasma exchange—experimental
- Immunomodulatory/Regenerative therapy: G-CSF has been tried in small studies, but needs to be validated in large multicentric studies
- Fecal microbial transplantation: has been tried in alcoholic ACLF in small studies with promising results
- Liver transplantation if needed

super added injury to liver or sepsis or bleeding causing ischemia to liver are recognized by the innate immune systems presence in liver cells such as TLRs and other Innate immune PRR (pathogen recognizing receptors) sensors and produce various cytokines which cause neutrophilic recruitment and also attracts the immune cells of adaptive immune system resulting in release of various proinflammatory cytokines which may spill over to systemic circulation effecting various extrahepatic organs. Perpetuating the events by the transmigration of gut microbes due to a leaky gut documented in such patients further enhance such response and also induces endothelial nitric oxide by upregulating the nitric oxide synthase enzyme.[32] These events result in various organ dysfunction or OF depending upon the severity of the cytokine storm and the degree of liver injury resulting in ACLF.

Management

The management principles comprise of:

- Treating the precipitating factors
- Support to the failing organ
- Continuous assessment and by day 3–7 decision for liver transplant.

The Model for End Stage Liver Disease (MELD) score and addition of sodium value (MELD-Na) score in addition to the scores of failing organs have been the principles to prognosticate and transplant such patients to improve survival.[32-34] **Table 9** briefly provides the components of management in ACLF.

Conclusion

ACLF is a syndromic condition that occurs in patients with underlying chronic liver disease (CLD) irrespective of the cause of CLD. These patients develop intense systemic inflammation, organ failure, and high short-term mortality and ensue in close temporal relationship with a precipitating event, which is regionally variable. Whether extrahepatic organ failure is an integral part of the syndrome or consequence is the difference in defining the syndrome in the West and Asia. Bacterial infection is frequent in these patients and in the West it is considered as a precipitating event, but in Asia it is considered as a frequent association in ACLF. However, irrespective the differences between the West and Asia the syndrome is seen across the world and about half of them need liver transplant.

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CHAPTER

135 Proton Pump Inhibitors—Long-term Use: Boon or Bane?

Manish Manrai, Rohit Upreti

Abstract

Proton Pump Inhibitors (PPIs) have been an important part of the physicians' arsenal in the fight against acid peptic disorders. PPIs are among the drugs which are most frequently prescribed both to outpatients and those admitted in the hospital including critically ill patients. The approved indications for PPI therapy include erosive esophagitis, peptic ulcer, NSAID-induced ulcer, Gastroesophageal Reflux Disease, *Helicobacter pylori* infection and management of pathologic hypersecretory conditions like Zollinger-Ellison syndrome. However, long-term use of PPIs has also been associated with multiple side effects including small intestinal bacterial overgrowth, pneumonia, increased bone fractures, Vit B12 deficiency among others. A sensible strategy for PPI prescription should be as per indications, avoiding broad off-label use and following deprescription strategies.

Introduction

The pharmacologic use of Proton Pump Inhibitors (PPIs) started in the late 1980s and since then they have been an important part of the armamentarium of physicians and gastroenterologists for treating acid peptic disorders.

PPIs are substituted benzimidazoles, which are similar to the H2 receptor antagonists (H2RAs) in structure but have a different mechanism of action. PPIs are given as prodrugs. Oral formulations are prepared as acid resistant delayed release enteric coated capsules or tablets so that they do not undergo destruction due to the acid in the stomach. PPIs easily diffuse across lipid membranes into acidified compartments like parietal cell canaliculus where the protonation of the prodrug takes place and gets converted to its active form, a thiophilic sulfenamide cation.[1] This cation irreversibly inactivates the H/K-ATPase **(Figure 1)** by forming a covalent disulfide bond with it.[1,2]

PPIs should be taken empty stomach because food decreases the bioavailability of all agents by around 50%. They are taken around 1 hour before a meal, so that the maximal activity of proton pump secretion is at the same time as the peak serum concentration of the PPI. They have a short half-life of approximately one and a half hour, but since they irreversibly inhibit the proton pump the secretion of acid remains inhibited up to 24 hours. In optimal doses PPIs inhibit around 90–98% of 24-hour acid secretion. When intravenous preparations are used, only the actively secreting pumps are inactivated. Therefore, during the first 24–48 hours of treatment, the intravenous formulations must be given as infusion or as repeated bolus injections.[1]

PPIs are the cornerstone of treatment regimens of a number of acid peptic disorders and other related conditions. The various definitions of long-term use of PPI that have been used in different studies vary from one repeated prescription over 12 months to continuous therapy for periods ranging from 4 to >12 months.[3] Prolonged use of PPI, however, is a two-edged sword and has been related with an excess of systemic adverse effects,

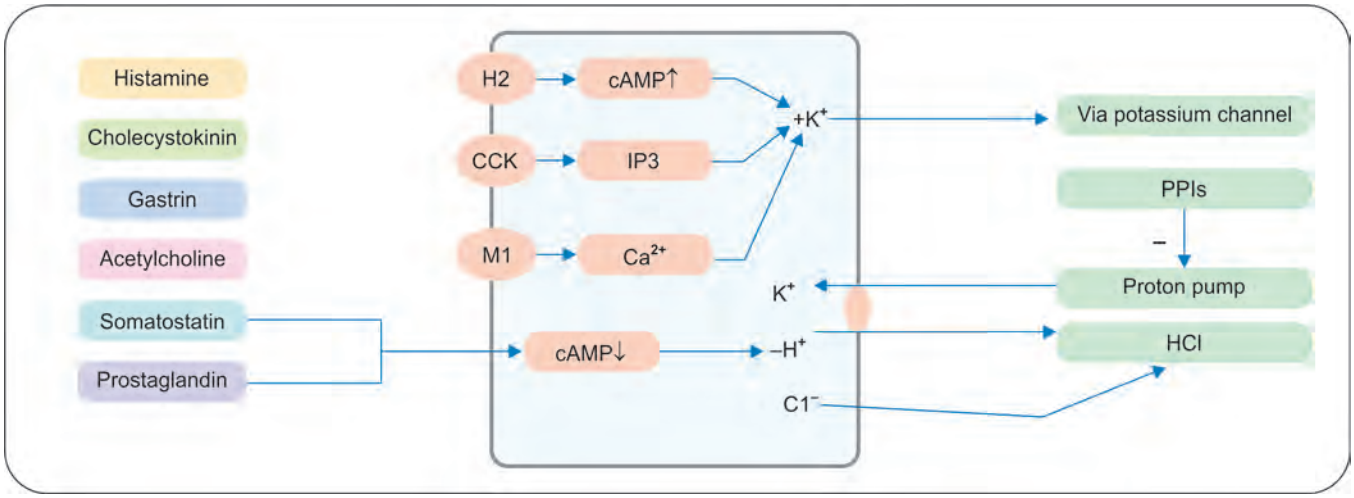


Fig. 1: Mechanism of action of proton pump inhibitor: PPIs irreversibly inactivates the H/K-ATPase by forming a covalent disulfide bond with it and thus inhibit the common pathway involved in the acid release from the cell

which lead to the subject that whether long-term use of PPI is a boon or a bane?

Long-term PPI Use: Is It a Boon?

PPIs have statistically proven benefit over placebo/H2RAs in management of diseases associated with increased acid production. The indications for PPI therapy, which are approved by FDA include Gastroesophageal Reflux Disease (GERD), erosive esophagitis, peptic ulcer, NSAID-induced ulcer (treatment and prophylaxis), *Helicobacter pylori* infection (along with antibiotics) and management of pathologic hypersecretory conditions (including Zollinger-Ellison syndrome).[4]

However apart from the above-mentioned indications, the existing evidence suggests overuse of PPIs with almost 25–70% of prescriptions lacking appropriate indication.[5] In fact, the "off-label" use of PPIs is among the highest (55% prevalence) in intensive care units.[6]

In patients of GERD, who present with reflux symptoms after meals, long-term inhibition of acid secretion is achieved by use of PPIs.[5-10] Since the effect of acid suppression remains for almost 24 hours, a single dose of PPI empty stomach in the morning is effective. There is evidence that PPIs can be used in prevention of recurrent reflux symptoms as well as esophageal erosions/ulcers.[7-9] The regular use of PPIs as maintenance therapy of GERD decreases the recurrence rates to less than 15% for 1 year compared to recurrence rates of more than 50% for patients without any maintenance therapy.[11,12] Long-term administration of PPIs may also prevent transformation of Barrett's esophagus to a neoplastic lesion.[13] Common indications of long-term PPI use along with the studies establishing their role have been summarized in **Table 1**.

TABLE 1 Indications of long-term use of PPIs

Indication	*Study*	*Inference*
NSAID ulcer prophylaxis	Sugano et al., 2012[10]	Decreased incidence
GERD	Pace et al., 2005[11]	Decreased recurrence

The other common indication of long-term PPI use is for prevention of NSAID-induced gastroduodenal ulcers recurrence by decreasing it to approximately one-tenth on comparison with patients treated with placebo.[10] Thus, they are the drug of choice for the prevention of aspirin/NSAID induced ulcers.

Long-term Use of PPI: Is It a Bane?

Increased usage of PPI for past many years now has led to the conundrum of their long-term effects. Prolonged PPI use has been implicated in adverse effect of several body functions and has been associated with increased incidence of various diseases. Common adverse effects of long-term PPI usage along with the studies establishing their role have been summarized in **Table 2**.

TABLE 2 Adverse effects of long-term use of PPIs

Side effect	*Study*	*Inference*
SIBO	Lo WK et al., 2013[22]	Increased risk
Gall bladder dysfunction	Cahan et al., 2006[26]	Increased risk
Pneumonia	Wongtrakul et al., 2020[29]	Increased risk
Acute interstitial nephritis	Xie et al., 2016[31]	Increased risk
Chronic kidney disease	Wijarnpreecha et al., 2017[32]	Increased risk
Hypomagnesemia	Park CH et al., 2014[33]	Decreased magnesium levels
Dementia	M A Khan et al., 2020[35]	No definite risk
Bone fracture	Nassar et al., 2018[37]	Increased risk of bone fracture

TABLE 3 Adverse effects of PPI based on their property of acid inhibition or unrelated to it

Due to acid inhibition	Pneumonia, GI infection, Carcinoid tumor, GI mucosal hypertrophy, Fractures, SIBO, Vit B12 deficiency, Gastric cancer, SBP
Unrelated to acid inhibition	Collagenous colitis, Acute interstitial nephritis, Dementia

These side effects can be separated either as per the mechanism or as per the involved site.

As Per the Mechanism

Adverse effects of PPIs occur either due to the fact that they cause acid inhibition or else they are unrelated to their property of acid inhibition.[14] These adverse effects have been shown in **Table 3**.

As Per the Site Involved

Gastrointestinal System

Increased risk of gastrointestinal infection—Use of PPIs has an association with increased risk of *Clostridium difficile* (*C. difficile*) infection.[15,16] Possible mechanism is that long-term PPI use alters the colonic microbiome and hampers the normal barriers against *C. difficile*, which proliferates using the available amino acids.[17,18]

Gastric neuroendocrine tumor—Prolonged PPI use leads to increased intra-gastric pH thereby causing increased plasma gastrin concentration, thus stimulating enterochromaffin like (ECL) cells proliferation.[19] There are only isolated case reports of PPI administration-related gastric neuroendocrine tumors in humans and presently to ascertain a pathogenic role, the data is scarce.[20] Therefore, at present there is insignificant clinical relevance of the risk of carcinoid tumor after long-term PPI use. Although periodic endoscopic screening may be considered during the period of use.

Gut microbiome changes and Small Intestinal Bacterial Overgrowth (SIBO)—The resultant decrease in the acid secretion and the bactericidal effect of the gastric juice due to PPIs leads to an increase in the microbial density of the gut especially with *Streptococcus* which colonize the oral cavity.[21] Lo et al. in a meta-analysis done in 2013 found that as compared to non-users, there was 7.5 times increased risk of SIBO in PPI users. Therefore, prolonged PPI administration is considered a risk factor for SIBO (Defined as presence of 100,000 bacterial colonies/mL in small intestinal contents).[22] However, the clinical importance of this altered microbiome in patients treated with PPIs is elusive at present.

Spontaneous bacterial peritonitis (SBP)—PPI administration is useful in few cases of cirrhosis as they reduce the risk of variceal rupture and ulcer occurrence.[23] Long-term PPI use leads to hypochlorhydria promoting bacterial translocation, colonic transmigration and may lead to Gram-negative organisms related SBP in cirrhotics.[24] Although, the available evidence at present does not recommend withholding PPIs whenever indicated in patients with liver disease; the evidence does suggest that PPI use is associated with augmented risk of SBP in cirrhotics.

Gastric cancer—In patients with *H. pylori* infection, long-term PPI usage increases mucosal inflammation, hastens mucosal atrophy, which might be a potential risk factor for gastric malignancy.[25] However, more data is required to establish causality between long-term PPI use and gastric malignancy in *H. pylori* patients.

Gall bladder dysfunction—Cahan et al. in 2006 found that PPI therapy reduces gallbladder motility in healthy volunteers.[26] Chronic PPI therapy may pose a risk for long-term gallbladder dysfunction and biliary complications.

Atrophic gastritis—PPIs can alter the gastric mucosal architecture and Li et al. found in a meta-analysis in 2017 that there was a higher presence of gastric atrophy in PPI group compared to the control group.[27]

Respiratory

Pneumonia—PPIs increase gastric pH by suppressing gastric acid release, promoting bacterial overgrowth which in turn leads to colonization of trachea and pneumonia. There is evidence to suggest that immune cell function may also be impaired by PPIs, thereby augmenting the risk of infectious complications.[28] Wongtrakul et al. in their recent meta-analysis concluded a significantly higher risk of development of pneumonia in cirrhotic patients with a history of PPI use than those without. Thus, prudent use of PPIs in patients with definite indication may be suggested.[29]

Renal

Acute interstitial nephritis—In patients on PPI treatment, an allergic reaction to the drug may cause interstitial nephritis.[30] As many as 70% of acute interstitial nephritis was reportedly related to drugs, of which 14% were caused by PPIs in biopsy-proven cases.[31]

Chronic kidney disease—The mechanism by which PPI use can lead to CKD is not well understood. One of the mechanisms proposed is the acute interstitial nephritis caused by PPI. Other postulated mechanisms include lysosomal acidification hydrogen/potassium adenosine triphosphatase enzyme system abnormalities, reduced renal tubular cells regeneration, altered gene expression, and elevated oxidative stress.[32] Although, there is a need of more data to ascertain this association, it is suggested that the indication of initiation as well as continuation of PPIs should be carefully assessed in patients with pre-existing risk factors for CKD development.

Nutrient Absorption

Hypomagnesemia—One of the postulated mechanism for hypomagnesemia related to PPI use is a reduction in the affinity of magnesium to its transport receptors caused by the pH change thereby decreasing the active transport of magnesium across the intestinal lumen. Park et al., in their meta-analysis, showed an increased incidence of hypomagnesemia in PPI users.[33]

Vitamin B12—The acidic environment of the stomach assists in the release of Vit. B12 bound with food and subsequently helps its binding to intrinsic factor. Lam et al. in 2013 found a 65% increased risk of B12 deficiency in PPI users more than 2 years.[34]

Neurological

Dementia—Long-term PPI use inhibits beta and gamma secretase, which may lead to an increase in the amyloid beta peptide levels in the brain. Khan et al. in their systematic review found lack of evidence pertaining to the proposed suggestion of PPI use and an increased risk of dementia.[35] They recommended that PPI use should not be curtailed because of concerns about dementia risk.

Drug Interactions

Anti-platelets—There is competitive inhibition of CYP2C19 to variable grades by PPIs, thus affecting the metabolism of clopidogrel. Omeprazole is the most noteworthy inhibitor of CYP2C19. The two meta-analyses done in this regard found an increased rate of adverse cardiovascular events in patients on simultaneous PPI-clopidogrel therapy.[36] While the pharmacological interaction between these two drugs is established beyond doubt, more data is required to ascertain the clinical significance of this interaction.

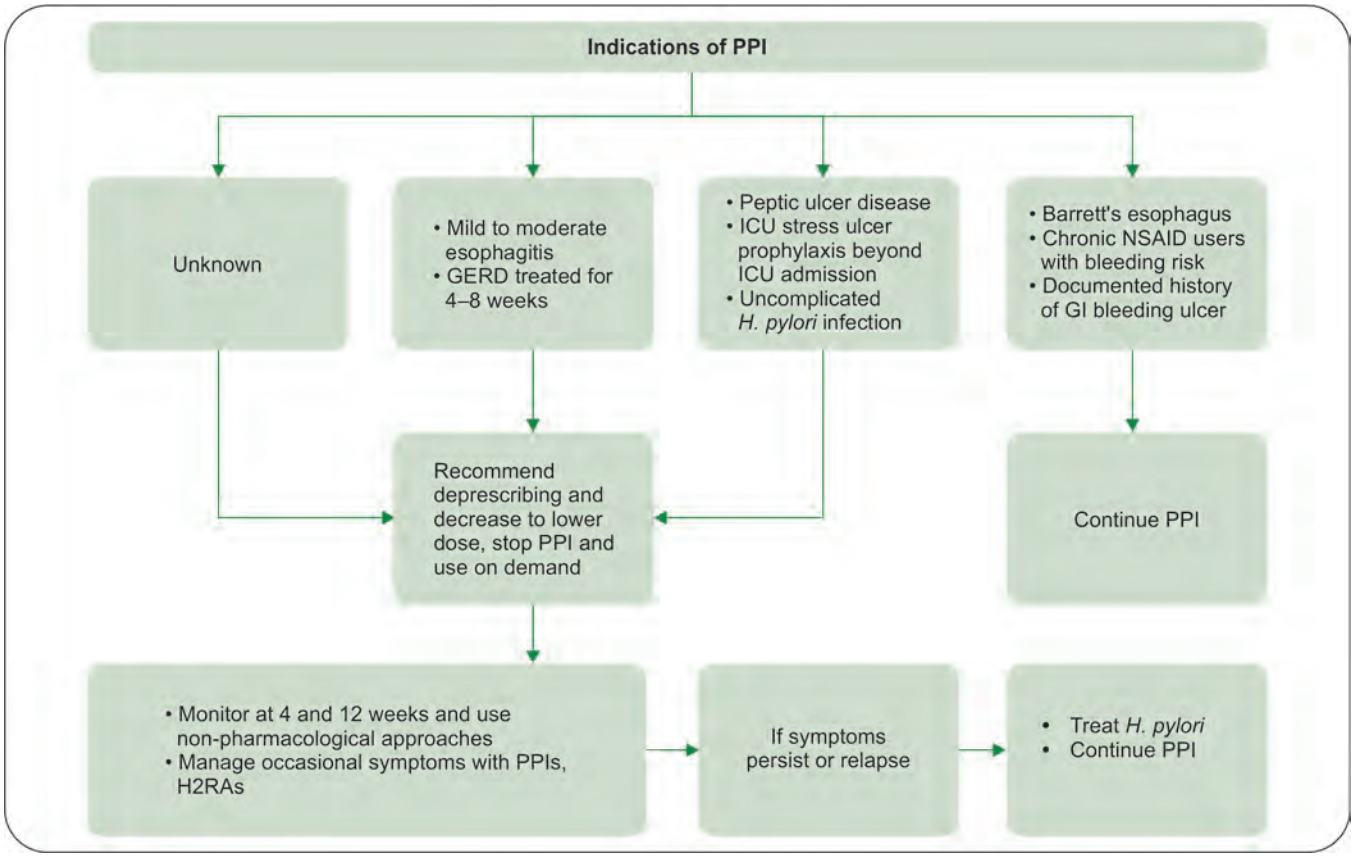
Endocrine

Alteration in bone density—The bone health and increased fracture susceptibility due to PPIs may be linked to impaired calcium absorption (acid suppression leads to decreased release of ionized calcium from insoluble calcium salts) and hypergastrinemia. In a meta-analysis conducted by Nassar et al. published in JBM in 2018 it was found that long-term PPI use might increase the fracture risk but has no significant alteration of bone mineral density (BMD).[37] Presently there is insufficient evidence to recommend regular BMD monitoring of patients on PPIs.

Hematological

PPIs have their anti-inflammatory properties as they can bind to neutrophils and can inhibit neutrophil accumulation and release of ROS. However, long-term use can also lead to neutropenia and thrombocytopenia.[38] In general, the recognized theories are the immune-

Flowchart 1: The algorithm for deprescribing PPIs



mediated and the toxic mechanism. Drug-induced antibodies against circulating hemocytes form the basis of immune mediated mechanism whereas the toxic mechanism is due to direct toxicity of the drug to hematopoietic cells.

All-cause Mortality

Xie et al., in their cohort study, demonstrated an increased risk of all-cause mortality in association with PPI use.[39] The speculated mechanism for this association was the probable role of oxidative stress, heme oxygenase-1 and accelerated senescence of human endothelial cells.

The Road Ahead

Presently, PPIs are among the most frequently prescribed class of drugs and are often continued for duration way beyond the indication. In view of this and with many recent studies suggestive of systemic adverse effects of long-term PPI use, a lot of research is going on to formulate a well-structured model to deprescribe PPIs.

Deprescribing PPIs

Patients on PPIs should be monitored for symptom recurrence and symptoms should gradually be managed with on-demand PPIs, stepping down to H2RA therapy, other over-the-counter agents (e.g., calcium carbonate) or nonpharmacologic approaches (weight loss, avoid meals 2–3 hours before bed time, head end elevation, avoid dietary triggers). Stepping down to H2RA involves discontinuation or tapering of the PPI followed by prescription of an H2RA. Any H2RA at any approved dose and dosing interval can be used.[40] Implementation of deprescription guidelines **(Flowchart 1)** will encourage clinicians to carefully evaluate the ongoing use of medications and potentially reduce the negative effects of polypharmacy.

Conclusion

PPIs have a robust helpful impact when used correctly for the standard indications. However, PPIs have also been incriminated with multiple systemic side effects. Although the evidence is limited for causality at present and this is an area of active research, there is enough evidence to indicate a tendency to develop adverse effects with long-term use of PPIs. Optimal strategy at this time for PPI prescription is to advise it to patients with clear indications, following of clear deprescription strategies and avoidance of broad off-label usage.

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CHAPTER

136 Eosinophilic Esophagitis—An Underdiagnosed Entity

Goundappa Loganathan, H Leena Shree

Abstract

Eosinophilic oesophagitis (EOE) is a locally immune mediated chronic oesophageal disease occurring as a consequence of allergen exposure. It is a male predominant widely prevalent but less well recognized disease with genetic preponderance and often associated with atopy. EoE has a progressive course from mucosal disease to subepithelial disease over decades resulting in fibro stenotic esophageal disease. The diagnosis is based on the constellation of symptoms, endoscopic and histological findings with >15 eosinophils/HPF confirming the diagnosis. The new genetic, molecular, cellular, animal, and translational studies show the cascade of coordinated type 2 inflammatory response. The newer classification based on histologic, endoscopic, and molecular features defines three endotypes each with distinct genetic, clinical, endoscopic, and histological features. Treatment principles include elimination of possible food allergen, mast cell stabilizer, proton pump inhibitor which has a cause and effect relationship, steroids, and biologicals. Earlier diagnosis with newer tools and biopsy help to diagnose EoE early in disease thus preventing progression to fibro stenotic disease thereby reducing morbidity. (Eosinophilic oesophagitis; Food allergens; esophageal eosinophilia; proton pump inhibitors; Allergy)

Introduction

Eosinophilic esophagitis (EoE) is a part of spectrum of eosinophilic disorders of the gastrointestinal tract histologically characterized by eosinophilic infiltration and inflammation consequent to exposure to an allergen, often food, resulting in esophageal dysfunction and progressive serious complications, though a definite cause eludes. This diagnosis from esophageal eosinophilia (1968) has progressed from initial association with reflux disorders to EoE in 1993. A male predominant disease, is associated with various allergic disorders including atopy and seen to increase progressively over these two decades. Etiopathobiology includes genetic and IgG 4 association and as a cause with familial susceptibility. Care of these patients involves primary care providers to multi-specialty departments.

Definition

EoE is defined as locally immune mediated chronic esophageal disease with clinical symptoms of esophageal dysfunction and histological eosinophil predominant inflammation with a progressive natural course.[1-5] It is IgG 4 mediated disease associated with atopy (20–80%), urticaria and anaphylaxis; positive family history (50%), asthma (30–50%) and allergic rhinitis (50–75%) in children.[6]

Natural History

- *Epidemiology:* It is a disease with global presence including America, Europe, Australia, and Asia, male predominant [3:1], ethnically variable (more common in Caucasians) with overall pooled prevalence of 22.7/100,000, 0.5–1 per thousand, 2–7% of gastroscopy,

12–23% of gastroscopy for dysphagia, and is seen to be increasing over time.[7]

- *Course:* EoE is a chronic and progressive disease. Earlier symptoms in children are due to inflammation and later in life due to subepithelial collagen deposition resulting in fibro stenotic EoE. Presence of strictures was observed in 17% and 71% with less than 2 years and 20 years of symptoms thus emphasizing the need for early diagnosis.
- *Temporal trends:* From 9 to 12.8/100,000 over 3 years in Ohio, USA, 0.35 to 9.5/100,000 in Minnesota, USA, over 15 years, 1.2 to 7.4/100,000 in Switzerland over 20 years indicating that there is an increasing incidence. The reasons for increase will be discussed in etiopathobiology in addition to awareness and increasing mucosal biopsies.

Etiopathobiology (Fig. 1)

- *Allergen and Hygiene Hypothesis:*[8] The strength of evidence stems from increased prevalence and incidence in developed countries which have better *hygiene* and association with most of the allergic disorders in a significant proportion. *Aero-allergen* exposure gains support by the increased incidence in summer or fall. Increased prevalence is noted in arid region, cold weather lacking vegetation, rural low density populated regions. This requires further research. *Food* elimination results in improvement of EOE, and hence is considered a risk. Various reasons mentioned stay unproven. Allergen/infection in an unprimed host living in virtual hygienic environment initiate Th2 response over Th1 which is mild and protective.
- *Helicobacter pylori (H. pylori)/Proton Pump Inhibitor (PPI) Hypothesis—Harmful or protective*: Presence of *H. pylori* polarizes the immune system toward a Th1 response and the lack of it leads to Th2 response. EoE has a strong inverse relationship with *H. pylori* and atopic disorders.[9]
  - *PPI* is hypothesized to increase upper gastrointestinal tract (GIT) permeability facilitating new route of antigen entry;
  - use of PPI is associated with food specific IgE antibodies.
  - PPI has shown anti-inflammatory/anti-eosinophilic effects.

  Use of PPI has resulted in histological resolution of inflammation and eosinophils in 30–40% making use of PPI as a candidate trial drug. PPI thus can cause EoE indirectly by removing the protective barrier and eliminating *H. pylori*; paradoxically PPI heals EoE by its anti-inflammatory and anti-eosinophilic activity; conclusive evidence is required to say if PPI is causative or curative.[10-17]
- *Early Life Exposure Hypothesis/Environmental Factor:*[18-23] EoE is associated with use of antibiotics in children delivered by caesarean, less than 1 year of age, premature babies, non-exclusively breast fed babies. Establishment of esophageal microbiome would help in understanding microbial dysbiosis as the cause.

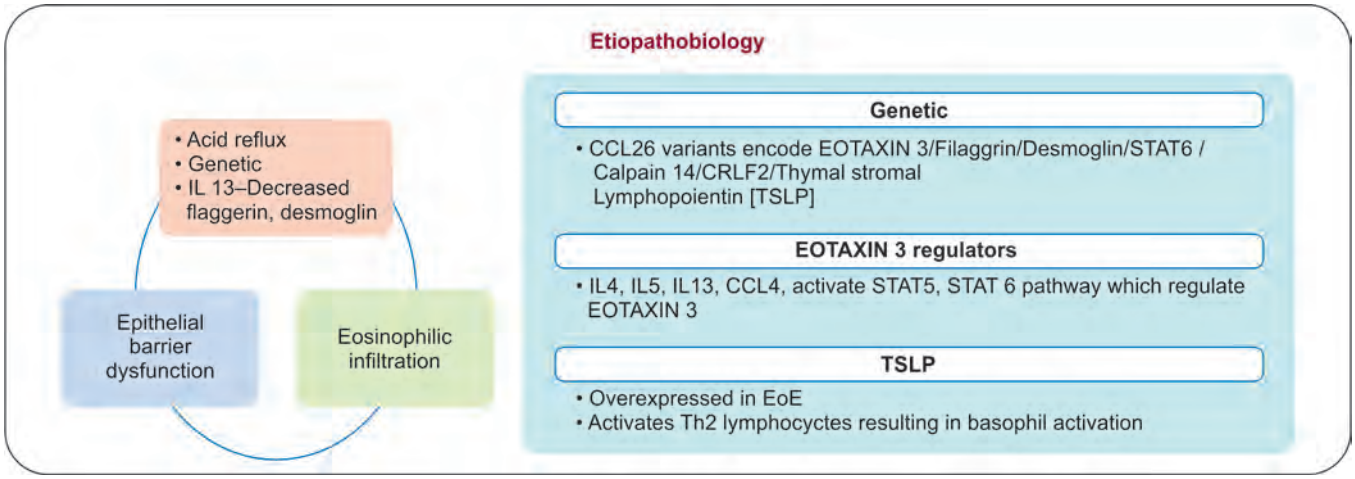

Fig. 1: Etiopathobiology shows the mechanism due to acid reflux, genetic, cytokine induced mechanisms

- *Familial/Genetic Susceptibility:* EoE is associated with connective tissue and auto-immune disorders.[24,25] EoE has racial and gender bias, predominance in white ancestry, inherited in non-Mendelian manner, a sibling risk ratio of 80%; parents had history of esophageal stricture and eosinophilic infiltrate in 10% and 8% respectively.

The new genetic, molecular, cellular, animal, and translational studies help to postulate a detailed pathway. This shows how, exposure to allergens results in a complex and coordinated type 2 inflammatory cascade. Delayed intervention can result in odynophagia, esophageal strictures, and food impaction.[26]

The genetics, epigenetics, and transcriptional analysis, the role of cytokines, chemokines, and other molecules, pathological and protective cells including commensal bacteria are vividly described.[26-28]

Diagnosis

The diagnosis of EoE is made on the constellation of clinical manifestations, endoscopic and histological findings.

- *Clinical:* There is a distinct phenotypic variability in symptomatology amongst people in early and advanced disease. Esophageal dysfunction symptoms include esophageal dysphagia in 60–100%, food impaction in 25%, heart burn in 30–60%, atypical chest pain in 8–44% and 1–8% of those with refractory reflux symptoms.[29] Dysphagia, refractory heart burn, and mucosal disruption on intubation are the predominant symptom/sign in advanced disease. Vomiting, food rejection and growth retardation are also observed.[30] Association of symptoms of atopy adds to the diagnosis.
- *Endoscopic:* Endoscopic Reference Scoring (EREFS) **(Table 1)** classification as given by Hirano et al. has scoring for visually observed endoscopy findings like edema, rings, exudates, furrows, and strictures graded separately at upper, middle, and lower third of esophagus. The inflammatory signs edema, exudates, and furrows had a sensitivity of 89%, 96%, 89%, and specificity of 88%, 76%. and 90%, respectively and correlated with eosinophilia. Composite inflammatory score, the sum of maximum of inflammatory variables namely edema, rings, and exudate excluding furrows and stricture showed a superior correlation amongst the diagnostic and post-treatment cohorts.[31,32] Schatzki's ring is one of the endoscopic manifestations of EoE.
- *Histologic:* Biopsy is mandatory in patients clinically suspected to have EoE even if the esophageal mucosa looks normal. Endosonography guided deeper biopsies would provide more information. A meta-analysis of EoE endoscopic findings in isolation have poor sensitivity, specificity, and predictive value[33] and the sensitivity increases to 100% when 6–9 esophageal mucosal biopsies are taken.[34,35] Presence of ≥15 eosinophils/hpf confirms the diagnosis of EoE.

Newer principles[36] **(Fig. 2)**:

- Removal of age cut-off
- Removing PPI from list of diagnostic criteria
- Evaluate for condition causing esophageal eosinophilia rather than excluding them
- Criteria should be clinically operational
- Should be utilizable in patients in whom diagnosis was made using earlier criteria, applicable clinically widely and for future research

Newer tools:

- Tetsuo Shoda et al.[37] using EoE diagnostic panel (EDP) and Consortium of Eosinophilic Disease Researchers (CEGIR), Endoscopic Reference Scoring (EREFS) and histologic scoring system (HSS) analyzed the

TABLE 1 Endoscopic reference scoring

Variable	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*
Edema	Distinct Vascularity	Decreased Vascularity	Absent Vascularity	
Rings	None	Mild ridges	Moderate/Distinct rings	Severe—Cannot pass scope
Exudate	None	Mild ≤10% of surface area	Severe > 10% of surface area	
Furrows	None	Mild	Severe	
Stricture	Absent	Present		

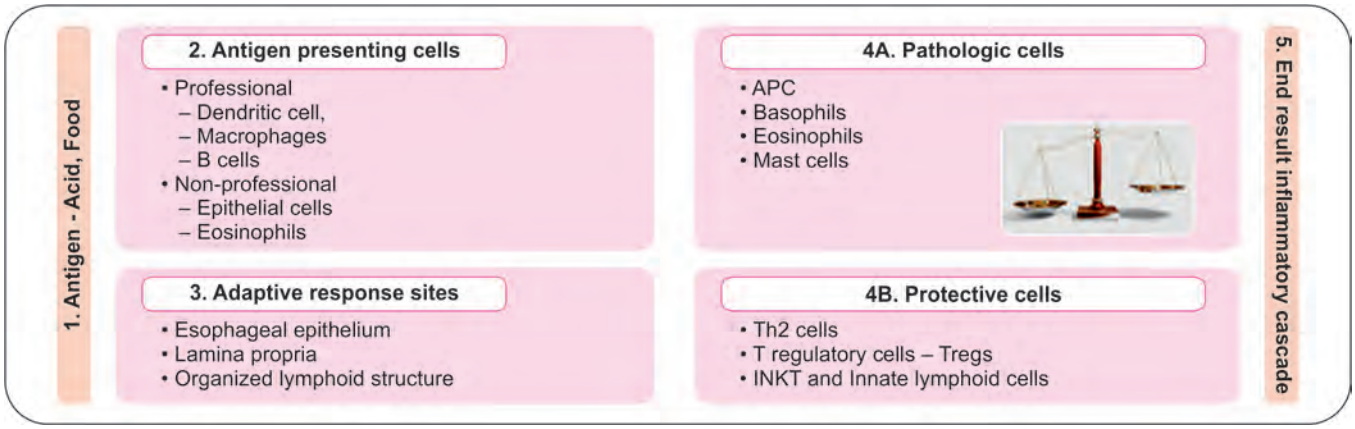

Fig. 2: Antigens presenting cells (APC) present the antigen to the adaptive response sites. Imbalance between pathological and protective cells result in inflammatory cascade

association of histologic, endoscopic, and molecular features. This study characterized three endotypes namely EoEe1, EoEe2, and EoEe3 each with distinct genetic, clinical, endoscopic and histological features providing effective therapeutic intervention **(Table 2)**.

Diagnostic criteria:

- Symptoms suggestive of esophageal dysfunction
- Presence of eosinophilic infiltrate (≥15 e/hpf) on esophageal biopsy
- Exclusion of other disease like Gastro Esophageal Reflux Disease (GERD) and Proton Pump Inhibitor Responsive Esophageal Eosinophilia (PPI-REE) after 8 weeks PPI trial.

AGREE Conference[36] 2018 includes the following:

- Symptoms of esophageal dysfunction.
- Esophageal mucosal biopsies with eosinophils ≥15/hpf (60 eosinophils/smm).
- Presence of exudates, grooves, rings, stenosis, luminal narrowing, and crepe' mucosa.
- Concomitant atopic conditions.
- Esophageal eosinophilic infiltration in isolation.
- Evaluation of potential contributors of esophageal eosinophilia.

- *Updated diagnostic algorithm*[36] **(Fig. 3)**
- *Emerging diagnostic tools:* Transnasal endoscopy, Endoscopic functional lumen imaging probe (FLIP), Cytosponge to obtain biopsy have sensitivity and specificity of 75% and 86%, respectively, esophageal string test and real time mucosal impedance measurements.[38] Absolute eosinophil count (AEC) is the single biomarker of relevance as on this date.[27]

Treatment

Treatment principles include elimination of potential antigen, attenuation or elimination of antigen induced allergic/immunogenic pathway induced inflammation early in the disease using PPI and steroids and to treat fibrostenotic complications of like strictures endoscopically in advanced disease. 3D acronym for Diet, Drugs, and Dilatation forms the basis of treatment of EoE.

Diet: Elimination diet: Elemental diet still is the most effective strategy but associated with poor compliance. A meta-analysis by Arias et al. observed efficacy of elemental diet in 90.8%, six food elimination diet (SFED—cow milk, wheat, egg, soy, peanut, and seafood) in 72.1% and allergy testing directed elimination diet in 45.5% of cases.[39] A novel 2-4-6 step up elimination diet strategy with each elimination diet step lasting for 6 weeks observed 43% remission in Two Food Elimination Diet (TFED Milk and gluten containing diet), 60% in those receiving TFED and four food elimination with addition of eggs and legumes (FFED) and 79% with six food elimination diet by additionally excluding nuts and seafood. This method helped to identify possible food antigen and avoided unnecessary food elimination.[40]

Drugs:

- *Steroids:* Dampening of EoE associated inflammation, improving mucosal barrier function and histologic

TABLE 2 EoE Endotypes

Variable	*EoEe1*	*EoEe2*	*EoEe3*
% of subjects	35%	29%	36%
Inflammation	Pauci -Inflammatory Near normal esophagus	High type 2 immune mechanism with steroid refractoriness Inflammatory	Higher frequency of narrow caliber esophagus Fibrostenotic
Epithelial differentiation genes	Small changes		Low expression
Onset	Pediatric	Adult	Adult
Allergy	Atopic	Atopic	Non-Atopic
Steroid sensitivity	Sensitive	Refractory	Refractory
Genetic	Low expression of ALOX 15 Mild phenotype	Inflammatory cytokines IL-4, TSLP are expressed Expression in ACTG2 gene	Enriched for epithelial genes that lose expression, of ACPP, CITED2, CTNNAL1, EML1, FLG, GRPEL2, MT1MPNLIPPR3, TSPAN12
Treatment response		Anti-Type 2 immune therapy (anti IL-4 Ralpha) Anti TSLP Biologicals	
Learning	• Adult and pediatric EoE have comparable pathogenesis • Adult and pediatric EoE are amenable to similar therapeutic interventions • Eosinophils levels may not indicate severity or help to subtype EoE • Endotyping offers useful subtyping of EoE • Biomarkers need to be developed • EoE exists in three disease endotypes with characteristic/unique clinical, endoscopic and molecular features • Endotyping could transcend eosinophil levels as gold standard		

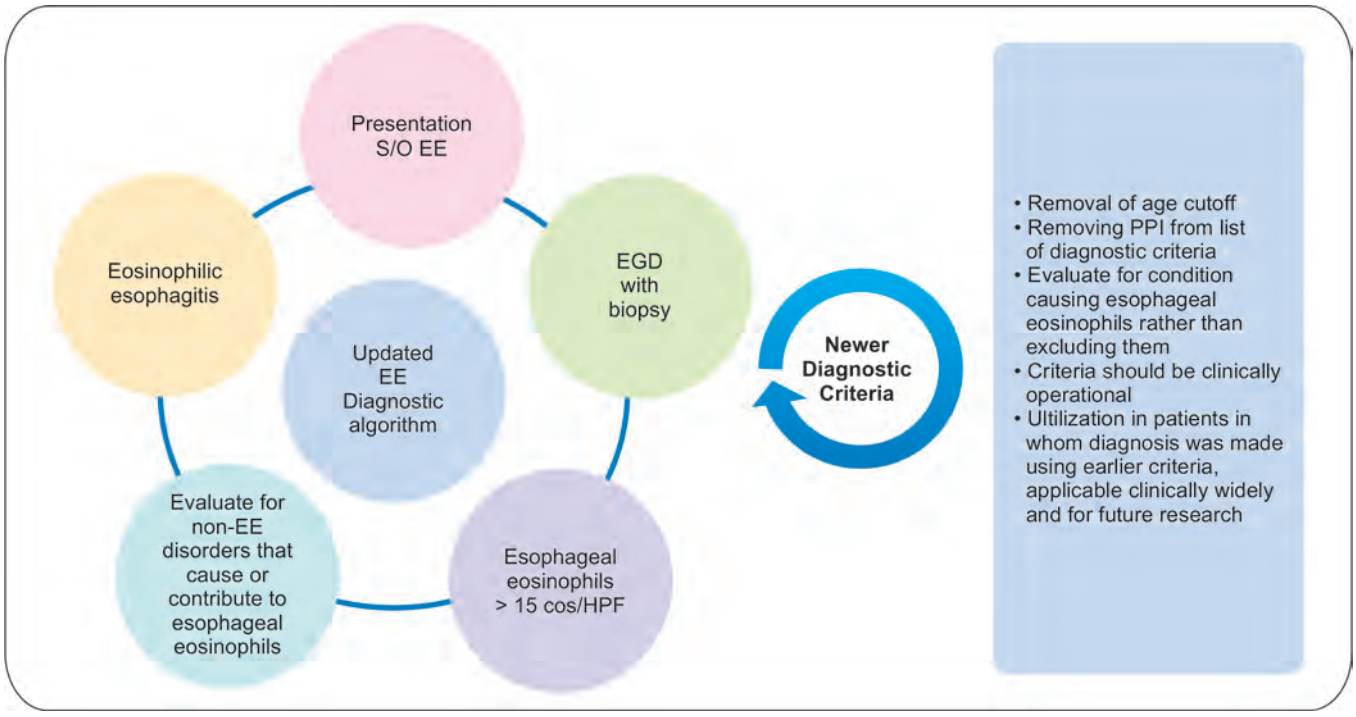

Fig. 3: Showing the updated EoE algorithm and the principles in newer diagnostic criteria

TABLE 3 Follow up and monitoring response

Variable	*Non-response*	*Response*	*Complete remission*
Symptom	Less than 30% symptom persistence in a symptom metric	90% decrease in symptom metric. Eosinophilia decrease by 30%	Greater than 90 % response in symptom metric EEsAI score < 20
Endoscopy	Persistent endoscopic finding < 30% decrease in EREFS	Improved endoscopic findings EREFS ≥ 2 but less than baseline	Normal esophagus EREFS < 2
Histology	Persistent eosinophilia ≥15 eos/HPF	Reduced eosinophilia 7–14 eos/HPF to 1–6 eos/HPF	Normal biopsy < 1 eos/HPF

EEsAI, eosinophilic esophagitis symptom activity index; eos/hpf, eosinophils/high power field; EREFS, eosinophilic esophagitis endoscopic reference score

remodeling; improved esophageal diameter and dispensability.[41-44] Induction regimen of oral 1 mg budesonide twice daily for 2–4 weeks to reach clinical response followed by maintenance regimen of 0.25 mg twice daily for not less than 6 months after which steroid can be discontinued if remission is maintained. Deep remission was achieved at 89 weeks in 9.4% of adult EoE patients with corticosteroid discontinuation at 104.7 weeks and relapse at 22.4 weeks. Relapse is managed with induction regimen for 1–2 weeks. Esophageal candidiasis in 20% and herpetic infection, adrenal insufficiency were reported following steroid use. Oral and aerosolized fluticasone is also used.

- *PPI:* The ability of PPI to reduce inflammation—PPI responsive esophageal eosinophilia (PPI-REE) has made it a first-line therapeutic modality. Use of PPI (8 weeks) by a meta-analysis showed clinical response in 60.8%, histological remission in 50.5%, sustained remission in 73–86%.[45,46]
- *Leukotriene B4 inhibitor:* Use of Montelukast a leukotriene B4 inhibitor results in mast cell inhibition thereby reducing cytokine release retarding or preventing inflammatory cascade.
- *Biologicals:* These include monoclonal antibodies against IL-13, IL-5, IL-4, anti-tumor necrosis factor alpha (TNF alpha) and antibodies against immunoglobin E. Studies indicate a promise for dupilumab, monoclonal antibody acting on IL-4 receptor by a negative regulation of Th2 response causing inhibition of IL-4/IL-13 signaling.[47]

Dilatation therapy: Advanced disease with fibro-stenotic manifestation need endoscopic dilatation, incising of Schatzki's ring.

Reduction in esophageal subepithelial activity (ESEA) could evolve as a relevant objective endpoint of treatment. ESEA can be known by deeper biopsies guided by endosonography. Presently available instruments—biomarkers and clinical techniques—are limited or not fully utilized. This remains as a need to meet.[48,49]

Treatment Response and Monitoring: spectrum includes non-response, response, and complete remission **(Table 3)**. All biomarkers now on use are investigational and include IL-3, IL-5, IL-6, IL-13, transforming growth factor alpha, and beta, TNF alpha, eotaxin 1, 2, and 3 thymic stromal lymphoprotein (TSLP) and major basic protein and neurotoxin derived from eosinophils.

Future Directions

Aimed at identifying the antigens responsible for the inflammatory cascade, early detection of EoE, noninvasive biomarkers for detection and monitoring, target directed therapies and prevention of relapse after achieving remission.

Conclusion

EoE is a chronic antigen induced immune mediated progressive disease of the esophagus characterized by eosinophilic infiltration. This progresses from inflammation to fibrostenotic disease. Earlier diagnosis by liberal biopsies in symptomatic but with normal esophageal mucosa can identify more patients. Endosonography guided deeper biopsies will give more information on subepithelial activity, which results in fibrostenotic disease. Earlier intervention improve the quality and quantity of life with less morbid and mortality indices. Increasing awareness amongst family physicians and patients with allergic disorders coupled with esophageal biopsies is desirable.

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CHAPTER

137 Non-Cirrhotic Portal Hypertension in India

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Abstract

Non-cirrhotic portal hypertension is an entity with a normal hepatic venous pressure gradient (HVPG) but significant portal hypertension. It could be due to pre-hepatic, hepatic, or post-hepatic causes. The most notable etiologies are extrahepatic portal vein obstruction (EHPVO) and non-cirrhotic portal fibrosis (NCPF) while other causes include schistosomiasis, congenital hepatic fibrosis, and regenerative nodular hyperplasia. The pathogenesis for NCPF and EHPVO is multifactorial and not very clear. However, there is evidence to suggest the role of a prothrombotic state and infection. EHPVO presents 10–20 years before NCPF and they both predominantly present with gastrointestinal bleed without other decompenstations. In severe cases, they may have ascites and encephalopathy as well. They differ in their association of portal biliopathy, associated autoimmune conditions, histology, and diagnostic modalities needed. Diagnosis is established easily for EHPVO by Doppler ultrasonography; however, NCPF requires exclusion of cirrhosis and may necessitate a liver biopsy. Treatment options include variceal ligation and beta-blocker for secondary prophylaxis of bleeding. A major complication of EHPVO is portal biliopathy which needs endoscopic therapy if cholangitis occurs. Shunt surgeries remain important in the long term; however, their role for bleeding has reduced due to better endotherapy and availability of newer modalities like TIPSS. With advent of better therapy, the prognosis of these conditions has improved and most patients live a healthy life.

Introduction

Portal hypertension (PHT) is usually defined by araised hepatic venous pressure gradient (HVPG) more than 5 mm Hg. HVPG is the difference in pressure between portal vein (PV) and inferior vena cava. The most common cause of PHT is cirrhosis in which case the HVPG is raised due to sinusoidal resistance. However, there is another group of diseases with PHT, but a normal HVPG, which are grouped under non-cirrhotic PHT (NCPH). Causes of NCPH are primarily vascular and may be prehepatic, hepatic, and posthepatic **(Table 1)**.

Non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal venous obstruction (EHPVO) are two common causes of NCPH and will be discussed in detail while others will be discussed briefly in the chapter.

Non-Cirrhotic Portal Fibrosis

NCPF is a disease without a specific known cause, because of which it is also termed as idiopathic PHT. Hallmark features include massive splenomegaly, often with hypersplenism with no liver cell failure.[1] The disease is commoner in developing countries. The disease accounts for 10–30% of cases of variceal bleed in several parts of the world including India.[2] However, a recent review compiling the studies from India showed a declining prevalence in prospective studies.[3] It is seen most commonly in the age group of 30–40 and has a male preponderance.

Etiopathogenesis

The accurate etiopathogenesis is unknown; infections and prothrombotic states are the factors which have been

TABLE 1 Important causes of non-cirrhotic portal hypertension

Prehepatic	*Hepatic*	*Posthepatic*
EHPVO Splenic vein thrombosis Massive splenomegaly	• Presinusoidal—PBC, PSC, schistosomiasis, NCPF, congenital hepatic fibrosis • Sinusoidal—Alcoholic hepatitis, drug induced fibrosis • Postsinusoidal—Budd Chiari syndrome, sarcoidosis, tuberculosis, veno-occlusive disease	• Posthepatic Budd Chiari syndrome (IVC web, RA thrombosis) • Restrictive cardiomyopathy • Severe tricuspid regurgitation

EHPVO, extrahepatic portal vein obstruction; IVC, inferior vena cava; NCPF, non-cirrhotic portal fibrosis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; RA, right atrium.

incriminated most commonly. Although data is limited, better obstetric hygiene and neonatal care are likely the reason behind to bring down the incidence of NCPF. This has been shown in Western countries and supports the role of hygiene in pathogenesis of disease.[1] India is more predisposed as populations have lack of clean drinking water, inadequate sewage facilities, and continuous gut inflammation due to antigenic exposure. Autopsy series from western countries showing high prevalence of PV thrombosis lend support to the role of prothrombotic factors. An imbalance of low ADAMTS13 and von Willebrand factor levels could be linked to promotion of PV radicals. This was first established from relation between therapeutic arsenic exposure (Fowler's solution) and NCPF in Europe. It has been shown to be associated with autoimmune diseases like inflammatory bowel disease (IBD) and celiac disease. Patients with HIV have shown a higher prevalence of NCPF.[4] Possible contributory factors could include opportunistic gastrointestinal (GI) infections, antiretroviral therapy or the effect of the viral by itself.

Extrahepatic Portal Venous Obstruction

EHPVO is a cause of PHT seen predominantly in children. The central pathophysiology involves a chronically blocked PV supplying blood via collaterals to a normally functional liver. EHPVO is the commonest cause of PHT (up to 80%) and uppergastrointestinal bleeding (up to 60%) in children in developing nations.[5]

In children, specific prothrombotic states are identified less commonly and methylene tetrahydrofolate reductase (MTHFR) deficiency is the commonest. Amongst adults and in western nations, primary myeloproliferative disorders (MPD) are common. Overall, prothrombotic states are found in one third to half the cases. Thrombosis may also occur due to inflammation in the local milieu or paraneoplastic thrombosis. In spite of all evaluation, up to 70% cases may remain idiopathic.

Etiopathogenesis

Perinatal history is important as sepsis and manipulation of the umbilical vein have been implicated as inciting factors.[6] At the time of diagnosis, most of the times a cavernoma is seen as the initial thrombosis is often missed as it is asymptomatic and there is formation of collaterals within 1–2 weeks followed by cavernoma in another week. These collaterals are able to compensate partially and overcome the prehepatic obstruction, but their insufficiency leads to formation of varices.

Diagnosis

The typical scenario when one should suspect NCPF and EHPVO is presentation with GI bleed with relatively well preserved liver function tests. Ultrasound of the abdomen provides a further clue since massive splenomegaly is seen in both conditions, which is larger than cirrhosis. Doppler shows a thrombosed PV with surrounding collaterals (cavernoma) in case of EHPVO and normal flow in NCPF.

Clinical Features

EHPVO presents in the first decade with peaks at 3 and 8 years of age.[7] NCPF on the other hand is seen more in young and middle aged adults median age of onset in Indian series being 30–32 years.[8] Patients often give a history of long standing dull aching pain in the left upper abdomen due to massive splenomegaly; however, it requires medical attention infrequently. Unlike cirrhosis, the episodes of variceal bleed are often not life threatening and well tolerated. Being a childhood chronic disorder affecting the

TABLE 2 Differences between NCPF and EHPVO

	NCPF	*EHPVO*
Nature of precipitating event	Mild, recurring	Severe, progressive
Affected age	Childhood and adolescence	Early childhood
Associated autoimmune diseases	Yes	No
Growth retardation	Not seen	Seen
Portal biliopathy	Not seen	Seen
Encephalopathy	Usually absent	Minimal HE usually occurs in natural history
HVPG	Normal or elevated	Normal
Investigation of choice for diagnosis	Liver biopsy	Ultrasound Doppler
Hallmark on liver biopsy	Obliterative portal venopathy	Normal liver architecture unless secondary biliary cirrhosis occurs

EHPVO, extrahepatic portal vein obstruction; HVPG, hepatic venous pressure gradient; NCPF, non-cirrhotic portal fibrosis.

liver blood supply, EHPVO is often complicated by anemia and growth retardation **(Table 2)**.

Incidences of variceal bleed are frequently precipitated by infections and recurrences tend to decrease after puberty. Hypersplenism is present in both the disorders. Although liver cell failure is rare, ascites may occur in up to one third of the patients. This usually occurs after a bleed and is related to low serum albumin levels or in cases of secondary biliary cirrhosis. The left upper abdomen pain may be exacerbated and acute at times of perisplenitis or splenic infarction.

On clinical examination, liver span is normal or slightly reduced. Peripheral clinical stigmata of cirrhosis are absent. Icterus may be seen in EHPVO in those with portal biliopathy.

Laboratory Parameters

Hypersplenism with anemia is the commonest finding. Liver function tests are usually normal; however, albumin levels in serum may be reduced at the time of bleed further creating a diagnostic dilemma with cirrhosis. Elevated conjugated bilirubin and cholestatic pattern (raised alkaline phosphatase) may be a harbinger of portal biliopathy in long standing cases.[7] Prolonged prothrombin time, reduced fibrinogen is seen in most patients. The shunted blood flow leads to impaired production of coagulation factors and lead to a low grade of disseminated intravascular coagulopathy.[9] Hyperdynamic circulation is seen in both conditions and along with raised nitric oxide has been proposed to lead to autonomic dysfunction. Cell mediated immunity may be hampered.

Findings on Esophagogastroduodenoscopy

Esophageal varices are seen in more than 80% of patients. Compared to cirrhotics, esophageal varices are larger and gastroesophageal varices are commoner.[10] Ectopic varices in the rectum and colon may lead to lower GI bleed in EHPVO.

Radiological Features

At clinical suspicion, ultrasound of the abdomen with Doppler for splenoportal axis is the initial investigation of choice. In NCPF, liver is normal in size and spleen is enlarged with a dilated and patent splenoportal axis. PV is thickened (>3 mm) and intrahepatic branches show a withered tree appearance. The etiological workup for cirrhosis is negative. NCPF may mimic early stage cirrhosis very often and only HVPG can reliably differentiate between them. The diagnosis of EHPVO in children is usually much simpler as the finding of a portal cavernoma replacing the PV has a very high sensitivity and specificity. In adults, with cirrhosis, it becomes difficult as cirrhosis may also lead to bland PV thrombosis. There is cavernomatous transformation of PV. CT and MR venography have better sensitivity and also provide a roadmap to surgery.[11]

Pathology

EHPVO can be reliably diagnosed by USG; however, a liver biopsy may be needed to differentiate early cirrhosis and NCPF. The characteristic pathological findings for NCPF by phlebosclerosis, periportal, and perisinusoidal fibrosis, aberrant vessels in portal tract, preserved lobular architecture, and "obliterative portal venopathy."[12] In cases of EHPVO, the PV is replaced by cluster of varying sized vessels more so around the hilum. Nodular arrangement and fibrosis, which are characteristic of cirrhosis are absent.

Natural History

The natural course of NCPF is usually much more predictable as compared to the complexity seen in EHPVO sometimes. A likely reason for this is the early insult in life, which leads to a long time available for the disease to progress insidiously. It may lead to short stature, parenchymal destruction, poor quality of life, hepatic encephalopathy, and portal biliopathy.

Once GI bleed is controlled after variceal eradication, long-term prognosis in NCPF is excellent. Liver cell failure and decompensation is usually absent but may occur at times of GI bleed or in nodular NCPF.[13] Uncontrolled upper GI bleeding from varices may lead to mortality.

While the general outcome of EHPVO is good, certain complications need to be monitored and treated carefully. Growth retardation occurs in up to half of the children. The postulated mechanism behind this is deprivation of hepatotropic factors and malabsorption due to portal hypertensive enteropathy.[14] They also have a poor health-related quality of life.

Portal biliopathy is defined as cholangiographic abnormalities, which occur in patients with *portal* cavernoma. This may be intrahepatic or extrahepatic. Long standing portal cavernoma in the biliary region causes compressive and ischemic changes on the biliary tree. Portal biliopathy usually remains asymptomatic may lead to jaundice, biliary colic, abdominal pain, and recurrent cholangitis. Another dreaded complication is minimal hepatic encephalopathy (MHE). It is understandably more after shunt surgery but it may occur even prior to surgery.[15] Usage of lactulose improves MHE. Prolonged portal biliopathy leads to extinction of liver parenchyma gradually and may mimic cirrhosis later. It may manifest as poor synthetic function, jaundice, and decompensation in the form of ascites.

Treatment

The event that can change the natural history of a patient with NCPH is massive upper GI bleed. Control of the index bleed and prevention of further bleed is the focus in most cases. Another aspect of the treatment is symptomatic splenomegaly and hypersplenism. Rest of the treatment revolves around complications like MHE, portal biliopathy, and growth failure.

Control and Prophylaxis of Variceal Bleed

Variceal bleed is an important complication in NCPH. In view of limited data as compared to variceal bleed, guidelines recommend the principles of management to remain same.[16] The patient should be resuscitated with fluids and be taken up for endoscopy within 24 hours. Endotherapy in the form of endovascular ligation is the mainstay of therapy in terms of intervention. Older studies used more of sclerotherapy. These techniques are successful in more than 80% patients. Vasoactive agents should be started prior to endotherapy to reduce the severity of bleed and possibly control it. The goal should be variceal eradication as role of beta blockers is not very clear although they are widely used. Non-selective beta blockers should be used for secondary prophylaxis.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is an option for treatment for complicated NCPH, especially those with recurrent or refractory bleed. However, it is best avoided in cases of renal dysfunction, malignancy, or prothrombotic conditions.

Surgery

The most common indication for surgical management is recurrent bleed or bleed refractory to endotherapy. Other indications are symptomatic hypersplenism, hepatopulmonary syndrome, or portopulmonary hypertension.[17] Surgery has now mainly been replaced by TIPS. The types of surgeries performed are:

- *Shunt procedures:* They bypass blood from the portal system to systemic circulation removing the carvernoma from the pathway. Shunts may be

physiological or non-physiological depending on whether they preserve the hepatic portal blood flow or not (maintained in physiological). As is expected, surgery reduces complications of PHT like varix size and spleen size; however, adverse effects from portosystemic shunting include risk of MHE and shunt nephropathy.[18] Selective shunts like distal splenorenal shunt are associated with less complication than proximal, non-selective shunts. Shunt surgery is undertaken only after a particular age (generally 8 years) and with a favorable anatomy (adequate shuntable vein diameter).[19]

- *Ablative procedures:* These surgeries are very morbid and include visceral devascularization with or without splenectomy. It has gone out of vogue due to advances in endotherapy and is reserved for emergency scenarios.

Salvage Emergency Therapy

In spite of newer endoscopic modalities, in 10% of the cases endotherapy fails. Options then include ablative procedures, TIPS, or balloon occluded retrograde transvenous obliteration.[16,17]

Routine anticoagulation is not recommended in EHPVO or NCPF according to the current available data. The management for portal biliopathy is generally supportive and not curative. Biliary stenting is done using ERCP for biliary strictures.[20]

Miscellaneous Causes of NCPH

Although infrequently seen in clinical practice, a few important causes of NCPH that merit discussion have been described here.

Schistosomiasis

Schistosomiasis is one of the most common causes of NCPH in the world but rarely seen in India. *Schistosoma mansoni* and *Schistosoma japonicum* are the two main species of Schistosoma that are known to cause liver disease. *S. japonicum* is distributed throughout the world and *S. mansoni* is endemic to Africa and Middle East. Both are however not found in India. The eggs are stuck in the portal venules and lead to granulomatous inflammation. Over a period, fibrosis occurs and portal pressures increase.[21] Chronic hepatic schistosomiasis is characterized by hepatomegaly with features of PHT. Diagnosis is based on detection of eggs in stool or rectal biopsy or ELISA test for antigen. On ultrasound, PV radicles show echogenic thickening giving the appearance of a mesh of fish scales. There may be complete reversal of periportal thickening with use of antihelminthic like praziquantel.

Congenital Hepatic Fibrosis

Congenital hepatic fibrosis (CHF) is a developmental disorder of the portobiliary system characterized histologically by defective remodeling of the ductal plate and progressive fibrosis of the portal tracts.[22] It is usually autosomal recessive in inheritance and presents in the first or second decade of life. Autosomal recessive polycystic kidney disease and ciliopathies are commonly associated disorders.[23] Clinical findings include an enlarged, abnormally shaped liver and splenomegaly with preserved liver functions. Biliary complications include cholangitis and an increased predisposition to cholangiocarcinoma. Imaging reveals dilatation of biliary system and enlarged caudate lobe and splenomegaly. Since no specific therapies are available, treatment of complications and eventually liver transplant may be needed.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules. It is common in Europe and Japan with preponderance amongst octogenarians.[24] There is a limitation of population based studies on NRH. It can be caused by various drugs (commonly chemotherapeutic agents and immunosuppressants), hematological, autoimmune, inflammatory, and neoplastic disorders. Pathogenesis appears to be related to adaptive hyperplastic reaction of hepatocytes in response to mechanical or functional abnormalities of portal hepatic blood flow. Pathologically, it is differentiated from cirrhosis by absence of perinuclear collagen and fibrous septa. Most patients remain asymptomatic, but some present with NCPH. Treatment is aimed at removal of inciting factor and management of primary disease.[25]

Conclusion

NCPH are important causes of PHT in developing countries like India. The most important disorders are NCPF in adults and EHPVO in children. The complications if managed well, patients can have a good prognosis and leave a healthy life.

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CHAPTER

138 Drug-induced Liver Injury

Harshad Devarbhavi

Abstract

Drug-induced liver injury is an under-diagnosed cause of liver disease. It mimics all forms of liver disease. The three patterns of DILI are hepatocellular, cholestatic, and mixed. Presence of hepatocellular jaundice in DILI is associated with a mortality of >10%; this is also known as "Hy's law". Combination anti-TB drugs, i.e., isoniazid, rifampicin, and pyrazinamide are the most common cause of DILI and drug-induced acute liver failure (ALF) in India followed by traditional and complementary medicines. Prompt recognition and cessation of the "culprit" drug is the key to managing patients with DILI followed by supportive therapy. Few antidotes include N-acetyl cysteine for paracetamol toxicity and drug-induced ALF, cholestyramine for leflunomide DILI, and steroids for drugs associated with hypersensitivity features or drugs causing autoimmune like hepatitis.

Introduction

Drug-induced liver injury (DILI) is underdiagnosed and underappreciated as a cause or contributor to liver injury. Drugs and toxins should be considered in the differential diagnosis of all types of liver injury across all ages, although the risks are higher in older individuals and in women. It is not clear why older individuals or women have an increased risk; this may be due to increased intrinsic risk or because older people take more drugs and therefore have more opportunities to experience adverse drug reactions (ADRs). This review will focus on recent concepts on DILI with particular emphasis on DILI from India.

DILI is a diagnosis of exclusion. A high degree of suspicion and consequently a careful history of prescription medication and over the counter drugs (pain killers) exposure as well as exposure to herbal and traditional medicines or dietary supplements (often overlooked by the physician) should be obtained. While most patients experience DILI within the first 2–3 months of therapy, in some instances (e.g. amoxicillin-clavulanate related DILI) symptoms can present with up to a month delay after treatment cessation or arise after months of exposure to a drug such as nitrofurantoin, minocycline, and alpha methyldopa.[1]

Causality Assessment

Since DILI is a diagnosis of exclusion there are no established diagnostic markers. Causality assessment methods are used to determine likelihood of a drug causing liver injury and the best known is the Roussel Uclaf causality assessment method (RUCAM).[2] Information on time to onset (latency), course of reaction upon medication discontinuation, time to resolution, risk factors, concomitant drugs exclusion of other causes, prior knowledge on DILI potential, and response to readministration are variables required to establish a compatible relationship with the suspected

causative agent. The degree of causality is assessed as definite (highly probable), probable, possible, and unlikely in descending order of strength.[2]

Case Definitions and Severity

Transient asymptomatic minor elevation of aspartate transaminase (AST) or alanine transaminase (ALT) is common during routine evaluation. In one study incidence of baseline liver chemistry abnormalities in a population of over 18,000 patients (without underlying liver disease), the baseline prevalence of any ALT elevation above the upper limit of normal (ULN) was 6% while the overall prevalence of ALT values of more than 3 × ULN was 0.076% (<1 in 1,000).[3]

Transient elevation of AST or ALT may occur following exposure to medication and may resolve on its own or with continuation of drugs or following decrease in dose. This phenomenon (*called adaptation*) is characteristic of antituberculosis (anti-TB) drug or statin therapy and depends on the frequency of liver biochemistry estimation. Awareness of this condition will prevent inappropriate withdrawal of medications such as in the treatment of tuberculosis where even a temporary cessation of treatment may have adverse disease outcome including risk of drug resistance.[4] Transient elevation of transaminases in patients with elevated liver enzymes while on statin therapy (e.g. in patients with coronary heart disease or diabetes)[5] is not an indication to stop therapy.

DILI is defined as an adverse hepatic reaction that is unexpected on the basis of the pharmacological action of the drug administered. International expert panel[1] recommended DILI to be considered when any one of the following thresholds are met *even in the absence of symptoms*:

- ALT or AST ≥ 5 × ULN
- ALP ≥ 2 × ULN in the absence of extrahepatic source driving the rise in ALP level
- Total bilirubin concentration exceeding 2 × ULN associated with any elevation of the aminotransferases or alkaline phosphatase.[1]

In the presence of symptoms including extrahepatic symptoms of hypersensitivity such as skin rashes or eosinophilia, ALT or AST ≥ 3 × ULN is deemed to be DILI. The symptoms related to DILI are often similar to that of acute liver injury or cholestasis due to other etiology including any of the following: fever, nausea, vomiting, jaundice, dark urine, right upper quadrant pain, skin rashes, and itching.[1]

The level of elevation of liver enzymes alone does not reflect liver function severity. Liver enzyme elevation is a reflection of liver injury not function, whereas bilirubin elevation (liver excretory function), or increased INR or decreased albumin (liver synthetic function) are more accurate indices of liver function.[6] The presence of jaundice, or development of ascites, coagulopathy, and/or encephalopathy indicates severe disease[1] and connotes poor prognosis.[7]

Hy's Law

Hyman Zimmerman observed the presence jaundice in the setting of DILI suggested severe hepatocellular functional impairment with potential for liver failure and 10–50% mortality.[6,8] Thus, "Hy's law" is used clinically and during drug evaluation to indicate highly significant and severe hepatotoxic potential of a drug when patients fulfill the following criteria, that is, AST or ALT more than 3 × ULN + bilirubin >2 × ULN (in absence of biliary tract disease).[8] Presence of jaundice during anti-TB therapy results in a mortality of 16–26% in India.[7,9] Patients with anti-TB DILI who fulfill Hy's law criteria have a mortality of 17%. Furthermore, development of acute liver failure during treatment of anti-TB drugs results in a mortality in two-thirds of patients.[10] Paradoxically in the Indian setting a substantial proportion of individuals who develop anti-TB DILI, never required the drugs in the first place, having received anti-TB drugs empirically on a presumptive basis.[10,11] Therefore, great caution should be exercised while administering anti-TB drugs empirically, especially in women, the elderly, and those with comorbidities.[12]

Patterns of Liver Injury

Most patients with DILI in clinical practice are characterized based on their liver biochemistry, these are categorized as hepatocellular, cholestatic, or mixed pattern of DILI.[1] Pattern of liver disease is based on Ratio (R value) of ALT (or AST) activity expressed as fold elevation over its ULN laboratory range to ALP activity. Pattern of DILI is hepatocellular when R is ≥5, cholestatic when R is ≤2 and mixed when R is 2–5.[1] The pattern of liver injury has implications for prioritizing immediate

investigations essential to exclude alternative causes of the event as well as prognosticate outcome.

Examples of drugs associated with above patterns and other additional patterns are listed below:[13]

- *Hepatocellular:* Isoniazid, rifampicin, pyrazinamide, diclofenac, lamotrigine, minocycline, nitrofurantoin, nevirapine, efavirenz, sulfonamides, disulfiram.
- *Cholestatic:* Chlorpromazine, erythromycin, penicillins, amoxicillin-clavulanate, sulfonamide, terbinafine, androgens, oral contraceptives.
- *Mixed pattern:* Phenytoin, carbamazepine, lamotrigine, sulfonamides.
- *Drug reaction with eosinophilia and systemic symptoms (DRESS):* Carbamazepine, phenytoin, phenobarbitone, allopurinol, lamotrigine, cephalosporins, dapsone, sulfonamide, nevirapine.
- *Autoimmune like hepatitis:* Nitrofurantoin, α-methyldopa, minocycline, diclofenac, statins, adalimumab, infliximab, herbals and complimentary medicines.
- *Nonalcoholic fatty liver disease (NAFLD):* Amiodarone, methotrexate, tamoxifen, 5-fluorouracil, amiodarone, didanosine, stavudine.
- *Vanishing bile duct (ductopenic) syndrome:* Azathioprine, amoxicillin-clavulanate, carbamazepine, chlorpromazine, erythromycin, phenytoin, terbinafine and cotrimoxazole.

Causes

Antibiotics are the most common cause of idiosyncratic DILI and drug-induced acute liver failure worldwide and also in India.[7,9,13-16] In India, first-line combination anti-TB drugs, isoniazid, rifampicin, and pyrazinamide are the commonest agents causing DILI accounting for 46% of all cases followed by complementary and alternative medicines at 14%.[9] Combination anti-TB drugs accounts for 67–72% of cases of drug-induced acute liver failure followed by anti-epileptic drugs (10%), and dapsone (5.5%) in a single center series.[9,17,18] DILI from anti-TB drugs appears disproportionately more severe than other drugs causing liver injury.[7] Almost three-fourths of anti-TB DILI occur within the first 2 months of administration of drugs although the risk of DILI persists throughout the course of treatment.[19] Paradoxically paracetamol-induced DILI and liver failure is very uncommon in India and accounts for less than 1% of DILI or drug-induced ALF.[9,18] This is in stark contrast to the high incidence of paracetamol hepatotoxicity in western countries. In a prospective India nationwide study,[9] drugs causing DILI in the descending order of frequency were as follows:

- Combination anti-TB drugs (46.4%)
- Complementary and alternative medicines (13.9%)
- Antiepileptic drugs (AED) (8.1%)
- Non-anti-TB antimicrobials (6.5%)
- Antimetabolites (3.8%)
- Antiretroviral drugs (3.5%)
- NSAIDs (2.6%)
- Hormones (2.5%)
- Statins (1.4%)
- Others (11.3%)

Although patients with pre-existing liver disease are not more likely than others to experience hepatic injury on exposure to drug, recovery from DILI in patients with chronic liver disease is generally poor.[20] Complementary and alternative medicines (73%) and anti-TB drugs (22%) are responsible for 99% of cases of drug-induced acute on chronic liver failure (ACLF) in India and Asia and is associated with 46% mortality, much more than other causes of ACLF.[21]

Mechanism of Liver Injury

Simplistically, the mechanism of DILI may be divided into two broad groups, that is, direct hepatotoxicity as exemplified by paracetamol overdose or idiosyncratic injury wherein the characteristics of the individual patient/subject plays a major role in causing DILI.[20] In idiosyncratic reaction, the dose of a drug does not play a role although most DILIs are encountered following exposure to drugs used in daily dose of 50 gm or higher.[22] **Table 1** summarizes the characteristics of mechanism of injury. A recently described third category is the indirect hepatotoxicity, wherein hepatotoxicity is secondary to the indirect action of agent on liver or immune system **(Table 1)**.[23]

Management

The first consideration in the management of DILI is to harbor a high index of suspicion regarding the role of medications in causing liver injury. The drugs implicated should be stopped immediately and alternate causes including viral hepatitis especially hepatitis E (which is common in Northern India)[24] and biliary causes

TABLE 1 Mechanism of drug-induced liver injury and associated features

Basis for injury	*Dose dependence*	*Incidence in humans*	*Latent period*	*Implicated agents*
Direct (intrinsic) hepatotoxicity	Yes	Common (1–100%)	Often short	Paracetamol, ferrous sulfate, i.v. amiodarone, IV methotrexate, aspirin, cancer chemotherapy
Idiosyncratic (unpredictable reaction)	No	Rare (1:10000)	Often long and variable	INH, rifampicin, pyrazinamide amox-clavulinate, sulfonamides, cephalosporins
Indirect hepatotoxicity	No	Intermediate	Delayed (months)	Steroids, anti-TNF, Anti-CD20, checkpoint inhibitors, protein kinase inhibitors

(by ultrasonography) should be excluded. Most episodes of DILI resolve with discontinuance of the culprit drug and with supportive treatment. There are very few antidotes for specific drugs producing DILI. These include N-acetylcysteine for paracetamol toxicity,[25] desferrioxamine for ferrous sulfate toxicity, L-carnitine for valproate DILI, and cholestyramine for leflunomide DILI. Patients who develop hypersensitivity skin rashes and eosinophilia or DRESS should be considered for steroid treatment, which should be continued for 4–8 weeks, although steroids have not been evaluated in a randomized fashion.[26]

Reintroduction of anti-TB drugs after an episode of anti-TB DILI needs special mention. The American Thoracic Society guidelines are the most up to date and elaborate.[27,28] Ethambutol has no hepatotoxic potential and needs to be continued during and after DILI. Rifampicin is the least hepatotoxic drug and needs to be considered first followed by isoniazid and pyrazinamide. These drugs may be administered sequentially with staggered doses. In case of a severe DILI at index presentation, pyrazinamide should be omitted during rechallenge.[27]

Conclusion

Anti-tuberculosis drugs are the most common cause of DILI and drug-induced acute liver failure in India. DILI is a diagnosis of exclusion. Awareness of the fact that drugs can mimic all forms of liver disease is crucial in diagnosing DILI. Occurrence of hepatocellular jaundice entails a mortality of >10%, and hence the implicated drug should be stopped immediately. There is emerging evidence of the increasing role of traditional and complimentary medicines in causing DILI all over the world including India.

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CHAPTER

139 Achalasia Cardia—Diagnosis and Endoscopic Treatment

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Abstract

Achalasia cardia is a primary esophageal motility disorder due to autoimmune neurodegeneration of esophageal myenteric plexus resulting in impaired relaxation of lower esophageal sphincter (LES) on swallowing and failure of peristalsis in distal smooth muscle segment of the esophagus. High resolution manometry (HRM) has greatly improved the sensitivity of diagnosing achalasia in the early stages of disease when endoscopy and barium esophagogram can be normal or equivocal. Manometrically achalasia cardia can be divided into three subtypes, which help in deciding treatment, and hence have prognostic significance. The primary distinction from other motility disorders (e.g., Jackhammer esophagus and distal esophageal spasm) is failure of LES relaxation in achalasia. So, most of the therapies are directed toward reduction in LES pressures. Treatment modalities in AC acts by causing either mechanical disruption of LES by per oral endoscopic myotomy (POEM), laparoscopic Heller's myotomy (LHM) and pneumatic dilatation (PD) or biochemical reduction in LES pressure (pharmacological therapy, e.g., nitrates and botulinum toxin). There is renewed interest in this motility disorder in the past few years as with the advent of third space endoscopy (i.e., POEM), the endoscopic management of achalasia has been revolutionized.

Introduction

Achalasia cardia (AC) is rare yet most common and best characterized esophageal motility disorder.[1] It is equally common in both sexes and most frequently observed in 40–60 years age.[2] AC is characterized by progressive degeneration of ganglion cells in the esophageal myenteric plexus resulting in impaired relaxation of lower esophageal sphincter (LES) on swallowing and failure of peristalsis in distal smooth muscle segment of the esophagus.[1] Presenting symptoms are dysphagia to both liquids and solids, regurgitation of undigested food, retrosternal chest pain, heartburn, weight loss, and symptoms due to aspiration pneumonia.[3] Upper GI endoscopy and timed barium esophagogram are the initial investigations and high resolution manometry (HRM) is diagnostic.[4] Therapy in AC is directed toward reduction in LES pressures either by biochemical reduction or mechanical disruption of LES. Mainstay of management of AC is by pneumatic dilatation (PD), per oral endoscopic myotomy (POEM) and laparoscopic Heller's myotomy (LHM) in surgical fit candidates. Biochemical reduction of LES by botulinum toxin (BT)/pharmacotherapy (nitrates, calcium channel blockers) are reserved for surgical unfit patients or patients with limited life expectancy due to short lasting efficacy. Esophagectomy is reserved for surgically fit patients with long standing symptoms who failed multiple therapies repeatedly.[2,5] In this chapter we shall focus on diagnosis and endoscopic treatment (BT, POEM, and PD) of AC.

Diagnosis

History and Clinical Examination

Dysphagia to both solids and liquids (85–91%), regurgitation of undigested food (75–91%), substernal chest pain and

TABLE 1 Clinical features favoring esophageal motility disorder over mechanical dysphagia

	Esophageal motility disorder	***Mechanical dysphagia***
Duration	Long standing	Short in malignant
Course	Intermittent	Progressively increasing
Relation with food and posture		
Relation with type of food	Both liquids and solids from the onset	Soilds then liquids later on
Relation with posture	Decreased with raising arms and erect position	No such
Relation with temperature of food	More in extreme temperatures (hot and cold)	None
Associated symptoms		
Regurgitation	Common	Unusual
Chest pain	Episodic pain highly suggestive	Usually painless
Weight loss	No or minimal	Profound

TABLE 2 Eckardt score

Score	***Dysphagia***	***Regurgitation***	***Retrosternal pain***	***Weight loss (kg)***
0	None	None	None	None
1	Occasional	Occasional	Occasional	<5
2	Daily	Daily	Daily	5-10
3	Each meal	Each meal	Each meal	>10

heartburn (40–60%), weight loss and aspiration pneumonia (8–10%) are the various symptoms of achalasia.[3,6,7] Appropriate history taking help to differentiate esophageal motility disorders from mechanical dysphagia **(Table 1)**. Liquids require better neuromuscular coordination than solids for esophageal emptying so dysphagia to both solids and liquids are present from the onset. Compression of the esophagus between spine and manubrium sterni in specific postures like raising arms in erect position increase the intraesophageal pressure and propel food in aperistaltic esophagus.

Achalasia is often misdiagnosed as gastroesophageal reflux disease (GERD) as retrosternal chest pain and heartburn are common. Reflux or lactate production by fermentation of undigested carbohydrates lead to heartburn. Chest pain is least responsive to treatment compared to other symptoms but can spontaneously disappear over time.[7] Weight loss is not as profound as in mechanical dysphagia. Aspiration pneumonia can occur due to regurgitation into bronchopulmonary tree can lead to cough and fever. Impaired belching due to compression of membranous trachea by dilated esophagus and inadequate relaxation of upper esophageal sphincter is a rare but noteworthy symptom in achalasia.[8] Eckardt score is a system for evaluation of achalasia symptoms and treatment efficacy which is based on degree of dysphagia, regurgitation, chest pain, and weight loss **(Table 2)**.[9] Clinical examination is usually unremarkable except emaciation and oral cavity ulcerations in some patients. Examination of the respiratory system may show diminished breath sounds, dull note on percussion, and crepitations over area of consolidation due to aspiration pneumonia.[6]

Diagnostic Tools

Primary Diagnostic Tools

Upper GI endoscopy and timed barium esophagogram are the initial investigations in any case of dysphagia. Once, mechanical obstruction is ruled out on endoscopy/barium swallow, HRM is diagnostic and helps subclassification.[10]

Upper GI Endoscopy

Normal upper GI endoscopy rules out mechanical causes of dysphagia. Upper GI endoscopy in AC shows dilated and often tortuous esophagus with food/liquid residue.

The contracted LES in AC does not open spontaneously and is usually traversed with a gentle pressure with the endoscope unlike neoplastic/fibrotic strictures.[6] The esophageal mucosa is usually normal in AC but can develop erythema and ulceration due to food stasis (stasis esophagitis). Stasis predisposes to esophageal candidiasis. Tertiary contractions may be noticed during endoscopy due to spontaneous, simultaneous contractions of esophageal smooth muscles. An esophageal epiphrenic diverticulum (EED) (pulsion type pseudodiverticulum) can be associated with AC, which makes endoscopic therapy challenging but yet feasible.[11]

Laboratory Work Up

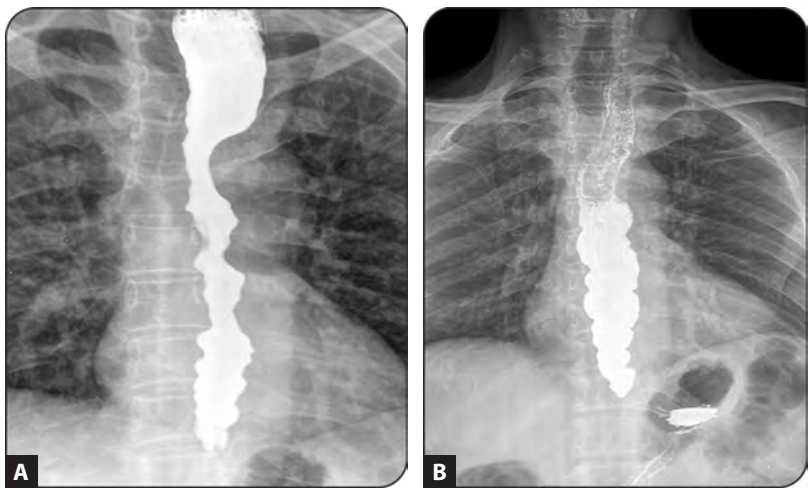
Complete blood count, serum creatinine, serum electrolytes, liver function tests, and thyroid profile can be done as a part of work up for endoscopic/surgical myotomy, which requires general anesthesia.

Imaging

Timed barium esophagogram: Timed barium esophagogram is the imaging of choice in AC. 100–250 mL of barium (45% weight/volume) is swallowed by the patient over 15–20 seconds and X-ray done at 1, 2, and 5 minutes.[12] The height and width of the barium column in esophagus is measured at 1, 2, and 5 minutes which denotes the esophageal emptying. In AC, there is delayed emptying of barium from the esophagus, tertiary contractions and bird-beak appearance **(Figs. 1A and B)**. It is done in both pre- and post-treatment states in AC to evaluate response to therapy. Hugely dilated esophagus or megaesophagus (>7 cm) can be seen in late/long standing cases of AC. Dilated, tortuous esophagus in late stage AC is termed as sigmoid esophagus. Both mega-esophagus and sigmoid esophagus denote decompensated disease, which implies poor response to therapy. Esophageal epiphanic diverticulum (EED) can rarely be found in association with AC.[12]

Other imaging: Chest X-ray may be required in AC to evaluate for aspiration pneumonia. Computed tomography (CT) of chest could be helpful to rule out pseudoachalasia. Endoscopic ultrasound (EUS) findings of marked (>10 mm)/asymmetric lower esophageal wall thickening suggest underlying malignancy.[13]

High resolution manometry (HRM) **(Table 3)***:* HRM is superior to conventional esophageal manometry for diagnosis and classification of AC with higher sensitivity and reproducibility. AC can be classified into three subtypes according to Chicago classification 3.0 **(Table 3) (Fig. 2A)**.[4] Type I AC represents later stage disease leading to dilated atonic esophagus due to minimal esophageal muscle activity. Type II AC is characterized by panesophageal pressurization indicating simultaneous contraction of esophageal muscles between upper and LES due to disorganized neuromuscular activity of esophagus



Figs. 1A and B: Timed barium esophagogram (TBE) in achalasia cardia. (A) Preprocedure TBE after 1 minute showing tertiary contractions and dilated esophagus and no esophageal emptying. (B) Preprocedure TBE after 2 minutes showing dilated esophagus with minimal esophageal emptying

(Fig. 2B). Panesophageal pressurization indicates that esophageal smooth muscle tone is still intact, and hence type II AC represents early stage of disease. Type II AC is the most common subtype of AC and most responsive to PD. Type III AC is characterized by premature, spastic contraction of the distal esophagus **(Fig. 2C)**. Type III AC is least common and least responsive to both endoscopic and surgical therapy.[2]

TABLE 3 High resolution manometry diagnostic criteria of achalasia cardia[27]

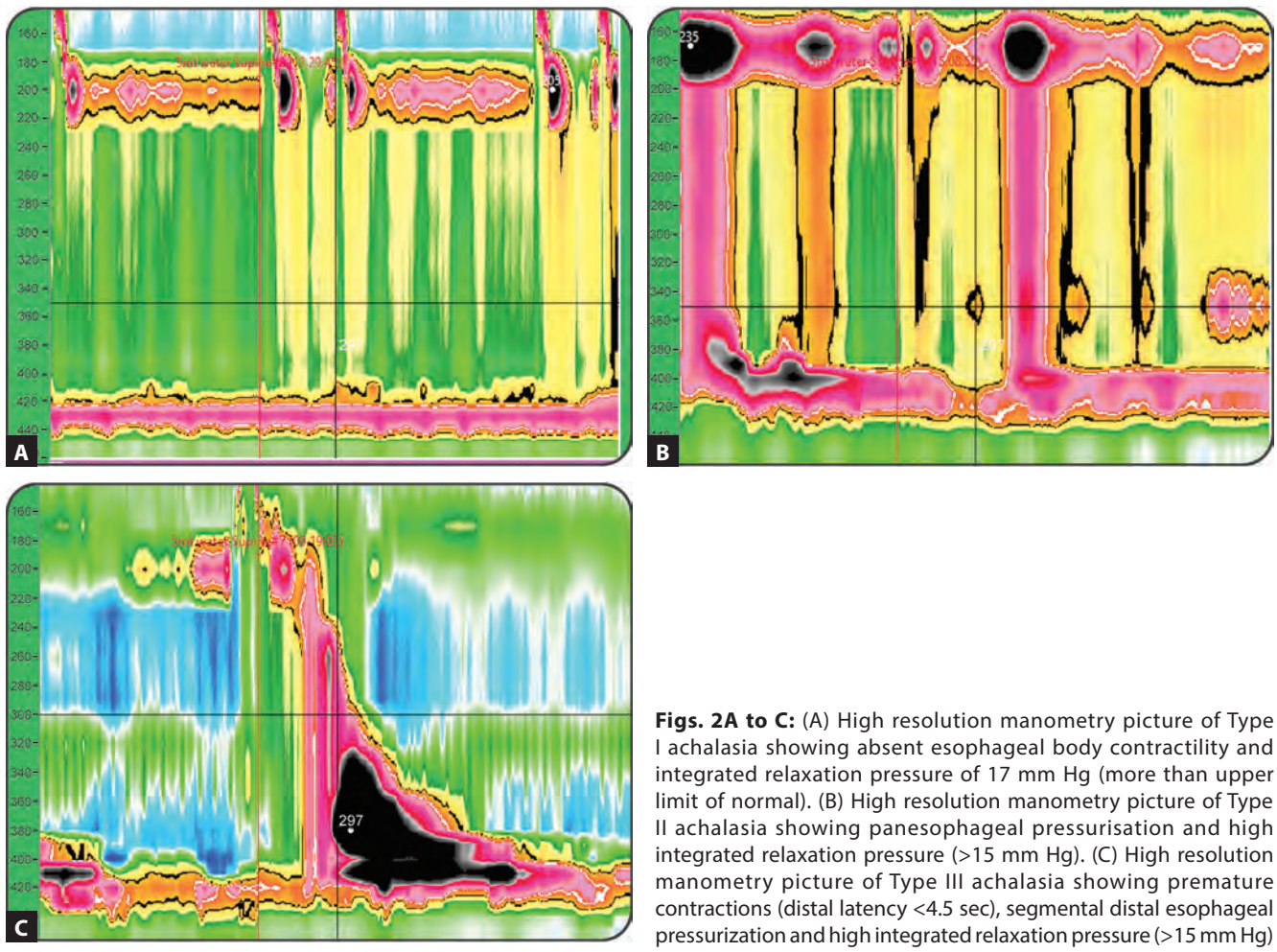
Integrated relaxation pressure (IRP) > upper limit of normal with 100% failed peristalsis
• Type I: No contractility, no esophageal pressurization, IRP >10 mm Hg
• Type II : Panesophageal pressurization in ≥20% swallows, IRP> 15 mm Hg
• Type III: Premature contractions (distal latency <4.5 s) in ≥20% swallows, Segmental esophageal pressurization, IRP>15 mm Hg

Differential Diagnosis (Table 4)

The differential diagnoses of AC are GERD, pseudo-achalasia, esophageal motility disorders, and mechanical dysphagia.

Management

The goal of management of AC is symptomatic relief of dysphagia and associated complications. Treatment directed at underlying pathology is not available as pathophysiology is poorly understood. Treatment of AC is directed by AC subtypes and surgical risk of the patient.[2] Mechanical disruptions of LES by PD, LHM, or POEM



Figs. 2A to C: (A) High resolution manometry picture of Type I achalasia showing absent esophageal body contractility and integrated relaxation pressure of 17 mm Hg (more than upper limit of normal). (B) High resolution manometry picture of Type II achalasia showing panesophageal pressurisation and high integrated relaxation pressure (>15 mm Hg). (C) High resolution manometry picture of Type III achalasia showing premature contractions (distal latency <4.5 sec), segmental distal esophageal pressurization and high integrated relaxation pressure (>15 mm Hg)

TABLE 4 Differential diagnosis of achalasia cardia

Suspected diagnosis	*Clinical clues*	*Diagnostic testing*
GERD	Normal clinical examination	• History of reflux, regurgitation and heartburn • Endoscopic findings of esophagitis, Lax LES, or hiatus hernia • 24 Hour pH monitoring
Pseudoachalasia	Hepatomegaly (may suggest liver metastasis) and supraclavicular lymph nodes	• Symptoms of dysphagia • Endoscopic finding of mechanical resistance at GE junction and may show GE junction tumor • EUS may show asymmetric, thickening of GEJ (>10 mm) • CT chest may show extrinsic compression by tumor or lung malignancy
Other motility disorders (Distal esophageal spasm, Jackhammer esophagus)	Hot and cold food sensitivity and disproportionate chest pain relative to dysphagia could be a diagnostic clue	• On high resolution manometry • Normal IRP • Distal esophageal spasm (DES) (>20% premature contractions: distal latency <4.5 sec) • Jackhammer esophagus (>20% swallows with distal contractile integral -DCI >8000 mm Hg.s.cm)
Mechanical dysphagia	Duration and course of dysphagia, relation to food/posture and associated symptoms can differentiate (*See* **Table 1**)	• Endoscopy usually shows mechanical obstruction (malignancy, web, strictures, etc.) • Biopsy can be taken if any growth is noted in endoscopy • Barium swallow findings show asymmetric, long segment strictures with shouldering

*Chicago Classification v.3.0[27]

are the mainstays of AC treatment. However, in patients with high surgical risk and/or limited life expectancy, biochemical reduction of LES pressure can be attempted (botulinum toxin ± pharmacotherapy). In this review we shall discuss endoscopic treatment of AC (botulinum toxin, PD, and POEM).

Botulinum Toxin

BT blocks release of acetylcholine (ACh) from the presynaptic cholinergic nerve terminals. Selective loss of inhibitory nitrinergic (NO producing) ganglion cells with partial preservation of cholinergic neurons is responsible for such therapeutic benefit.[14] Hundred units of vacuum dried BT powder is dissolved in sterile saline solution (4 mL) and 1 mL (25 U) each is then injected into all four quadrants via sclerotherapy needle under endoscopic guidance at 1 cm above the Z line (squamocolumnar junction). Doses >100 U do not have increased efficacy. BT decreases LES pressure in one third of patients and improves dysphagia in two-thirds of patients of AC for up to 6 months. Up to 50% patients require reinjection by 612 months.[15] The short lasting effect is due to growth of new cholinergic neurons leading to loss of efficacy. Side effects like esophageal perforation, mediastinitis, and heartburn/chest pain can occur post BT, but BT is usually safe.[16] Repeat injections can be done for patients in whom surgical risk remains high even on follow-up but it can lead to fibrosis precluding continued BT injections/other endoscopic therapy. Hence, repeated BT injections should be used in patients with high surgical risk and poor life expectancy.[17]

Pneumatic Dilatation

PD is a recommended initial treatment for AC.[2] PD is done with Rigiflex balloon dilator (Microvasive, Milliford, MA, USA) available in three sizes (outer diameter: 30 mm, 35 mm, and 40 mm). Initially 30 mm balloon is used followed by progressively larger size balloon (graded approach) except in case of young male in whom 35 mm can be used initially due to poor response rate with 30 mm.[18,19] Graded dilatation is performed for index dilatation. Repeated dilatation on follow-up when required for recurrent symptoms is known as "on demand approach." Patient is kept on overnight fast. Conventionally the procedure is done under fluoroscopic guidance with conscious sedation although a novel technique without fluoroscopy under endoscopic guidance has been described.[20] Initially a guide wire (preferably 0.038 inch diameter) is passed into the stomach under endoscopic guidance and scope is withdrawn to the GE junction (GEJ). The length between

the incisors and GEJ is noted along length of endoscope. Endoscope is then withdrawn maintaining position of the catheter. Rigiflex balloon is passed over the guide wire into the stomach marking a tape in the dilating ballon catheter corresponding to distance from incisors to GEJ (balloon catheter working length 90 cm and diameter is 14 Fr). Alternatively small amount of radiographic contrast can be injected at the GEJ prior to placing catheter to mark the GEJ. Balloon (length 10 cm) is then placed across the GEJ under fluoroscopic guidance (by help of radiopaque marks in the balloon catheter). Small volume of dilute contrast can be used for radiographic visualization of balloon. As the placement of balloon waist is confirmed across GEJ, the balloon is gradually inflated with air to 10–15 psi until the balloon waist disappears and maintained for 1 minute **(Fig. 3)**. Adequacy of dilatation confirmed by waist obliteration, blood smearing of the balloon, chest pain, and mucosal tear/widening of GEJ. Adverse events are esophageal perforation (3–5%), hematoma formation, diverticula formation.[21] Incidence of GERD post PD is around 2–4%. Tachycardia, persistent chest pain more than 4 hours should alert the endoscopist for possible perforation. Contrast esophagogram should be done if perforation is suspected based. Small perforations can be managed conservatively with antibiotics and parenteral nutrition whereas large perforations with free flow of barium into mediastinum warrant urgent thoracotomy and repair. Hence, patients with high surgical risk should not be subjected to PD.[21] Age less than 40 years, chest pain, type III achalasia, and pretreatment esophageal diameter less than 4 cm are poor predictors of treatment success with PD. Response rate for chest pain is around 50%.[22] Based on available evidence (meta-analysis of three RCTs and one large RCT), clinical efficacy of PD is comparable with LHM although long-term durability (especially in young males) was higher in LHM compared to PD as higher proportion (24%) of patients had recurrent symptoms after PD requiring redilatation compared to LHM (14%).[23,24] PD was compared with POEM in a recent RCT which showed significantly higher success rate at 2 years follow-up with POEM compared to PD (92% vs. 54%). This low response rate in PD could be due to dilatation with only 30–35 mm balloon and inclusion of 40 mm balloon would increase response rate to 76% **(Table 5)**.[25]

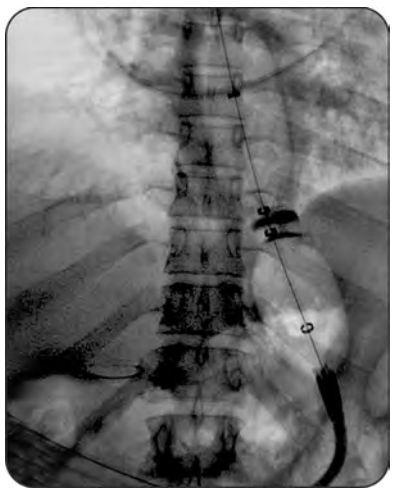


Fig. 3: Pneumatic dilatation in achalasia by Rigiflex balloon dilator. The waist of the balloon is seen between the two crus of diaphragm and radiopaque marks can be seen in the balloon catheter

Per Oral Endoscopic Myotomy

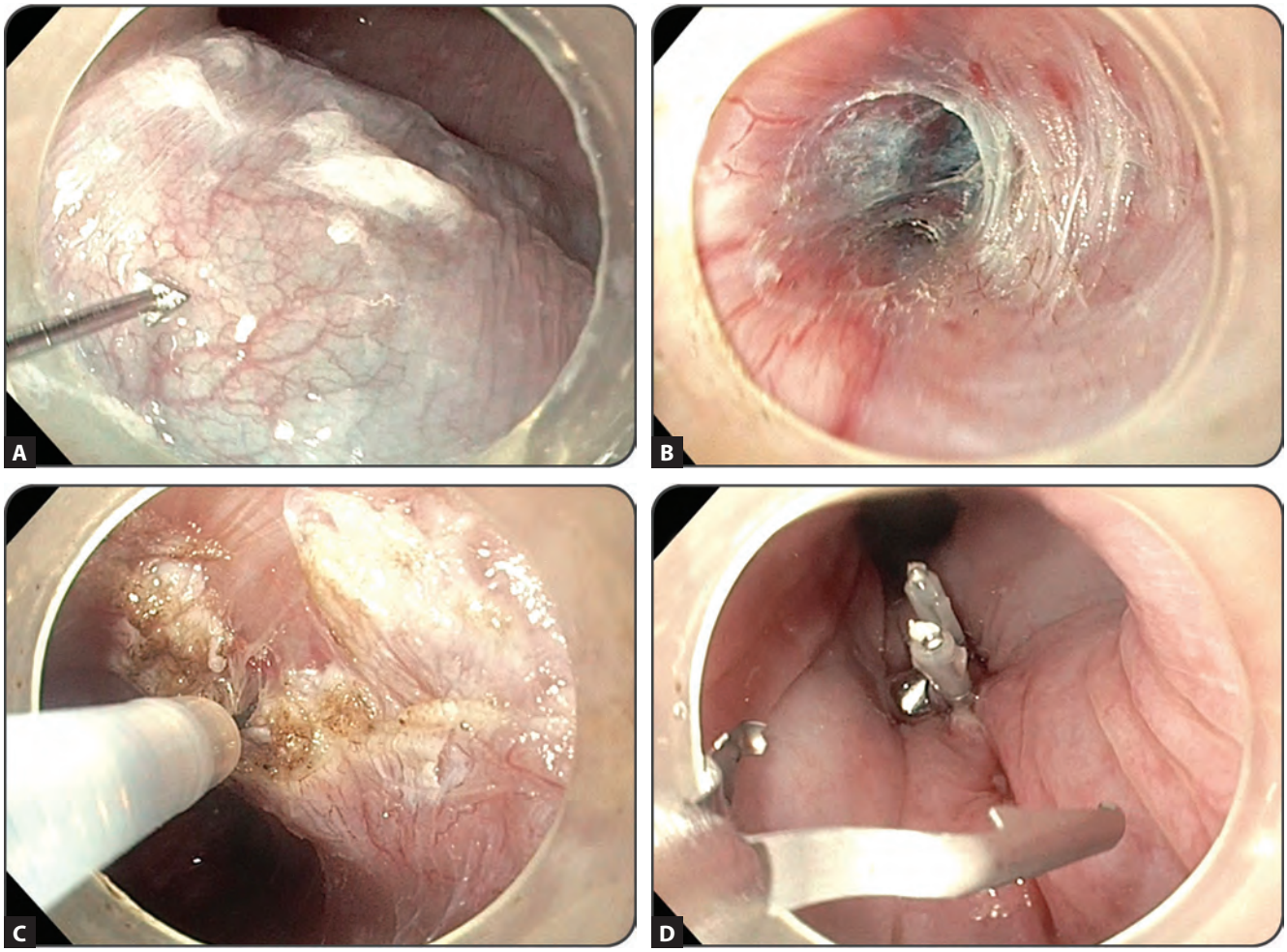
POEM is a form of natural orifice transluminal endoscopic surgery (NOTES), which uses submucosal endoscopy to perform myotomy and is efficacious for both treatment naive and treatment failure cases. The procedure is done under general anesthesia with endotracheal intubation and carbon dioxide insufflation.[26] There are four steps of POEM: mucosal incision, creation of submucosal tunnel, myotomy, and closure of mucosal incision **(Fig. 4)**. Normal saline (10 mL) mixed with 0.3% indigocarmine is injected approximately 13 cm proximal to GEJ and 2-cm longitudinal incision is made anteriorly or posteriorly with the use of triangular tip (TT knife) **(Fig. 4A)**. Endoscope with transparent cap inserted into submucosal tunnel and tunnel is extended by injection and cautery **(Fig. 4B)**. Attention should be given not to injure the mucosal layer by keeping the scope close to circular muscle layer. The tunnel should be one third of the esophageal circumference and should extend 3 cm distal to the GEJ. GEJ is identified by palisade vessel visualization/narrowing of tunnel/visualization of aberrant longitudinal muscle bundle/by transillumination of ultra-slim gastroscope in the submucosal tunnel. Myotomy should begin at 2–3 cm distal to mucosal entry and initially circular muscle is cut with TT knife until longitudinal muscles are visible **(Fig. 4C)**. Then myotomy should continue in the plane between circular and longitudinal muscle fibers. Prior to closure, 20 mL saline with 80 mg gentamicin is injected into the tunnel

TABLE 5 Landmark randomized controlled trials comparing outcome of various treatment modalities for achalasia cardia

Name/year	*Comparison*	*n*	*Success*	*Follow-up*	*Adverse events*	*GERD*	*Drawbacks*
Moonen et al., 2016[22]	PD vs. LHM + Dor Fundoplication	n-96 n-105	82% 84%	5 years	5% 11%	12% 34%	Re-dilatation required in 25% of PD patients—considered as treatment success
Boeckxstaens et al., 2016[24]	PD vs. LHM + Dor Fundoplication	n-96 n-105	86% (2 years) 90% (2 years) p=0.46	43 months	4% 12%	15% 23%	• Follow-up short as effect may decrease over time • Rigorous PD protocol over 2 years—only 3rd series of PD within 2 years of 2nd series considered as failure
Ponds et al., 2019[25]	POEM vs. PD	n-67 n-66	92% 54%	2 years	0% 3.03 %	41% 7%	• Only allowed PD up to 35 mm • Considered re-dilatation as treatment failure
Werner et al., 2019[38]	POEM vs. LHM + Dor fundoplication	n-112 n-109	83% 81.7% (p=0.007 non-inferiority)	2 years	2.7% 7.3%	44% 29%	• Length of myotomy was not standardized • POEM was not accompanied by any anti-reflux procedure where LHM was done with for fundoplication

and then mouse incision is closed by application of 5–10 clips at a distance of 5 mm applying first clip at the distal end of the longitudinal incision **(Fig. 4D)**. A water soluble contrast esophagogram is done at postoperative day 1 (POD1) to exclude leak and ascertain smooth passage of contrast into stomach. Routine CT most procedure is not warranted. Patients, who tolerate oral diet and timed barium esophagogram has shown no leak, can be started on liquid diet on POD1, pureed diet on POD2 and regular diet from POD4. Initial clinical success with POEM is 82–100% and intermediate term efficacy at 2 years is 78–91% at 2 years follow-up.[27-29] The choice of anterior (1 o'clock) or posterior myotomy (5–6 o'clock) is operator dependent and based on clinical scenario as there is equal efficacy of both the approaches with shorter procedure time in posterior approach.[30,31] Adverse events can be insufflation related (pneumoperitoneum: 16–30%, 8% require decompression, pneumomediastinum: 8.7–11%, 2.7% require decompression, mediastinal emphysema: 4.9%, and subcutaneous emphysema: 21–36%), bleeding (early or delayed) an mucosal perforation (2.6%).[32] Low/extra low flow CO_2 can reduce the incidence of pneumoperitoneum (up to 10%). Tense capnoperitoneum manifested by high end tidal CO_2 can be treated with Veress needle.[33] Minor bleeding during dissection can be controlled with coagrasper or electrocautery knife. Significant delayed bleeding is rare (0.7%) and can be tackled by reentering the tunnel and coagulating the culprit vessel.[34] Mucosal perforation can be closed with clips ± endoloops, fibrin glue, suturing by overstitch device or fully covered metal stent. The prevalence of increased esophageal acid exposure, reflux esophagitis, and GERD symptoms after POEM ranges from 13% to 58%, 18% to 65%, and 17% to 40%, respectively.[35] Novel modifications of POEM by addition of fundoplication (POEM-F) like in LHM have been shown to reduce reflux in pilot studies.[36] Anterior gastric wall is retracted at GEJ to form endoscopic fundoplication wrap. Increased procedure time, cost, and uncertain durability are the drawbacks of this novel procedure. Preservation of sling fibers by identifying two penetrating vessels at distal end of myotomy can reduce degree of esophagitis.[37] A short course of proton pump inhibitor (PPI) for 1 month is recommended for all patients and further continuation of therapy should be based on pH metry, symptoms, and endoscopic finding of esophagitis.[2]

POEM has been shown to be superior to PD and non-inferior to LHM in two recent RCTs. It is emerging as one of the first-line options to treat AC **(Table 5)**.[25,38] Results of POEM are better than LHM, especially in type III achalasia due to ability to perform long myotomy based on length of spastic distal segment of esophagus.[2] POEM is also better than LHM in case of sigmoid esophagus and other spastic motility disorders.[39]



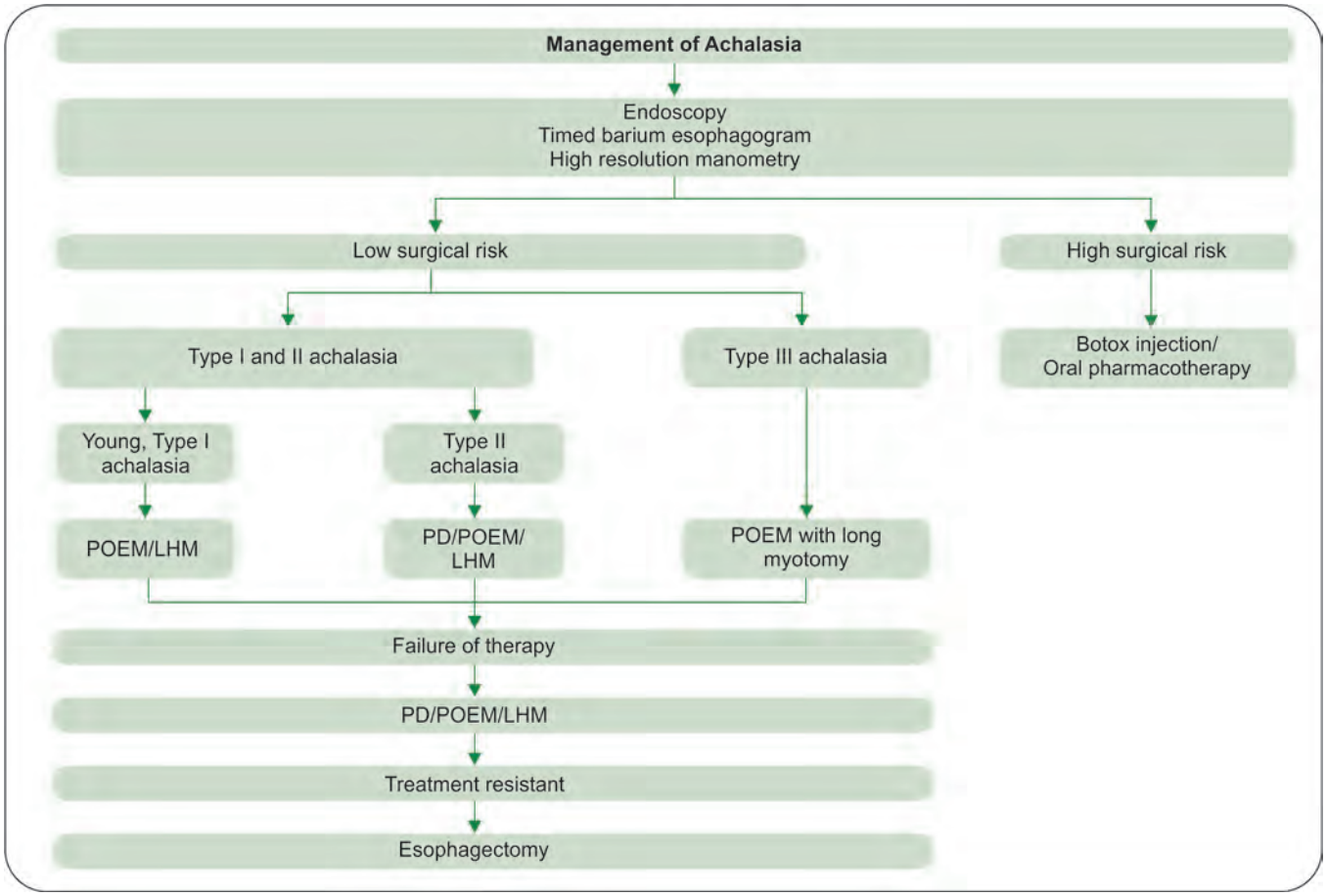
Figs. 4A to D: Steps of per oral endoscopic myotomy. (A) Mucosal incision, (B) Submucosal tunneling, (C) Myotomy, (D) Closure of mucosal incision

TABLE 6 Comparison of treatment efficacy of various treatment modalities in achalasia cardia

	PD	*LHM*	*POEM*
Type I AC	63.3–85%	81%	91.3%
Type II AC	90–93%	93–100%	96.3%
Type III AC	33.3–40%	80–86%	87.5–98%
Overall efficacy	44–84%	57–89.3%	75–97%
Follow-up (yrs)	≥5 years	≥5 years	1–3 years
GERD	2–4%	2–33%	20–54%

AC, achalasia Cardia; GERD, gastroesophageal reflux disease; LHM, laparoscopic Heller's myotomy, POEM, per oral endoscopic myotomy; PD, pneumatic dilatation

Flowchart 1: Diagnosis and management algorithm for achalasia cardia



Conclusion

Diagnosis of achalasia is based on clinical history and investigations like endoscopy, timed barium esophagogram, and HRM. Treatment of achalasia should be individualized **(Table 6) (Flowchart 1)**. Patients with high surgical risk should undergo BT/pharmacotherapy. For patients with low surgical risk options are PD, LHM with fundoplication, and POEM. In young (<40 years), type I achalasia POEM/LHM should be the first option of treatment as response rates to PD is low. In type II AC, PD can be used as initial option along with POEM/LHM as results to PD is best in type II AC. For type III AC, POEM with extended myotomy is recommended. On failure of therapy, any of the three modalities can be used as salvage therapy but POEM is preferred in both prior endoscopic failure. Esophagectomy should be reserved for end stage AC that is surgically fit with leg standing symptoms after repeated failure of different therapies.

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CHAPTER

140 Non-Variceal Upper GI Bleed—Clinical Approach

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Abstract

Non-variceal upper GI bleed could be caused by peptic ulcer disease, Mallory Weiss tear, erosive gastritis/duodenitis, esophagitis, and malignancy. The resuscitation and management go hand in hand. The hematocrit may be initially high due to adjustments in the vascular spaces and the physician should not be misled by it. Gastrointestinal endoscopy has revolutionized both the diagnosis and treatment of non-variceal upper GI bleed. Risk stratification tools enable physicians to assess the risks of mortality and rebleeding.

Introduction

Upper gastrointestinal (GI) bleed with source of bleeding in esophagus, stomach, or proximal duodenum comprises the major cases of non-variceal upper GI bleed of which peptic ulcer disease (related to *Helicobacter pylori* infection, use of NSAIDs, low dose aspirin) happens to be the most common cause.[1] Despite great advances in the field of medical gastroenterology, the annual incidence remains at around 50–150 per 100,000 population with a mortality of around 10–35%.[2]

The common causes of non-variceal upper GI bleed are peptic ulcer (20–50%), Mallory Weiss tear (15–20%), erosive gastritis/duodenitis (10–15%), esophagitis/esophageal ulcer (5–10%), malignancy (1–2%), angiodysplasias/vascular malformations (5%).[2] *Severe GI bleeding* is described as GI bleeding that is associated with shock or orthostatic hypotension, decrease in hematocrit by 6% or decrease in hemoglobin by 2 g/dL or transfusion requirement of at least two units of PRBCs. *Occult GI bleed* describes subacute bleeding that is not clinically visible. *Obscure GI bleed* refers to a type of bleeding wherein the site of bleed could not be determined after routine upper GI endoscopy, colonoscopy, and even a small bowel radiography.[3]

Initial Assessment

History and Physical Examination: Simultaneous to resuscitation, history taking and initial assessment of the vital signs is done. It is important to ask for history of nasopharyngeal malignancy, hemoptysis, heartburn, alcohol use, use of medicines (NSAIDs, aspirin), dysphagia, excessive vomiting, liver disease, chronic kidney disease.[3] Regarding physical examination, special attention should be paid to signs of hypovolemia like tachycardia, hypotension, orthostatic hypotension along with a close examination of the skin, lips, and buccal mucosa. The abdomen should be examined for tenderness, scar or any lump along with a rectal examination. Signs of chronic liver disease should be specifically looked for as they can help us differentiate variceal from non-variceal bleed.

Laboratory Studies

In addition to routine tests, it is important to do the blood grouping and cross matching of the patient as PRBC transfusion may be needed. The hematocrit of the patient may not reflect the actual amount of blood loss in the immediate period as the vascular space needs time to

adjust to the blood loss and administration of crystalloid intravenous fluid. Special attention should be paid to the mean corpuscular volume (MCV), serum ferritin, total iron binding capacity (TIBC), total leukocyte count (TLC), platelet count, prothrombin time (INR). The blood urea nitrogen (BUN) is usually higher than the serum creatinine in upper GI bleed cases due to intestinal bacteria acting on the blood proteins and increasing absorption of urea. Elderly patients, especially those who are known cases of cardiac ailment, need to have an ECG done.

Management

A case of upper GI bleed necessitates hospital admission, but those patients having mild bleed, being hemodynamically stable, near normal blood tests, with easy access to hospital care may be treated on outpatient basis. On the other hand, those patients who are hemodynamically unstable, have lost a large amount of blood, are having serious associated comorbidities need ICU admission.

Treatment of an upper GI bleed patient should start along with the examination and history taking. Once intravenous access has been established, crystalloids like normal saline are the fluid of choice and attempt should be made to keep the pulse below 100/min and the systolic blood pressure above 100 mm Hg. Blood transfusion with PRBC may be needed to keep Hb >7 g/dL.[4] The hematocrit level should be monitored every 4–8 hours. In cases of severe acute upper GI bleed or in patients with altered mental status, endotracheal intubation may be needed.

The advent of proton pump inhibitors (PPIs) has revolutionized the management of non-variceal upper GI bleed along with availability of endoscopic therapy. But then there are cons of PPIs like no change in blood transfusion requirements and no change in rebleeding rates (except in cases of PUD).[3]

Role of Endoscopy

GI endoscopy has brought in major advantages in the management of upper GI bleed, be it variceal or non-variceal. Important points to note are:

- Patient must be hemodynamically stable with heart rate of less than 100/min and systolic blood pressure greater than 100 mm Hg.
- There must be no respiratory difficulty, altered sensorium or ongoing hematemesis as these cases might needs endotracheal intubation first.
- Correction of coagulopathy and decreased platelet count is paramount.
- Emergency versus urgent endoscopy—those patients who have active high volume bleed need to undergo *emergency endoscopy* (within 6 hours) after medical resuscitation and preferably after having access to an ICU bed. *Urgent endoscopy* (within 12 hours) is suitable for patients who do not have ongoing hemorrhage and are hemodynamically stable.[3]
- Role of gastric lavage in upper GI bleed cases is controversial as some societies do not approve of it. However, in cases with large volume bleeding, careful gastric lavage and prokinetic agents like metoclopramide or erythromycin can help in endoscopic visualization.
- Around 1% of patients may experience complications like aspiration pneumonia, inadvertent bleeding, perforation, hypotension, hypoxia.

Endoscopic techniques of hemostasis have revolutionized the management of upper GI bleed. Amongst these techniques are the contact probes of which the multipolar electrocoagulation probe is the most commonly used. It enables to tamponade a bleeding vessel and then thermal energy is used to seal off the offending vessel. Risks include perforation, coagulation injury. Another useful technique is the use of endoscopic injection therapy mostly done with epinephrine, diluted to a concentration of 1:10,000 or 1:20,000 into or around the site of bleeding. It is easily available, cheap, safe in patients with coagulopathy, less chances of perforation or thermal burns. Then there are the endoscopic hemoclips that apply mechanical pressure to the bleeding site. Hemostatic spray is a kind of inorganic powder with clotting abilities.

Risk Stratification

There are several stratification tools to help patients with non-variceal upper GI bleed. These scores help identify patients with higher risk of mortality and rebleeding.[5,6] It enables physicians to assess patients who need higher medical care or urgent endoscopy. Amongst these scores, the pre-endoscopy scores are:

- BLATCHFORD SCORE—includes blood pressure, BUN, hemoglobin, heart rate, syncope, melena, liver disease, heart failure
- CLINICAL ROCKALL SCORE—includes patient's age, presence of shock, coexisting illnesses

- ARTIFICIAL NEURAL NETWORK SCORE- includes 21 variables to predict the presence of stigmata of recent hemorrhage and the need for endoscopic therapy.
- AIMS65—agregate of five variables like albumin <3 g/dL, INR >1.5, altered mental status, systolic BP ≤90 mm Hg, age >65 years.

Amongst the post-endoscopy scores, COMPLETE ROCKALL SCORE is most popularly used. It includes the Clinical Rockall Score and the endoscopic findings. This scoring system correlates well with mortality but not with risk of rebleeding.

Role of Surgery[3]

There are some situations where surgery plays an important role in non-variceal upper GI bleed cases:

- Cases of severe and ongoing hemorrhage wherein endoscopy and colonoscopy procedures fail to localize the bleeding site and control it.
- Cases of massive hemorrhage who are hemodynamically unstable need either an urgent angiography or urgent surgical exploration.
- Cases of severe, recurrent obscure GI bleed may benefit from surgical exploration.

Individual Etiologies

We shall now address some special issues pertaining to non-variceal upper GI bleed.

Peptic ulcer: With the advent of PPIs, it has been observed that worldwide, incidence of bleeding peptic ulcers has decreased whereas, bleeding from ulcers due to intake of NSAIDs, aspirin have gradually increased. However, in the developing countries it has been seen that the prevalence of *H. pylori* infection is nearly 80% whereas, in the developed countries it ranges between 20–50%. Amongst the patients taking NSAIDs gastric ulcers tend to be more common than duodenal ulcers. The Forrest classification[7] is used in cases of bleeding peptic ulcers to categorize the endoscopic findings:

Forrest 1A—active spurting bleed
Forrest 1B—oozing bleed
Forrest 2A—non bleeding visible vessel (NBVV)
Forrest 2B—adherent clot
Forrest2C—flat pigmented spot
Forrest 3—clean based ulcer

Patients with active arterial, NBVV, adherent clot are at high risk for rebleeding and would benefit from endoscopic therapies. Adherent clot is defined as a blood clot overlying an ulcer that is resistant to several minutes of vigorous jet water irrigation. When a clean based ulcer is found at the time of endoscopy, the chances of rebleeding are less than 5%. However, if it is a clean-based ulcer in the stomach, it is suggested that a biopsy of the ulcer edge and the gastric mucosa should be taken to rule out malignancy. In cases of gastric and duodenal ulcer suspected to be due to *H. pylori* infection, endoscopic mucosal biopsies of the normal looking antrum and greater curvature (midbody) should be taken. The role of PPIs in reducing rebleedingin peptic ulcer cases is more pronounced in people of Asian origin than others. Luminal gastric pH needs to be higher than 6.8 is needed for normal clotting function. H2 receptor antagonists can do this job but tolerance to this drug is the major hindrance. In case of PPIs this problem does not occur, thereby ensuring mortality benefit especially in Asian patients.[3]

Routine second look endoscopy in bleeding peptic ulcers is not always recommended[8] unless the first examination was inadequate due to poor visualization, technical issues with hemostasis or clinically significant rebleeding has occurred. Repeat upper GI endoscopy is advisable in cases of gastric ulcer after 6–10 weeks of acid suppression therapy. Those patients who continue bleeding despite two sessions of endoscopic hemostasis are suitable for angiographic embolization or surgery. Urgent surgery is advisable for those patients who have massive hemorrhage, who cannot be resuscitated. Also, if the endoscopic expertise is not available for treatment of a large or pulsating visible vessel and if on endoscopy, a bleeding malignant ulcerated mass is found, surgery is a more suitable option.

Following endoscopic hemostasis of patients with high-risk endoscopic stigmata (active arterial bleeding/NBVV/adherent clot), patient should be put on high dose intravenous PPI in a hospital setting. Drugs like NSAIDs, warfarin should be withheld. Those patients who need aspirin for cardiovascular illnesses may be started on the drug by day 7.

It is recommended to test all cases of bleeding due to peptic ulcer disease for *H. pylori* infection. Bleeding can however cause false negative result of *H. pylori*. Antibiotic therapy should be initiated for those found to be positive

for *H. pylori* infection. It is important to confirm the eradication of *H. pylori* once treatment is completed.[3] In cases of bleeding due to aspirin use, concomitant therapy with a PPI in future can reduce the rebleeding rates significantly. On the other hand, those patients who need to continue NSAIDs long-term, need to opt for selective COX2 inhibitors.

Esophagitis: Esophagitis may be caused due to gastroesophageal reflux disease (GERD), infections like Candida, Herpes simplex virus, Cytomegalovirus and also pill induced esophagitis,ultimately leading to upper GI bleed. GERD causing esophagitis and upper GI bleed is treated with a PPI for a period of at least 8–12 weeks along with lifestyle modifications. It is essential that these cases need to undergo a repeat endoscopy and biopsy to rule out Barrett's esophagus. For all the rest etiologies, endoscopic biopsy/brushing is taken and treatment is done according to etiology.[9]

Ulcer hemorrhage in hospitalised patients: There are two types of conditions usually seen in cases presenting with ulcer hemorrhage within the hospital—Stress Related Mucosal Injury/Stress Ulcer(SRMI) and Inpatient Ulcers. SRMI is characterized by diffuse bleeding from erosions and superficial ulcers, usually due to decreased mucosal protection and mucosal ischemia. It is most commonly seen in the stomach, and the most common risk factors are severe coagulopathy and mechanical ventilation for more than 48 hours. Prophylactic treatment with an H2 receptor antagonist or PPI can prevent bleeding in cases who are at high risk for SRMI. In those cases who present with UGI bleed, whether it is due to SRMI or inpatient ulcers, good medical treatment can help heal the lesions. Endoscopic therapy is feasible only in focal inpatient ulcer hemorrhage.[10]

Dieulafoy's lesion: This lesion comprises of a large submucosal artery that protrudes through the mucosa and can cause massive bleeding. Most commonly, such lesions occur in the gastric fundus, within 6 cm of the gastroesophageal junction. Whenever such a lesion is identified and treated endoscopically, it is suggested to mark the site with submucosal injection of ink for future need of easy identification and retreatment.[3]

Mallory-Weiss tears: This is characterized by mucosal or submucosal lacerations that start at the gastroesophageal junction and extend to a hiatus hernia sac distally. Usually the patients with Mallory-Weiss tear, present with non-bloody vomiting that is followed by hematemesis, probably due to raised intra-abdominal pressure. This lesion usually self heals but in cases with severe bleeding, endoscopic hemostasis may be attempted with hemoclips or multipolar electrocoagulation.[3]

Cameron's lesion: This lesion is described as linear erosions or ulcerations in the proximal stomach at the end of a hiatus hernia sac, near the diaphragmatic pinch due to mechanical trauma and local ischemia. It is a common cause of obscure GI bleed. Medical management is done with PPI and Iron supplements if needed.[3]

Neoplastic etiology: Tumors of the upper GI tract, mostly esophagus, stomach, or duodenum that are large, ulceroproliferative masses can present with upper GI bleed. Endoscopic hemostases is a temporary measure till the definitive management can be initiated. Those tumors that continue to bleed despite endoscopic hemostases need to undergo angiography with embolization. Wherever possible, GIST tumors should undergo resection.[3]

Gastric antral vascular ectasia (GAVE): This type of lesion is characterized by rows of ecstatic mucosal blood vessels that start from around the pylorus and extend proximally to the antrum. Also called "Watermelon Stomach", the exact cause of this lesion is not known, but may be due to mucosal trauma from contraction waves in the antrum. It has been found to be associated with cirrhosis, scleroderma, end stage renal disease. GAVE is targeted with endoscopic hemostatic methods like laser, MPEC, argon plasma coagulation. Besides these, medical management of anemia like iron supplements, blood transfusion may be needed.

Portal hypertensive gastropathy: This comprises of ectatic blood vessels in the proximal gastric body, cardia due to increased portal venous pressure and severe mucosal hyperemia. Management options are with beta-blockers, TIPS, liver transplantation. Endoscopic management does not have much role.

Hemobilia: Patients of hemobilia present with upper GI bleed and deranged liver function tests. It may occur as a complication in cases of liver biopsy, ERCP, TIPS or those who are suffering from hepatocellular carcinoma or parasitic infection of the hepatobiliary system. Side viewing endoscopy (SVE) is needed for diagnosis and

arterial embolization with arteriography may be used for treatment.

Hemosuccus pancreaticus: This kind of lesion is associated with pancreatic pathology or as a complication of ERCP or due to rupture of splenic artery aneurysm into the pancreatic duct. SVE is needed for diagnosis while angiographic embolization or surgery is needed for treatment purposes.

Aortoenteric fistula: This is a condition wherein patient presents with acute and massive hemorrhage with very high mortality rates. In some cases, there might be a herald bleed that may precede. Primary aortoenteric fistula is the communication between native abdominal aorta and third part of duodenum. Secondary aortoenteric fistula is a communication between the small intestine (most commonly, third part of duodenum) and an infected abdominal aortic surgical graft. In both the cases, surgery plays the more important role in management, and endoscopic hemostasis has no role.

Conclusion

The resuscitation and management of non-variceal upper GI bleed goes hand in hand. Prompt action on the part of the treating physicians as well as timely use of endoscopy for diagnosis and management can help save valuable lives.

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CHAPTER

141 Recent Updates in Management of IBS

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Abstract

Irritable bowel syndrome is a symptom complex resulting from an interplay of various gastrointestinal and extraintestinal factors. Previously thought to have been resulted as a pathology in the gut brain axis, the pathophysiology and management of IBS has been reconditioned recently. The introduction of new diagnostic criteria and concept of mutidimensional clinical profile has changed the management of IBS completely. In this chapter we have concised the most updated knowledge on the diagnosis and management of IBS and its various subtypes.

Introduction and Epidemiology

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder characterized by chronic abdominal pain and altered bowel habits, which are unexplained by any organic cause during routine workup.[1] It is not a disease, but a complex of symptoms arising out of pathologies of diverse clinical significance. IBS is a global problem with prevalence ranging anywhere from 1% to 45% of the general population having symptom complex satisfying the diagnostic criteria of IBS.[2,3]

More than one third of patients in GI practice have functional GI disorders (FGID) and of all the FGIDs, IBS accounts for the most common diagnosis.[4] The documented prevalence of IBS in Asians ranges from 4% to 9% depending on the criteria used.[5-7] IBS is twice as prevalent in women as compared to men globally.[8] However, there is no sex predilection in South Asia, South America, and Africa.[9] IBS significantly affects the quality of life and imposes a large burden to the patient and the health-care system.

Rome IV Criteria for Diagnosis of IBS: Something New Something Borrowed

Manning and Thompson in 1978 introduced the concept of making positive diagnosis of IBS using a set of criteria,[10] which led to an exemplar shift in the diagnostic approach in patients with IBS.

This was followed by Rome I, Rome II, and Rome III criteria pertaining to the origin of newer scientific evidences.

The Asian consensus[11] was published in 2010 considering the differences in dietary habits and stool frequency patterns in Asians, which was different from the criteria used to define stool frequency and stool form as they were based on the Western studies.

Rome IV criteria were published in 2016,[12] a decade after Rome III was introduced. Rome IV criteria emphasized on the gut brain interaction rather than the older concept of psychogenic predominant pathogenesis of IBS.

As per the Rome IV criteria IBS is defined as—Recurrent abdominal pain on average at least 1day/week in the last

3 months, associated with two or more of the following criteria:*

- Related to defecation
- Associated with change in frequency of stool
- Associated with change in form (appearance) of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Following changes are notable in Rome IV as compared to ROME III:

- Term abdominal discomfort has been deleted considering the dubious nature of the term and also that it is not present in every language.
- Abdominal pain to be present on at least 1 day/week based on scientific evidence[13]
- Bloating and distention are recognized as common symptoms
- Improvement with defecation has been replaced with related to defecation as it has been
- Found that many patients report increase in pain with defecation

ROME III Criteria: At least 3 months, with onset at least 6 months previously of recurrent (at least 3 days/month) abdominal pain or discomfort associated with two or more of the following:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form of stool

ASIAN Consensus: Recurrent abdominal pain, bloating, or other discomfort for ≥3 months associated with one or more of the following:

- Relief with defecation
- Change in stool form (show patient the Bristol Stool Scale)
- Change in stool frequency

ROME IV Criteria: Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following criteria:*

- Related to defecation
- Associated with change in frequency of stool
- Associated with change in form (appearance) of stool

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Rome IV also mentions about the location of pain, which can be present anywhere in the abdomen in contrast to the older criteria which considered lower abdominal pain as consistent with IBS.[14]

In context to Asian population, a Chinese study compared the diagnosis of IBS using the Rome III criteria as well as Rome IV criteria and showed lower sensitivity of Rome IV as compared to Rome III in Asian population and concluded that Rome IV positive patients were subgroup of Rome III with more severe manifestations of the disease.[15]

Rome IV also recognizes overlap syndrome amongst various FGIDs as observed in various studies.[16-18] This is an important step based on scientific evidence as it will help the clinicians to diagnose and manage such patients.

In 2019, Second Asian consensus on IBS[19] was published representing the current knowledge and management protocols in context to Asian population. The consensus emphasized that IBS is a disorder of Gut brain interaction rather than predominantly the psychopathological phenomenon. The consensus also encouraged the treatment based on micro-organic pathology.

Subtyping and Assessing the Severity of IBS: The Concept of Multidimensional Clinical Profile

The concept of multidimensional clinical profile was introduced to categorize patients on the basis of the severity of their symptoms along with psychological evaluation and physiological dysfunction **(Table 1)**. This helps the physicians to address other issues apart from only the categorical diagnosis.

Severity assessment helps physicians to rationally approach any patient, and necessitate the aggressive management of patients with severe symptoms. Various scales have been used to assess the severity of IBS, but none have been accepted till date.

Multidimensional clinical profile also emphasizes on the micro-organic basis of IBS such as abnormal gut transit, post-infectious IBS, low-grade inflammation, gut dysbiosis, dietary intolerance, abnormal intestinal permeability, and central as well as peripheral nervous dysregulation **(Flowchart 1)**.

Subtyping of IBS is essential as it helps in defining the targeted therapy and those with mixed type and unclassified types need modifications of the pathophysiological process such as alteration of Gut microbiota or neurohumoral regulation.

TABLE 1 Severity assessment of IBS patients on the MDCP model[20]

Clinical features	*Mild*	*Moderate*	*Severe*
Psychometric correlate	FBDSI, <36 IBS-SSS, 75–175	FBDSI, 36–109 IBS-SSS, 175–300	FBDSI, >110 IBS-SSS, >300
Physiological factors	Primarily bowel dysfunction	Bowel dysfunction and CNS pain dysregulation	Primarily CNS pain dysregulation
Psychosocial difficulties	None or mild psychosocial distress	Moderate psychosocial distress	High psychosocial distress, catastrophizing, abuse history
Sex	Men = women	Women > men	Women >>> men
Age	Older > younger	Older = younger	Younger > older
Abdominal pain	Mild/intermittent	Moderate, frequent	Severe/very frequent or constant
Number of other symptoms	Low (1–3)	Medium (4–6)	High (≥7)
Health-related quality of life	Good	Fair	Poor
Health-care use	0–1/yr	2–4/yr	≥5/yr
Activity restriction	Occasional (0–15 days)	More often (15–50 days)	Frequent/constant (>50 days)
Work disability	<5%	6–10%	≥11%

IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhea-predominant IBS; IBS-M, mixed IBS; FODMAP, fermentable oligo-, di-, monosaccharides, and polyols.

Multidimensional Clinical Profile of Irritable Bowel Syndrome

- Categorical diagnosis (symptom-based criteria)
- Clinical modifier (IBS-C, IBS-D, IBS-M, post-infectious, FODMAP sensitive)
- Impact (mild, moderate, severe)
- Psychosocial modifier
- Physiological dysfunction and biomarkers

Treatment

An incorporative approach including patient education, cognitive behavioral therapy, diet, and lifestyle modification are required for the management of IBS.

This usually needs an involvement of the dietician and a clinical psychologist.

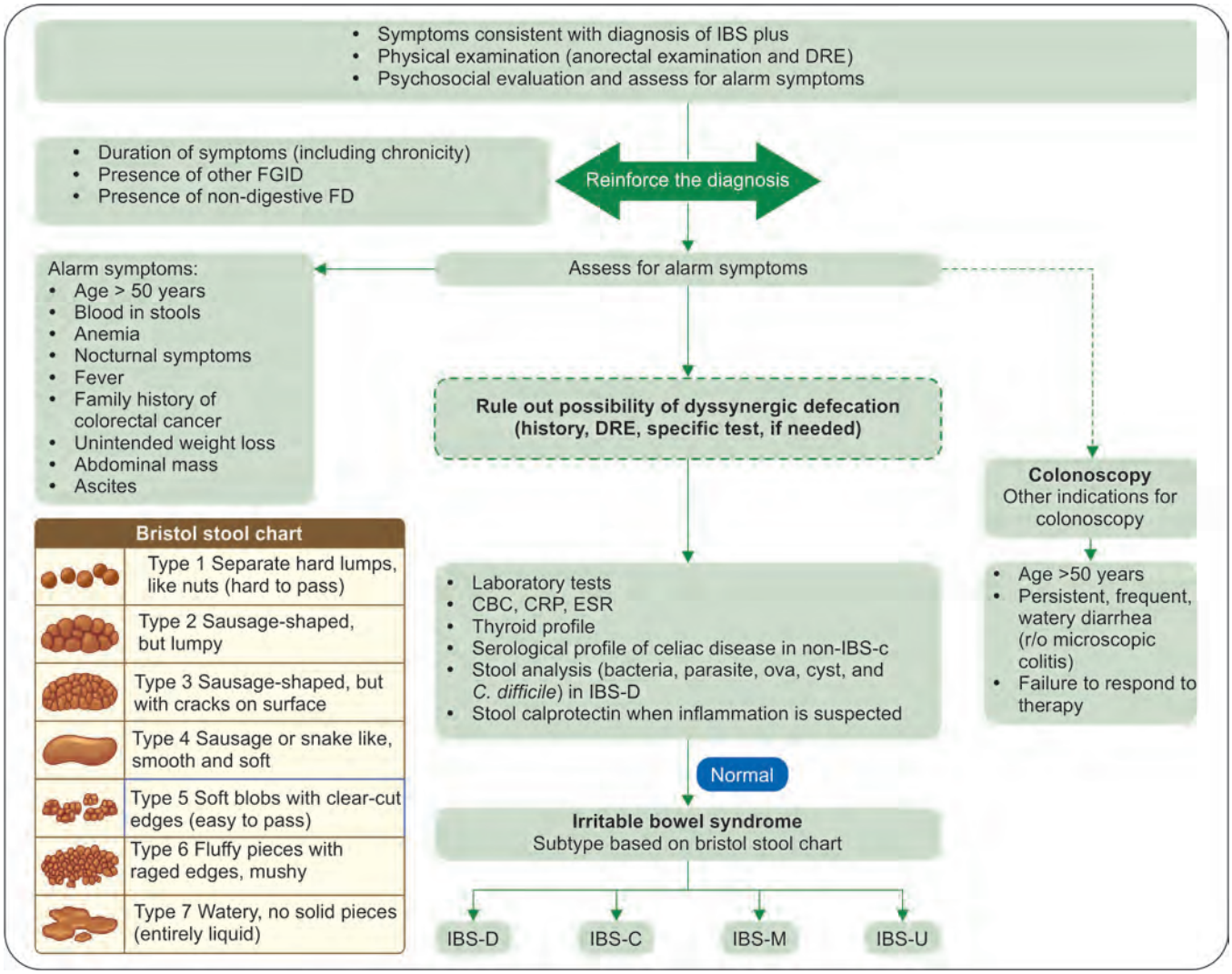
A step up approach depending on the severity of the predominant symptom and the multi-disciplinary clinical profile is helpful in guiding the treatment **(Table 2)**.

The current first-line therapies are directed toward individual symptoms; however, the newer therapies are based on altering the micro-organic pathophysiology.

TABLE 2 Current step up therapy for treatment of IBS

Predominant symptom	*First step*	*Second step*
Constipation	• Fiber supplementation • Polyethylene glycol • Lactulose/Lactitol • Stool softener	• Lubiprostone • Linaclotide • Prucalopride • Sodium picosulfate • Bisacodyl
Diarrhea	Loperamide	• 5HT3 antagonist (alosetron) • Bile acid sequestrant (cholestyramine) • Rifaximin • Clonidine
Pain	• Antispasmodic (anticholinergics) • Peppermint oil	• Tricyclic anti-depressants (TCA) • SSRI • SNRI • Psychological therapy
Bloating	• Diet modification • Treat constipation	• Probiotic • Rifaximin • TCA • SSRI

Flowchart 1: Diagnostic algorithm and management of IBS



Newer Therapies for IBS

Lumen Directed Therapy: Targeting the Low Grade Inflammation Dysbiosis and Intestinal Permeability

Nonabsorbable Antibiotics

Multiple case control studies from around the globe have inferred microbial dysbiosis in patients with IBS.[21] Thus, use of non-absorbable antibiotics for management of IBS was suggested.

Neomycin was initially used in patients with IBS; however, the use was limited due to adverse effects.

Rifaximin was tested initially in small scale trials in patients with IBS.[22,23] Subsequently, in a large randomized trial,[24] positive effects were found in 8–10% patients of IBS who did not have constipation. This effect was present during the 10 weeks of follow-up; however, the effect gradually decreased thereafter. Therefore in another retreatment trial[25] repeat administration of rifaximin was assessed and it was found that retreatment was efficacious as in naïve patients without the concern of antibiotic resistance.

Rifaximin has pleiotropic effects on the gut apart from managing the gut dysbiosis. Variable effects include anti-inflammatory effects, restoring the gut barrier function

and effects on visceral hyperalgesia through unknown mechanisms.

Pre-Probiotics and Synbiotics

Probiotics are live microorganism, which when consumed in prescribed amounts confer multiple health benefits. The available data[26] exhibit an overall positive effect of pre-probiotics on the symptoms of IBS; however, comparative analysis of the bacterial species is lacking.

Probiotics affect the luminal dysbiosis, low grade inflammation, and helps restoring the mucosal integrity in patients with IBS. Apart from the direct effects, probiotics also indirectly modulate the gut-brain interaction.[27,28]

Synbiotics are combinations of pre- and probiotics with synergistic actions. Synbiotics are hypothesized to be beneficial in IBS; however, results are inconsistent and data is sparse.

Fecal Microbiota Transplant (FMT)

Alteration in gut microbiota is one of the proposed mechanisms in the pathogenesis of IBS. Fecal microbiota has been efficacious in treating patients with pseudomembranous colitis with great success. Hence, its role in other luminal as well as non-luminal disorders has been hypothesized. So far many small case series and randomized trials have been published and have assessed IBS severity score as the outcome measure. However, the results were conflicting.

Sahly et al.[29] in 2020 published a double blind randomized controlled trial assessing the efficacy of single donor FMT in 30 gm and 60 gm doses as compared to placebo and found significant response (89.1% vs. 23.6% $p<0.0001$) in reduction in IBS symptoms. However, mild self limiting GI symptoms after FMT need a word of caution.

Mast Cell Stabilizer and Other Anti-inflammatory Drugs

Low grade inflammation in the gut as well as presence of inflammatory cells especially lymphocytes and mast cells have been found in patients with IBS and are considered as one of the microbiologic change.

Mesalazine, used as an anti-inflammatory drug in IBD was found to have no role in patients with IBS.[30,31]

Mast cells being predominant inflammatory cells are one of the targets for recent therapies of IBS. Mast cells are also involved in pathogenesis of visceral hypersensitivity in patients with IBS.[32] Mast cell stabilizer ketotifen was found to increase the discomfort threshold to rectal distension in patients with IBS and had significant effects on abdominal pain and QOL.[33] This effects was hypothesized due to H1 receptor antagonism of ketotifen, which is a secondary action. Another H1 receptor antagonist, Ebastine, was also found to significantly decrease abdominal pain over a 12-week treatment period.[34]

Dietary Modifications

Worsening of symptoms has been reported by many patients after ingestion of certain foods. It has been postulated that food acts through various mechanisms including osmotic, chemical, mechanical and neuroendocrine effects. These pathologic mechanisms can potentiate the already present microbiologic pathology present in the gut. It has also been found that food material containing incompletely digestible carbohydrates, fats, and high caloric diet are incompletely absorbed in the small intestine and are a cause of significant bloating and abdominal discomfort due to fermentation by the gut microbiota. Thus, current recommendations evaluate patients after modifying intake of such food as well as alcohol, caffeine, milk, or any lactulose containing diet.

If these recommendations are cashed on improving symptoms the FODMAP diet **(Fig. 1)**[35] eliminating foods containing fermentable oligosaccharides, disaccharides, monosachharides, and polyols are adviced.[19]

Food eliminating Gluten has also been advocated in non-celiac IBS patients on the basis of evidence of decrease in intestinal inflammation and mucosal injury on gluten free diet.

Therapeutic Updates on Constipation Predominant IBS

Guanylate Cyclase C Agonist

The stimulation of enterocyte guanylate cyclase c (GCC) receptors activates the apical CFTR that leads to water secretion by the gut mucosa.[36] *Linaclotide* is an orally administered 14 amino acid containing peptide that acts as an agonist of GCC. In a dose dependent manner linaclotide softens the stools and also improves symptoms of abdominal pain, bloating, and discomfort.

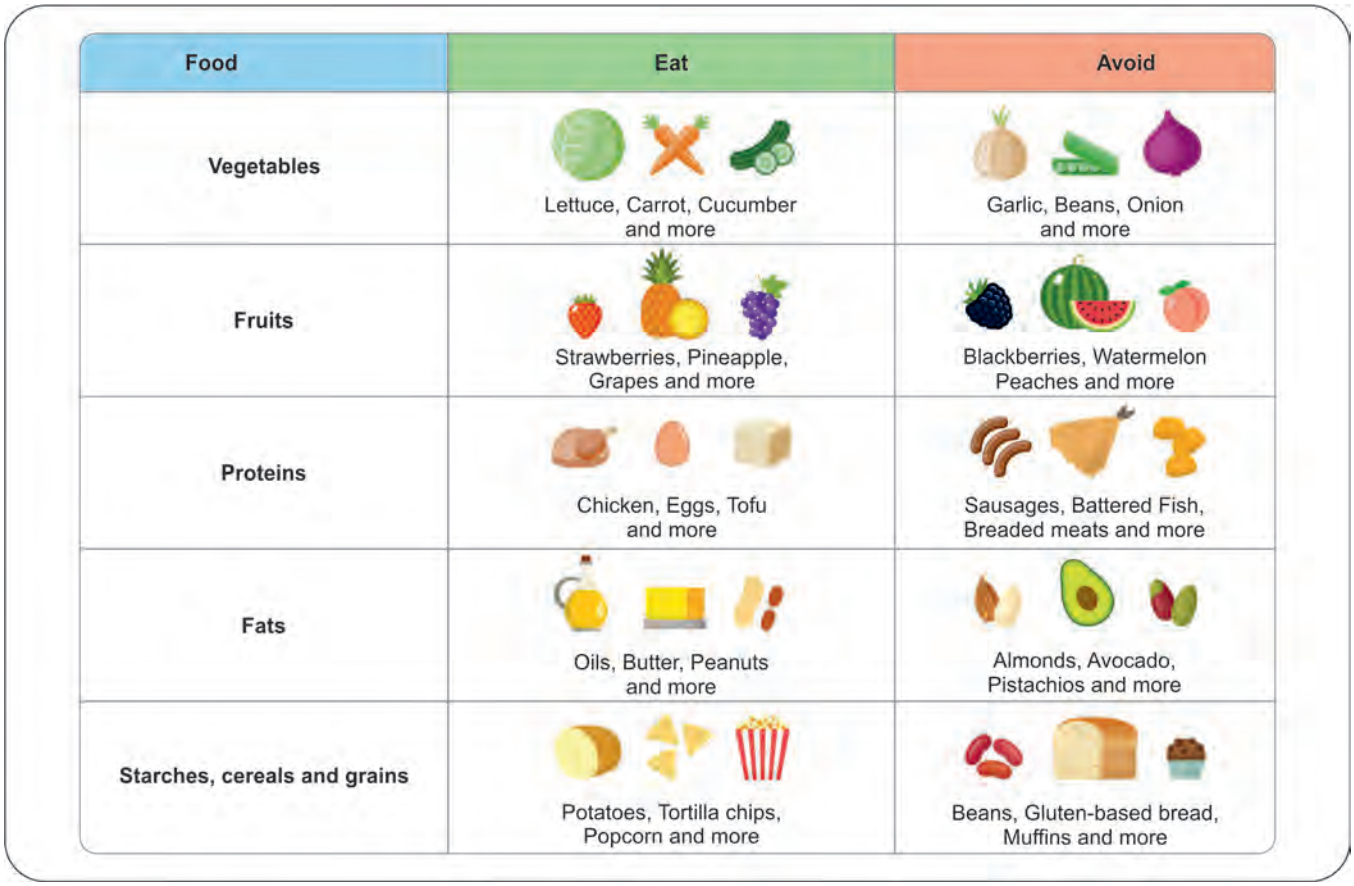


Fig. 1: Low foodmap diet

290 µg daily was shown to improve stool frequency and ease of defecation.[37,38] The most common side effect is diarrhea, which can be managed by reducing the dose.

Plecanatide is another 16 amino acid GCC agonist approved for management of chronic constipation and recently FDA approved for IBS-C.

Lubiprostone

It is a fat soluble molecule that activates type 2 chloride channels in the enterocytes releasing more water into the intestinal lumen increasing water content of the stool. At a dose of 8 µg twice daily *lubiprostone* has shown efficacy in reduction of symptoms and stool consistency.[39] Most common side effects are nausea and diarrhea.

5-HT4 Agonists

Activation of 5-HT_4 enhances the gut motility by amplifying the release of acetylcholine from nerve endings.

5-HT4 agonist *Tegaserod* was shown to be efficacious in management of IBS-c; however, it was withdrawn owing to potential cardiovascular risks.[40,41]

A novel 5-HT_4 receptor agonist *Prucalopride* has been approved for treatment of chronic constipation and has been evaluated in IBS-C considering the anecdotal reports of improvement in bloating, abdominal pain, and discomfort in the trials for constipation.[42]

Ghrelin Receptor Agonists

Ghrelin is a gut hormone involved in appetite control and gut motility in upper as well as lower GI tract. *Relamorelin* is a novel injectable ghrelin receptor agonist studied as a motility amplifier in patients with diabetic gastroparesis.[43] It has also been evaluated in women with chronic constipation and has been found to improve gastric emptying rate and stool frequency but had no effect on stool consistency. Further studies are warranted in patients with IBS-C.

Tenapanor

Small molecule inhibitor of GI N^+/H^+ exchanger isoform 3, *tenapanor* increases water secretion in the gut improving global symptoms of IBS-C. At a dose of 50 mg BD *tenapanor* offers a newer mode of treatment in this class.[44]

Therapeutic Updates on Diarrhea Predominant IBS

Eluxadoline

This is a novel mixed μ opioid receptor and κ receptor agonist and δ agonist evaluated for treatment of IBS-D. It was studied in a dose of 75 mg and 100 mg per day for 26–52 weeks.[45] Eluxadoline helps improve overall symptoms and particularly stool consistency and frequency.

However, pertaining to risk of pancreatitis due to sphincter of Oddi dysfunction it should not be used in patients with history of pancreatitis, SOD or alcohol abuse or any liver dysfunction.

5-HT3 Antagonists

Serotonin modulates the gut motility and sensitivity through a variety of receptors. Alosetron is a 5-HT_3 antagonist was found to be efficacious in treatment of IBS-D.[46] However, this drug was associated with risk of ischemic colitis and severe constipation.

Ramosteron is a novel 5-HT_3 antagonist[47] found to be effective in improving global symptoms of IBS-D including pain scores, which were not improved by Ondansetron when compared for management of IBS-D.

Drugs Acting on Bile Acids

Bile acids are known to be important in stimulating secretion in the bowel and enhance gut motility that are relevant in causing diarrhea. Several studies have revealed the increase bile acid loss as a cause of IBS-D.[48] FGF19 is produced from the ileum that acts as an important factor in regulating bile acid synthesis in the liver. In bile acid diarrhea there is reduced feedback inhibition by FGF19. Cholestyramine is most commonly used bile acid sequestrant along with newer agents like colestipol and colesevelam.[49]

Farnesoid X activated receptor is also involved in inhibition of bile acid synthesis in liver by various mechanisms. Obeticholic acid is one of the various FXR receptor agonists that has been found to reduce bile acid synthesis and improve secondary bile acid diarrhea.[50]

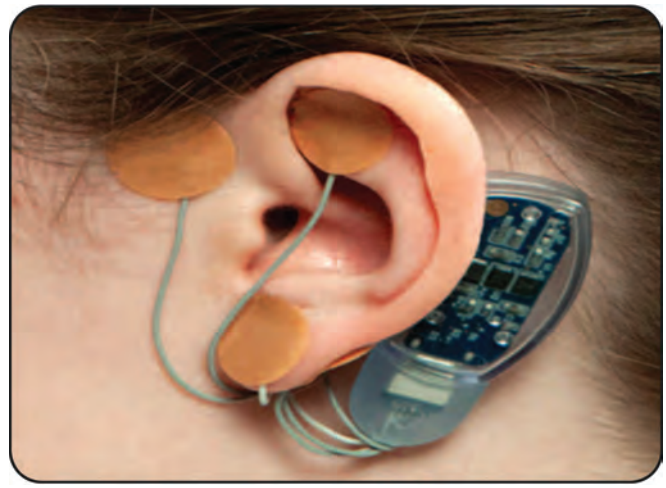


Fig. 2: IBStim device

On the contrary, increased bile acids in the lumen stimulate water secretion and motility and improve constipation. Chenodeoxycholic acid was found to improve bowel function and bowel motility when tested.[51]

Elobixibat or A3309, through antagonism of ileal bile acid transporter reduces reuptake, and hence increases luminal bile acid content. Elobixibat has also been found to improve colonic transit and improve symptoms in patients with IBS-C.[52]

Modulating the Central Pain Mechanism

IBStim Device: The Cranial Nerve Stimulator (Fig. 2)

Recently approved for use in patients for modulating abdominal pain in IBS patients, this device is approved for adolescents of age group 11–18 years. It modulates the pain pathways in the CNS by low frequency electrical stimulation of peripheral cranial nerves. It is single use device and works for 5 days.[53]

Conclusion

IBS is chronic relapsing remitting functional GI disorder. With enhanced understanding of the micro-organic basis of the disorder newer therapies are directed at modifying the pathology of the disease rather than the individual symptoms. It is however very necessary to clinically diagnose the patient with respect to the recent diagnostic criteria and order important battery of investigations for making a positive diagnosis of IBS.

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CHAPTER

142 Evaluation of Occult GI Bleed

Sanjay Bandyopadhyay

Abstract

Occult gastrointestinal bleeding signifies bleeding from the gastrointestinal tract that often goes unrecognized by the patient. It usually manifests as positive fecal occult blood test, or if continues for a long period of time, it may progress to iron deficiency anemia. A thorough evaluation of gastrointestinal tract including esophago-gastro-duodenoscopy and colonoscopy clinches the diagnosis in most of the cases. Recently, introduction of capsule endoscopy and balloon enteroscopy have made a major impact by identifying small bowel causes of bleeding. The primary concern is to rule out malignant causes, particularly in elderly. For patients with no identifiable pathology, long-term prognosis appears favorable with oral supplement of iron.

Introduction

Gastrointestinal (GI) bleeding can have a multitude of clinical presentation. The bleeding may be mild, moderate, or severe depending on the severity or rapidity of bleeding. Patient may present with clinically obvious symptoms of hematemesis, melaena, hematochezia, or, in some cases, fresh bleeding per rectum. Furthermore, bleeding may be hidden with patient totally unaware of its existence. This review will focus on this later type of bleeding called occult GI bleeding.

Occult GI bleeding is defined as bleeding that is unknown to the patient, and includes patients with positive fecal occult blood test (FOBT) and/or iron deficiency anemia (IDA).[1] On the other hand, *obscure* GI bleeding is that which is evident to the patient but is from a source that is not readily identifiable by routine esophagogastroduodenoscopy (EGD) and/or colonoscopy.[1]

Causes

Any lesion presents anywhere in the GI tract may present with occult GI bleeding.[2] In a review of five prospective studies on patients with occult GI bleeding, majority was found to have upper GI source (29–56%) followed colorectal source (20–30%). Surprisingly, synchronous lesions were found in up to 17% cases. All these studies used only OGD and colonoscopy, and hence, no source was identified in 29–52% cases. **Table 1** shows the potential causes of Occult GI bleeding.

History and Physical Examination

A detail history and targeted physical examination should form the basis of clinical evaluation. Abdominal pain with aspirin or other non-steroidal anti-inflammatory drug use suggests ulcerative mucosal injury. Unintentional weight loss suggests a malignancy. A past history of GI bleeding or abdominal surgery may give important diagnostic clues. Initiation of anticoagulants or antiplatelet medications in the preceding weeks may precipitate bleeding in an undiagnosed lesion. A family history of GI bleeding may suggest hereditary hemorrhagic telangiectasia (associated with vascular lesions on the lips, tongue, or palms) or blue rubber bleb nevus syndrome (a syndrome with venous

TABLES 1 Causes of occult gastrointestinal bleeding

Mass lesions	• Carcinoma (common) • Adenoma (usually > 1.5 cm)
Inflammation	• Erosive esophagitis (common) • Ulcer (any site, including peptic ulcer, common) • Cameron lesions • Erosive gastritis • Celiac disease • Ulcerative colitis • Crohn's disease • Colitis (non-specific) • Idiopathic cecal ulcer
Vascular	• Vascular ectasia (common) • Varices (any site, rare) • Portal hypertensive gastropathy (PHG) (common) • Portal colopathy • Gastric antral vascular ectasia (GAVE) • Dieulafoy's ulcer (rare) • Hemosuccus pancreaticus (rare) • Hemobilia (rare)
Infection	• Hookworm • Whipworm • Strongyloidiasis • Ascariasis • Tubercular enterocolitis • Amebiasis
Other	• Long-distance running • Factitious

malformations in the GI tract, soft tissues, and skin). A history of gastric bypass surgery may suggest impaired iron absorption.[1] Examination of skin may indicate the presence of an underlying condition like dermatitis herpetiformis (in celiac disease); erythema nodosum (in Crohn disease); an atrophic tongue and brittle, spoon-shaped nails (Plummer-Vinson syndrome); and freckles on the lips and in the mouth (Peutz-Jeghers syndrome).[3] Stigmata of chronic liver disease may suggest bleeding due to portal hypertension. Anemia may be obvious on clinical examination. Palpable hard nodular liver or palpable abdominal lump may be signs of underlying advanced disease.

Diagnostic Studies

The choice of diagnostic modality should depend on clinical suspicion of potential site and probable cause of underlying disease, and any associated symptoms. Upper GI bleeding from lesions up to the second part of duodenum can be detected by EGD. Classically, small bowel bleedings are evaluated by enteroscopy. Older methods like Push enteroscopy reach only the proximal small intestine. However, bleeding sources in mid and distal small bowel need evaluation with wireless capsule endoscopy (WCE), deep enteroscopy, and computed tomography (CT) or magnetic resonance (MR) enterography.[4] Lower GI bleeding (colonic and terminal ileal source) can be detected with colonoscopy. Laparotomy with intraoperative enteroscopy remains an option for those rare patients who have recurrent bleeding from a source not yet identified with the previously mentioned methods. Small bowel barium studies have a very low diagnostic yield and been largely replaced by capsule endoscopy. EGD and colonoscopy will find the bleeding source in 48–71% of patients. In patients with recurrent bleeding, repeat EGD and colonoscopy may find missed lesions in up to 35% of those who had negative initial findings.[3] If a cause is not found after EGD and colonoscopy had been performed, capsule endoscopy has a diagnostic yield of 63–74%.[4]

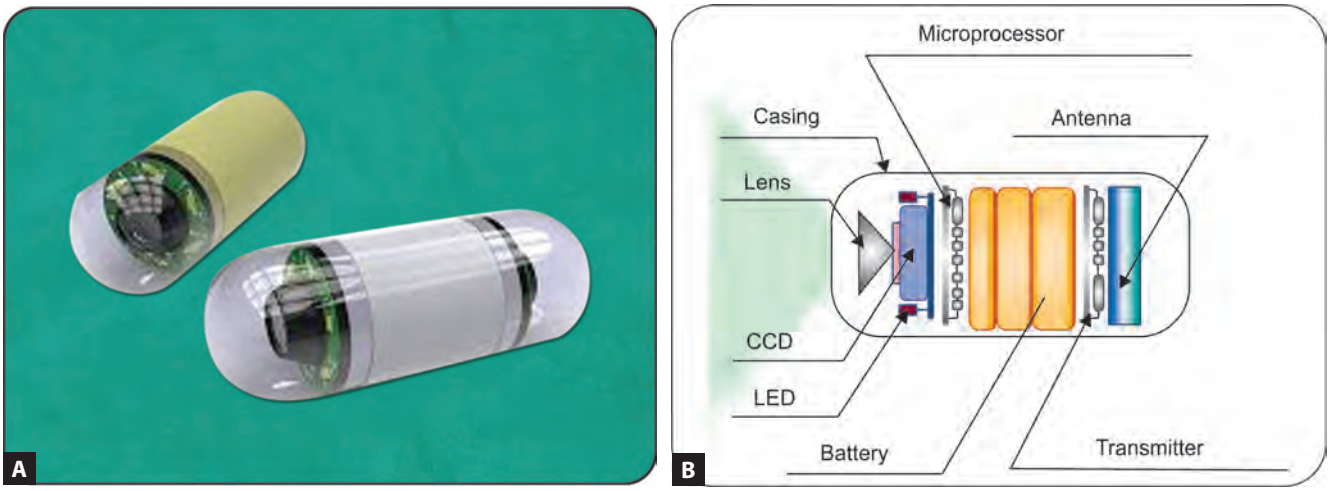
Capsule Endoscopy and Different Methods of Enteroscopy

These tools are particularly useful for establishing the source of bleeding in small intestine—a notoriously difficult site to examine with other methods.

Capsules used for endoscopy contain light-emitting diodes, a lens, a camera, batteries, and a radiofrequency transmitter **(Figs. 1A and B)**. Captured images are transmitted to a data recording device worn by the patient, downloaded to a computer workstation, where the images are analyzed.[5] The capsule is disposable and, because of its small size, readily passes through the GI tract. Capsule retention is a potential complication but, fortunately, occurs in less than 1%.[6]

Push enteroscopy consists of per oral insertion of a specialized, long, flexible tube up to 50–60 cm beyond the ligament of Treitz. This allows thorough examination of the distal duodenum and proximal jejunum, and biopsies can be taken if needed. It is rarely practiced nowadays.

Deep enteroscopy has been a major advance in the evaluation of the small bowel as it offers scope for therapy and tissue biopsy, though multiple sessions may be needed for complete examination.[7] There are several forms of deep enteroscopy, including double-balloon enteroscopy (DBE), single-balloon enteroscopy (SBE), and spiral



Figs. 1A and B: Components and designs of capsule endoscopy system: (A) Capsule; (B) Schematic diagram of components of capsule

enteroscopy (SPIRUS) **(Figs. 2A to C)**.[7-9] The principle involves the use of an endoscope and an overtube, although procedures are emerging that may not require an overtube. Initially scopes are inserted as deep as possible; careful withdrawal of the scope then allows evaluation of the entire small bowel. With DBE, balloons are used to grip the intestine while inserting the endoscope. By inflating the overtube balloon enough to grip the intestinal wall, the endoscope can be inserted further without forming redundant loops in the small intestine and then the overtube can in turn be inserted while the endoscope balloon is inflated. The single balloon technique in theory is technically simpler than DBE. Spiral enteroscopy uses a special overtube with raised helices at the distal end, and clockwise rotation of the overtube pleats the small bowel onto the overtube and prevents looping. Data to date suggest that DBE allows greater depth of insertion than the other two.[7]

Evaluation

There are two different clinical presentations of occult GI bleed:

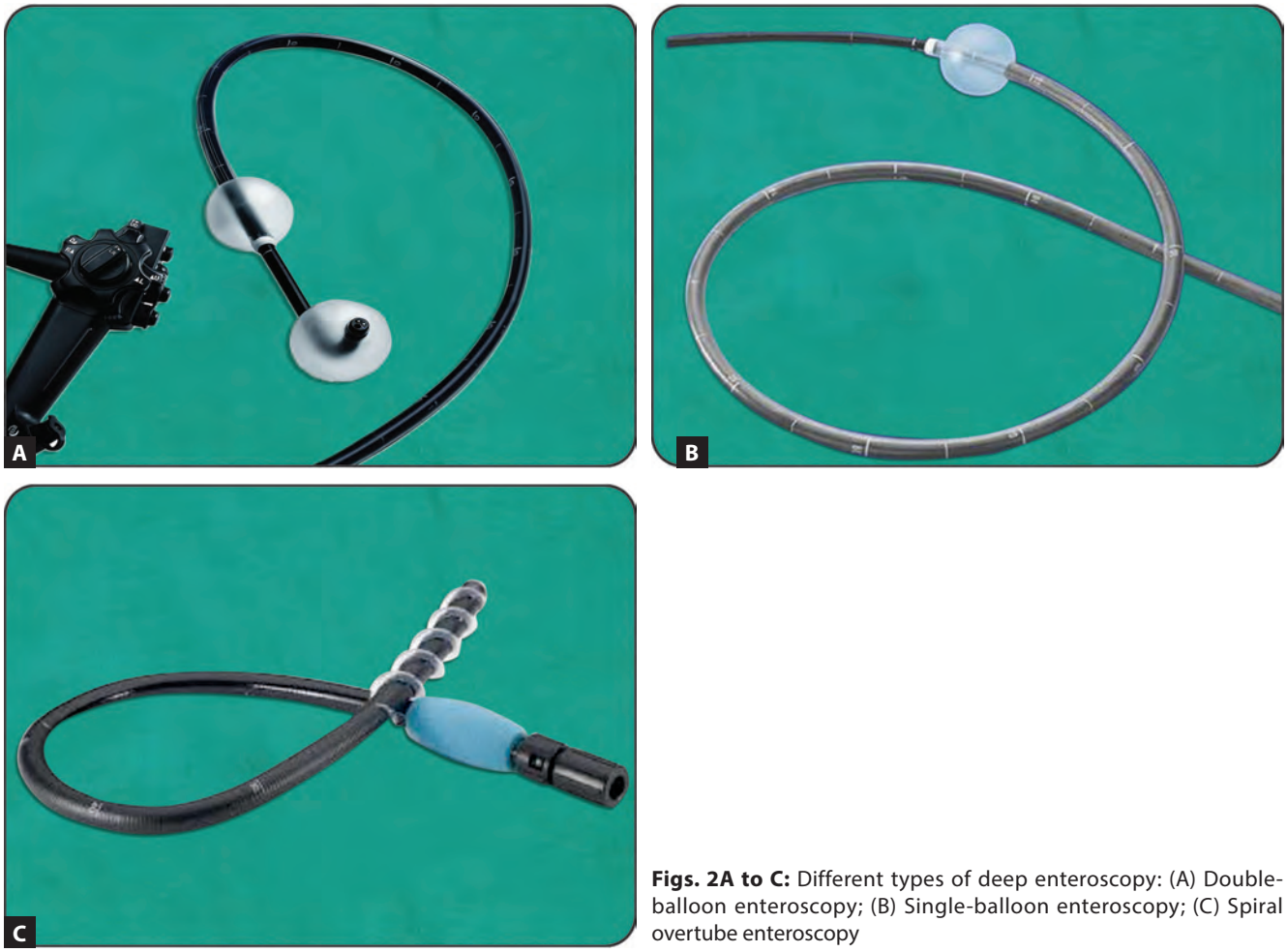
- Positive FOBT without iron deficiency anemia
- Iron deficiency anemia with or without a positive FOBT

Positive FOBT without Iron Deficiency Anemia

Normal fecal blood loss varies from 0.5 to 1.5 mL/day.[10] However, loss of up to 100 mL of blood per day may not cause any visible change in the color of the stool.[11] FOBT, usually classic guaiac-based tests, is often used in day-to-day clinical practice by physicians. Other types of FOBT like fecal immunochemical tests and the heme porphyrin test are not available in India. The likelihood of positive test depends not only on the sensitivity of a particular test but also on the frequency and rate at which the causative lesion bleeds, bowel motility, and the anatomic site of the bleed.[12] Guaiac-based tests are best at detecting blood from the lower rather than the upper GIT as the pseudoperoxidase activity of heme, detected by guaiac-based tests, is continuously degraded as it moves down the GIT.

Oral iron therapy is commonly believed to cause positive guaiac tests, but prospective studies have proven this belief to be wrong.[13] Finally, bismuth (found in certain antacids and antidiarrheal drugs) makes the stool dark and even black in appearance, but does not cause a blue guaiac reaction and should not be mistaken for blood.

Flowchart 1 illustrates the approach proposed by the American Gastroenterological Association (AGA) for patients with positive FOBT.[4] Colonoscopy is preferred because of its high sensitivity for detecting colonic mucosal lesions, and its intervention capabilities with biopsy, polypectomy, and treatment of bleeding lesions.[4] Barium studies have lower sensitivity than colonoscopy and are generally not recommended. CT colonography may be an alternative to colonoscopy, if bowel preparation is a problem.[14] However, it does not have therapeutic capabilities.



Figs. 2A to C: Different types of deep enteroscopy: (A) Double-balloon enteroscopy; (B) Single-balloon enteroscopy; (C) Spiral overtube enteroscopy

Identification of an abnormality consistent with the magnitude of bleeding makes further workup after colonoscopy unnecessary. If colonoscopy is negative, further studies are not required in the asymptomatic patient unless anemia develops.[4] Exceptions are patients with upper GI symptoms, in whom EGD should be performed along with colonoscopy.

Fecal blood content in therapeutically anticoagulated patients is usually within normal limits. Hence, a positive FOBT should not be attributed to low-dose aspirin or anticoagulation, and as such, will require at least endoscopic evaluation.[15]

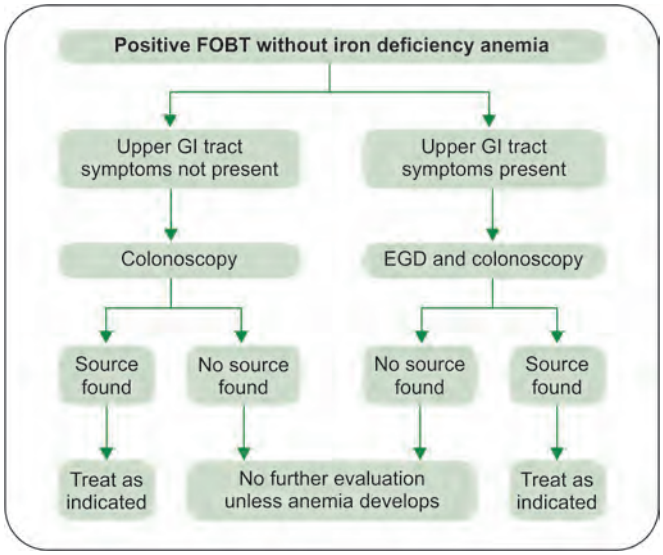
Iron Deficiency Anemia with or without a Positive FOBT

Worldwide IDA is the most common cause of anemia. Under normal circumstances, iron balance is tightly regulated at the level of intestinal mucosa. Average daily loss of iron is 1 mg coming from microscopic GI bleeding and sloughed intestinal cells.[16] In India, more than 50% of population is iron-deficient.[17]

The approach recommended by AGA for evaluation of patients who have IDA with or without a positive FOBT has been illustrated in **Flowchart 2**.[18] Men and postmenopausal women with IDA are assumed to have GI blood loss, unless proved otherwise. However, premenopausal women who have IDA that cannot be explained by heavy menses, or those who have GI symptoms, should be evaluated for a GI cause.

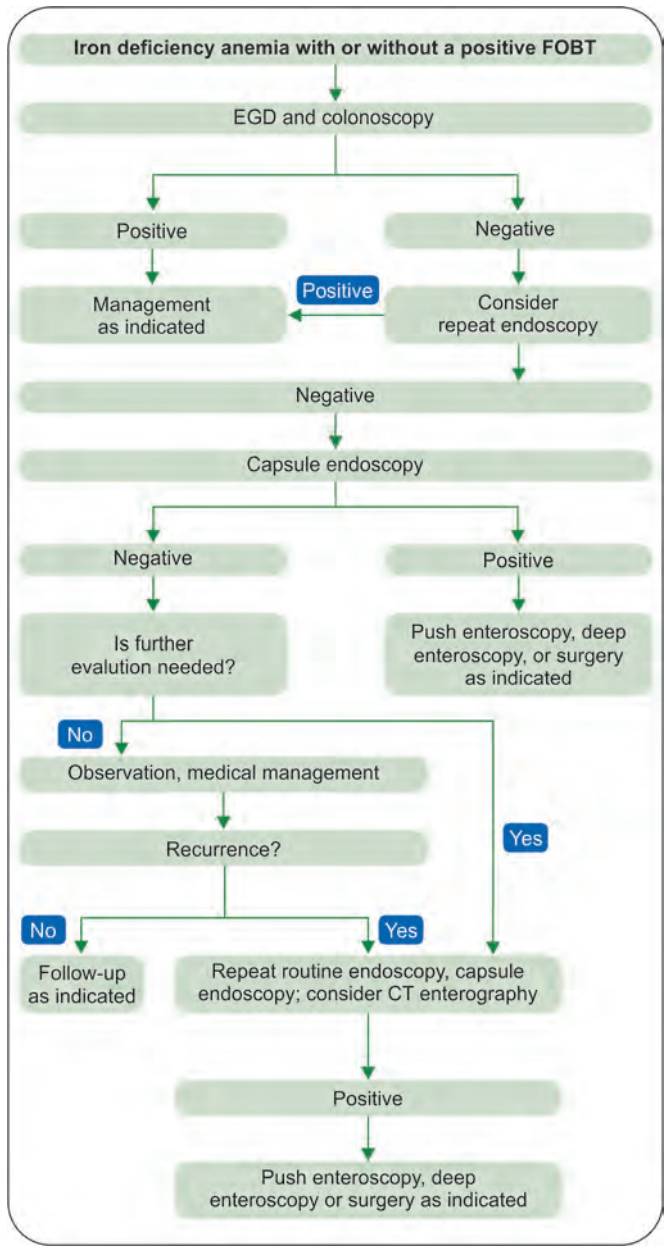
Endoscopic evaluation should start with EGD and colonoscopy. During EGD, biopsies should be taken from duodenal mucosa to look for celiac disease, an often ignored cause of IDA.[19] If EGD and colonoscopy are normal, they are called obscure occult GI bleed.

Flowchart 1: Evaluation of the patient with a positive FOBT



EGD, esophagogastroduodenoscopy; FOBT, fecal occult blood test; GI, gastrointestinal

Flowchart 2: Proposed algorithm for diagnosis of iron deficiency anemia with or without a positive FOBT



CT, computed tomographic; EGD, esophagogastroduodenoscopy; FOBT: fecal occult blood test

The prevalent expert opinion suggests that they should undergo repeat upper endoscopy and colonoscopy, at least once. If these repeat studies are negative, capsule endoscopy should be the next investigative procedure with a focus on small bowel.

Whenever capsule endoscopy identifies a lesion on small bowel, further course of action depends on the nature of the lesion.

- If the identified lesion needs a tissue diagnosis or if the lesion requires endotherapy (like endoscopic hemostasis, endoluminal ablation, resection, or dilatation), balloon enteroscopy should be performed. The choice of route of balloon enteroscope insertion (either antegrade, i.e., orally or retrograde, i.e., inserted anally) will depend on the estimated site of lesion as observed on running the capsule endoscopy video.
- If capsule endoscopy shows a lesion that can be managed medically or that requires surgery, balloon enteroscopy is not justified.

If capsule endoscopy fails to identify a lesion, it may be repeated on another occasion (second-look capsule endoscopy). Alternatively, CT or MR enterography may be considered.

Sometimes, CT or MR enterography are performed before capsule endoscopy to check for luminal patency sufficient to allow unobstructed passage of the capsule.[20]

Surprisingly, in some cases, the diagnosis may be obvious on CT or MR precluding the need for capsule endoscopy. Radioisotope scan using radioactive technetium bound red blood cells (RBCs) are not favored due to significant radiation exposure, imprecise localization, and lack of therapeutic potential.[21] Angiography and guided

intervention is reserved for acute brisk bleeding that do not fall in the category of occult GIB or IDA.[20,22]

A small percentage of cases may not have any lesion identified even after exhaustive evaluation. In them, covert non-GI blood loss should be considered. Also, the diagnosis and type of anemia need to be rechecked by a hematologist.[1]

Treatment

Essentially, the treatment should focus on the underlying cause of occult bleeding. Anemia is treated with oral ferrous sulfate in a dose of 325 mg twice or thrice daily. Ferrous fumarate or gluconate is acceptable alternative for those unable to tolerate ferrous sulfate. Parenteral iron therapy is reserved for those with malabsorption disorders or severe oral intolerance.[23] For patients with positive FOBT but no identifiable GI pathology, the long-term prognosis appears favorable. Majority of these true obscure cases respond to oral iron thrapy.[24]

Conclusion

A multitude of diseases of GIT can present as occult GI bleed, manifesting as a positive FOBT or IDA. Majority of these bleeds are caused by ulcerative diseases of the upper GIT while malignancy is rare. Routine endoscopy (UGI endoscopy and colonoscopy) is the first step in evaluation of these patients. Some patients have common lesions but with an unusual or atypical appearance; others may harbor rare/uncommon diseases. Capsule endoscopy and deep (often balloon-assisted) enteroscopy are useful to identify the diseases of small bowel. The later often offers scope for curative intervention. The outcome of therapy depends on identification of a specific bleeding lesion, severity of bleeding, and, finally, access to advanced diagnostic/therapeutic modalities.

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CHAPTER

143 Endoscopic Ultrasound for the Internist

Surinder S Rana

Abstract

Endoscopic ultrasound (EUS) is a relatively new innovation in the field of gastrointestinal (GI) endoscopy that combines the endoscope and ultrasound transducer for examining the GI tract wall and structures beyond. The ability to place the ultrasound transducer very close to the structures/organs being evaluated allows use of high frequencies that provide very high resolution images. EUS is used for both diagnostic as well as therapeutic purposes. The diagnostic indications can be either for primary diagnosis where EUS is used as a primary diagnostic modality for diagnosing diseases like evaluation of idiopathic acute pancreatitis as well as diagnosis of chronic pancreatitis or as a secondary diagnostic modality for detailed evaluation of already diagnosed disease like submucosal lesions, dilated bile duct, and pancreatic cystic lesions or EUS guided FNA of GI as well as surrounding structures like lymph nodes or locoregional staging of GI cancers. Therapeutic EUS has phenomenally expanded in last one decade and a number of procedures like pseudocyst/walled off necrosis drainage, celiac plexus blockade/neurolysis, intra-abdominal abscess drainage, mediastinal abscess drainage, vascular interventions, intratumoral therapy, and biliary as well as pancreatic drainage can be safely done under EUS guidance. Development of newer technologies like EUS elastography and contrast EUS is going to further expand the role of EUS. It is important for an internist to be aware of the indications and strengths of EUS in various abdominal, thoracic as well as pelvic diseases.

Introduction

Endoscopic ultrasound (EUS) is a relatively new innovation in the field of gastrointestinal (GI) endoscopy that combines the endoscope (for visualizing the mucosa of the GI lumen) and ultrasound transducer for examining the GI tract wall and structures beyond it.[1] The desire to see the structures beyond the GI lumen led on to development of EUS. Over last three decades, EUS has evolved tremendously from a research tool to important investigational tool in routine clinical practice. The ability to place the ultrasound transducer very close to the structures/organs being evaluated allows use of high frequencies that provide very high resolution images.[2] These images are much better than those obtained by transabdominal ultrasound as well as other cross-sectional imaging techniques. Therefore, there has been gradual expansion in its clinical indications and it has evolved from a purely diagnostic modality to an important therapeutic tool. Its advent has made the locoregional staging of many GI cancers accurate and also made a number of GI therapeutic procedures safer. The advent of EUS guided fine needle aspiration (FNA) has made it the procedure of choice for tissue diagnosis of various benign as well as malignant GI lesions. It has changed the daily clinical practice of not only gastroenterologists, but also surgical gastroenterologists, oncologists, pulmonologists, radiologists, as well as internists. Therefore, it is very important for an internist to be aware of the current

indications, strengths as well as limitations of EUS. This review discusses in brief the diagnostic and therapeutic indications of EUS.

Types of EUS Scopes

Broadly, there are two types of EUS scopes (echo-endoscopes). The first developed echoendoscope was a radial echoendoscope with a 360-degree transducer that has a scanning plane of ultrasound perpendicular to the long axis of the echoendoscope. This is a purely diagnostic echoendoscope and no intervention or FNA can be done with this scope. To overcome this limitation, linear echoendoscopes were developed in which the scanning plane of transducer is parallel to the long axis of the echoendoscope so that the entire needle can be seen in real time during FNA/interventions.[3]

Apart from these two commonly echoendoscopes, a new echoendoscope has recently been developed. The forward viewing echoendoscope has a forward endoscopic view instead of oblique endoscopic view of linear echoendoscope and has a shorter and more flexible tip. Therefore, it is more easily maneuverable and can be used instead of oblique viewing echoendoscope in difficult anatomical situations. However, absence of elevator at the tip of echoendoscope makes the interventions difficult with this scope. Therefore, this scope is usually used in those situations where linear echoendoscope cannot be used because of anatomical constraints.

Indications of EUS

The clinical indications for EUS can be divided into two broad categories: diagnostic and therapeutic **(Table 1)**. The diagnostic indications can be either for primary diagnosis where EUS is used as a primary diagnostic modality for diagnosing diseases like evaluation of idiopathic acute pancreatitis as well as diagnosis of chronic pancreatitis or as a secondary diagnostic modality for detailed evaluation of already diagnosed disease like submucosal lesions (SMLs), dilated bile duct and pancreatic cystic lesions (PCL) or EUS guided FNA of GI as well as surrounding structures like lymph nodes or locoregional staging of GI cancers.

Therapeutic EUS has phenomenally expanded in last one decade and a number of procedures like pseudocyst/walled off necrosis drainage, celiac plexus blockade/neurolysis, intra-abdominal abscess drainage, mediastinal abscess drainage, vascular interventions, intratumoral therapy and biliary as well as pancreatic drainage can be safely done under EUS guidance.

EUS as a Primary Diagnostic Modality

Idiopathic Acute Pancreatitis

EUS provides high-resolution images of pancreas and biliary tract, and therefore is an important investigation for evaluation of patients with idiopathic acute pancreatitis. It is an excellent modality for diagnosis of occult cholelithiasis or choledocholithiasis, microlithiasis, or gallbladder sludge **(Fig. 1)**, pancreatic duct anomalies like pancreas divisum, occult pancreatic neoplasm and importantly, exclude chronic pancreatitis.[4] Studies have shown that EUS is a useful and minimally invasive tool for the diagnostic evaluation of idiopathic pancreatitis and in case of negative EUS examination relapses of pancreatitis are infrequent.[5,6] EUS may also help in

TABLE 1 Indications for EUS

Diagnostic EUS	*Therapeutic EUS*
Primary diagnostic modality • Idiopathic acute pancreatitis • Diagnosis of chronic pancreatitis especially early chronic pancreatitis	• Drainage of pancreatic fluid collections • Biliary and pancreatic duct drainage in cases of failed ERCP • Transmural gallbladder drainage • EUS-guided celiac plexus neurolysis/blockade • Drainage of mediastinal and intra-abdominal abscesses and collections • EUS-guided vascular interventions • EUS-guided palliative oncological interventions • EUS-guided gastrojejunostomy
Secondary diagnostic modality • Dilated common bile duct • Pancreatic cystic lesions • GI submucosal lesions • Locoregional staging of GI cancers • EUS guided fine needle aspiration or biopsy • EUS guided aspiration of minimal pleural effusion/ascites	

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; GI, gastrointestinal

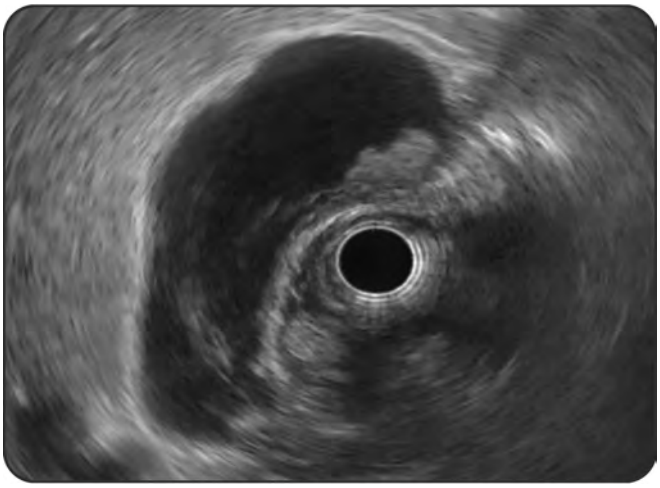

Fig. 1: EUS: gallbladder sludge in idiopathic acute pancreatitis

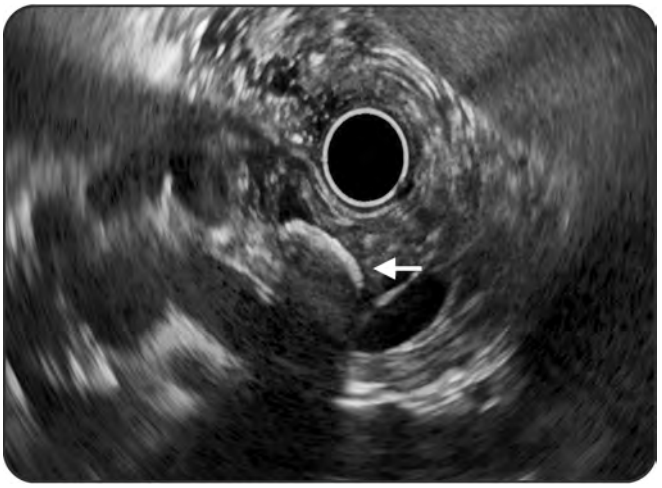

Fig. 2: EUS in a patient with chronic pancreatitis. Ductal calculi (arrow) noted

diagnosing uncommon causes for AP such as pancreaticobiliary ascariasis and parathyroid adenomas.

Diagnosis of Chronic Pancreatitis

EUS has unique capability of demonstrating subtle structural alterations in the pancreatic parenchyma as well as ducts even before conventional imaging modalities demonstrate any abnormality **(Fig. 2)**.[7] The conventional imaging modalities like computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) can pick up advanced morphological changes of chronic pancreatitis (CP) only, and therefore they have very low sensitivity for diagnosis of early CP. EUS by demonstrating early parenchymal and ductal changes can help in early diagnosis of CP. In patients with presumed acute recurrent pancreatitis, EUS can help in excluding underlying CP.

However, EUS is not a panacea for diagnosis of CP. Being a highly sensitive imaging modality, there is a concern for overdiagnosis of CP. To overcome these limitations, advanced and complicated scoring systems incorporating multiple parenchymal and ductal EUS features have been used for diagnosis of CP. Despite these scoring systems, concerns about interobserver variability as well as aging, smoking, obesity, and chronic alcohol consumption causing EUS changes in pancreas mimicking CP persist. Therefore, EUS findings of CP should be interpreted in an appropriate clinical context and, if required, should be confirmed and followed up by serial EUS examinations. Newer EUS techniques like EUS elastography that evaluate the stiffness of pancreas appear to be promising techniques for confident diagnosis of early CP.[7] However, further studies are required to determine their exact role in diagnosis of early CP.

EUS as a Secondary Diagnostic Modality

EUS for Submucosal Lesions

SMLs are usually asymptomatic lesions with normal overlying mucosa detected on routine endoscopy and require further evaluation for confirmatory diagnosis. Endoscopy and biopsy have limited role in evaluation of SMLs because of normal overlying mucosa. The ability of EUS to image structures beyond GI lumen makes it ideal modality for investigations of SMLs. EUS is an excellent modality to differentiate extramural compression and SML as well as determine the type and nature of SML.[8-10] EUS can help in presumptive diagnosis of SML by accurately estimating the size, the layer of origin, the echo-pattern and the margins of the lesion. The diagnostic accuracy of EUS can further be enhanced by cytological or histological analysis of specimens obtained by EUS guided FNA/fine needle biopsy (FNB).

EUS for Unexplained Dilated Common Bile Duct

EUS transducer from duodenum closely images the CBD, and therefore has very high diagnostic accuracy for lower and mid CBD lesions.[11-13] Isolated CBD dilatation is commonly encountered in clinical practice because

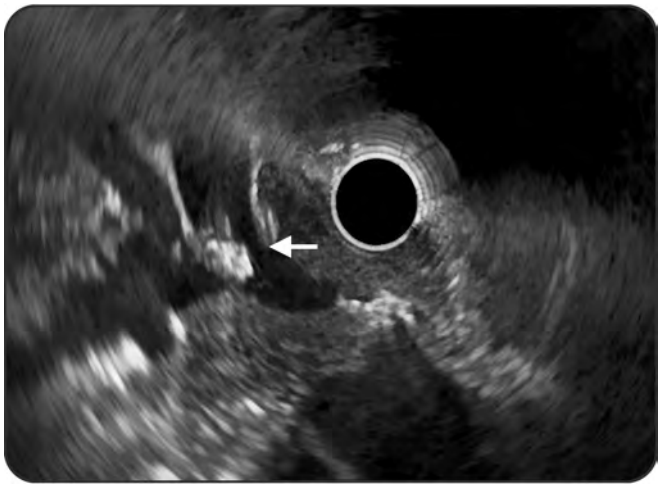

Fig. 3: EUS in dilated common bile duct (CBD). A stone noted in lower CBD (arrow)

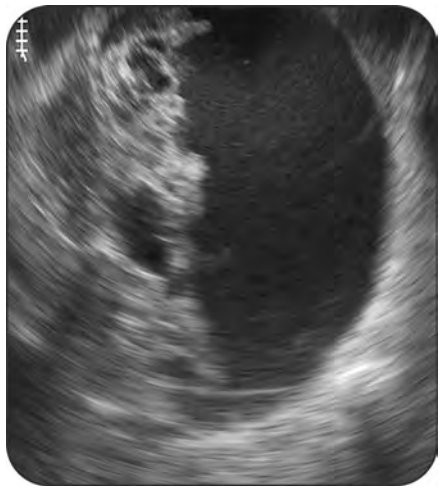

Fig. 4: EUS: mucinous cystadenoma of pancreas

of wide spread use of cross-sectional imaging modalities for patients with non-specific abdominal symptoms. In many of these patients cross-sectional imaging modalities like ultrasound, CT, and MRCP fail to identify the etiology of dilated CBD and many of these patients required endoscopic retrograde cholangiopancreatography (ERCP) for confirming the diagnosis. ERCP is an invasive procedure with inherent risks of serious adverse effects like post ERCP pancreatitis. In these clinical situations EUS has been demonstrated to be an excellent diagnostic modality for identifying underlying etiology of unexplained CBD dilatation **(Fig. 3)**. More importantly, if EUS is normal, there is extremely less likelihood of presence of any significant underlying disease and patient therefore should be reassured and no further follow-up is required.[11-13]

EUS in Pancreatic Cystic Lesions

Evaluation of patients with PCL requires a confident differentiation of malignant, potentially malignant and benign PCL. EUS is a useful modality for evaluation of PCL as it can provide information about the detailed morphology of cysts **(Fig. 4)** as well as enable guided FNA to obtain cyst fluid for cytological, biochemical as well as molecular analysis.[14-17] Cyst fluid carcinoembryonic antigen (CEA) levels more than 192 ng/mL have been shown to have highest sensitivity and specificity for differentiating mucinous from non-mucinous PCL.[14] Cyst fluid molecular markers hold considerable promise for proper evaluation of PCL. New EUS based technologies like contrast-enhanced EUS, EUS guided cystoscopy, needle-based confocal laser endomicroscopy, and through-the-needle forceps biopsy provide important information for accurate diagnosis of PCL.

EUS for Locoregional Staging of GI Cancers

EUS can accurately define the walls of the GI tract and thus is an accurate modality to assess the transverse spread of malignant lesion. It can also accurately assess the extraluminal involvement of the malignant lesion by identifying lymph nodal as well as arterial and venous involvement. Therefore, over last decade EUS has thus become an important investigation for preoperative assessment for majority of the GI cancers including esophageal, gastric, pancreaticobiliary, as well as rectal cancers.[18] EUS from esophagus can also evaluate the mediastinum, and therefore EUS is an important imaging modality for accurate staging of non-small cell lung cancer. Combining EUS with endobronchial ultrasound (EBUS) allows access to all mediastinal lymph node stations, and therefore is an important staging modality for lung cancer.[18,19]

EUS-guided Tissue Acquisition

Linear echoendoscope is used to perform EUS-guided FNA with great precision in real time as the needle is visualized in real time throughout the procedure. The advantage of EUS-guided FNA is its ability to acquire

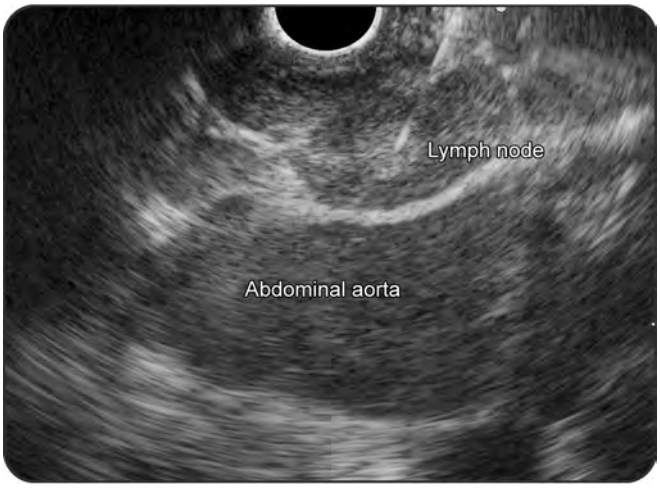

Fig. 5: EUS-guided FNA from preaortic lymph node

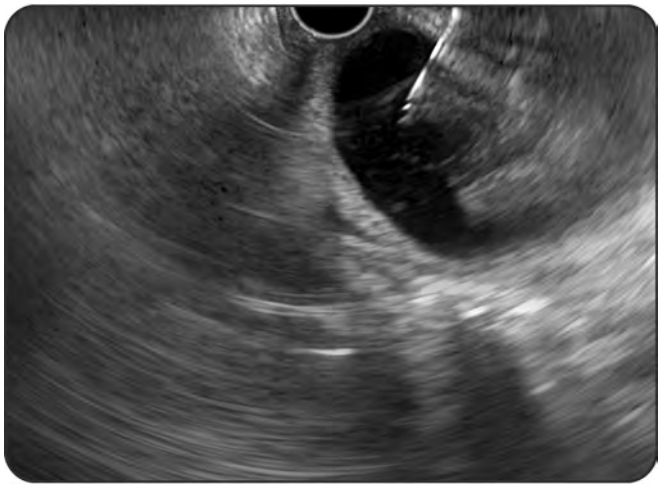

Fig. 6: EUS-guided drainage of pancreatic pseudocyst

tissue from difficult to access anatomical locations in abdomen, retroperitoneum, mediastinum, and perirectal spaces.[20] EUS guided FNA is now routinely used in clinical practice to acquire tissue for histological diagnosis from pancreas, lymph nodes in mediastinum and abdomen **(Fig. 5)**, GI SMLs, perirectal lesions, left lobe of liver, left adrenal, and mediastinal masses. EUS can also be used for aspirating minimal amount of ascites and pleural effusion.[21-23] It can also be used for visualizing as well as sampling peritoneal as well as pleural deposits in patients with undiagnosed pleural effusion as well as ascites.[21,23,24] Despite being in GI endoscopy practice for more than a decade, EUS FNA has important limitations like false positivity in pancreatic masses in CP and autoimmune pancreatitis and false negativity because of technical difficulty, marked desmoplastic background, sampling error, or interpretative errors. Moreover, certain diseases like lymphoma and autoimmune pancreatitis require cote biopsy for confident diagnosis. To overcome these limitations of EUS FNA, newer FNB needles have been developed for use with EUS.[25,26] EUS guided FNB has been demonstrated to provide samples with increased cellularity along with preserved histologic architecture, and therefore seems to be an ideal tissue acquisition technique for histological as well as molecular testing.

Therapeutic EUS

EUS has the ability to visualize organs and lesions adjacent to GI tract and thus provide an opportunity to target them for various therapeutic procedures. The advantages of EUS is its ability to provide a real time imaging of the targeted area and also, importantly, avoiding adjacent vascular and other structures.[27] Various EUS guided interventional procedures that are being performed are drainage of pancreatic fluid collections, biliary and pancreatic duct drainage in cases of failed ERCP, transmural gallbladder drainage, celiac plexus neurolysis (CPN)/blockade, drainage of mediastinal and intra-abdominal abscesses and collections, various vascular interventions, endoscopic gastrojejunostomy and is useful for targeted chemotherapy and radiotherapy.

CPN is a procedure of chemical ablation of the celiac plexus using absolute alcohol or phenol for relief of intractable pain because of pancreatic cancer. It is usually done under ultrasound, or CT guidance or surgically. Advent of EUS guided CPN has made this procedure very safe with rare adverse effects. Although EUS, CPN is safe and effective, but the pain relief is usually short lasting and patient may require repeated procedures for effective pain relief.[28]

EUS guided transmural drainage of pancreatic fluid collections including pseudocysts **(Fig. 6)** as well as walled off necrosis has evolved as its treatment of choice and is preferred over surgical as well as percutaneous drainage.[29,30] Being minimally invasive, safe, effective, and absence of external percutaneous drainage catheter are important advantages of EUS guided drainage of pancreatic fluid collections. Developments of fully covered lumen apposing metal stents (LAMS) have further improved results of EUS guided drainage of pancreatic

fluid collections. Similarly, abscesses or collections in locations adjacent to GI tract like mediastinal, left lobe of liver, lesser sac, and pelvic collections can be drained under EUS guidance.[27]

EUS-guided transmural drainage of biliary tract and pancreatic duct is an effective alternative to percutaneous or surgical drainage of these ducts in patients with failed ERCP.[27] Although these procedures are effective but are technically challenging, and therefore should be performed only by experts in centers with radiological and surgical back up. Similarly, EUS can be used for draining gallbladder in cases of acute cholecystitis not responding to antibiotics and has been shown to be safer and effective alternative to percutaneous drainage of gallbladder with added advantage of absence of percutaneous drain.

Advancement in accessories for EUS has led on to exploration of unthinkable therapeutic areas. Various palliative oncological interventions like EUS-guided brachytherapy, fiducial marker placement, ethanol ablation, and EUS-guided delivery of antitumor agents can be performed and studies have shown them to be safe and effective.[27] EUS has expanded into vascular interventions field also with various EUS guided interventions like EUS guided glue or coil injections into gastric/ectopic varices as well as pseudoaneurysms being safely performed. EUS-guided intrahepatic portosystemic shunt has also been performed as an alternative to TIPS (transjugular intrahepatic portosystemic shunt) for the treatment of consequences of portal hypertension. Advancement in EUS had made it possible to perform various surgical procedures like gastrojejunostomy safely in a minimally invasive fashion under EUS guidance.[31]

Conclusion

EUS is an important investigation in the armamentarium of an endoscopist. EUS has been shown to have a significant impact in management of patients with various GI disorders with significant change in both the diagnosis as well as management.[3] The advent of EUS-guided FNA for tissue diagnosis as well as therapeutic EUS has led on to wider clinical applications of EUS. Locoregional staging of various GI cancers is one of the important clinical applications of EUS in clinical practice. Development of newer technologies like EUS elastography and contrast EUS is going to further expand the role of EUS. It is important for an internist to be aware of the indications and strengths of EUS in various abdominal, thoracic, as well as pelvic diseases.

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CHAPTER

144 Gastroesophageal Reflux Disease—What's New!

Piyush Dadhich, Shraddha Sharma, Shreyans Singhvi, Gautam Bhandari, Sunil Kumar Dadhich

Abstract

Gastroesophageal reflux disease (GERD) is a frequently encountered disease in clinical practice that significantly hampers the quality of life of patients. Long-term complications of GERD are another area of concern that necessitates timely diagnosis and treatment. Both acid and non-acid reflux have been implicated into the pathophysiology of GERD. Ambulatory 24-hour pH monitoring is the gold standard test for diagnosis. Proton pump inhibitors (PPIs) along with lifestyle modifications are the mainstay of treatment. However, they have their own range of side effects, which precludes their long-term use. Moreover, 20–40% patients show persistent symptoms despite adequate PPI therapy. Management of refractory GERD requires optimization of PPI therapy, addition of a nighttime H_2 receptor antagonist, baclofen and neuromodulators. However, promising results have not been obtained with any of these so far. Newer enantiomers of PPI, potassium-competitive acid blockers, and TLESR-reducers are under trial phase. However, due to the disturbing recurrent nature of symptoms, patients' preference for surgical and endoluminal therapies is apparent. This chapter briefly outlines the pathophysiology and current treatment options for GERD with focus on recent advancements in medical, endoluminal, and surgical management strategies of the disease.

Introduction

Gastroesophageal reflux disease (GERD) is a global disease. While the prevalence in western population is 18.1–27.8%, it is believed to be lower in the East Asian population (<10%). The overall prevalence of GERD in India is 7.6%.[1,2]

GERD is associated with deleterious effects on day-to-day activities, reduced work efficiency, and sleep, ultimately affecting the quality of life. Further, long-term complications like stricture, Barrett's esophagus, and adenocarcinoma also necessitate timely diagnosis and treatment.

Definitions[3]

- **GERD**—Troublesome symptoms sufficient to impair an individual's quality of life or injury or complications that result from the retrograde flow of gastric contents into the esophagus, oropharynx, and/or respiratory tract.
- **NERD**—GERD symptoms without erosions on endoscopy in absence of recent acid-suppressive therapy.
- **Erosions on endoscopy (EE)**—EE with/without GERD symptoms.
- **Barrett's esophagus (BE)**—Endoscopic presence, confirmed histologically of columnar-lined esophagus. It is known to have malignant potential.
- **Extraesophageal GERD syndrome**—This includes:
  - Conditions with established association with GERD (cough, laryngitis, asthma, and dental erosions).
  - Conditions with only a proposed association (pharyngitis, sinusitis, idiopathic pulmonary fibrosis).

Causative and Protective Factors

- **Causative Factors**

Older age	Pregnancy
Obesity	Smoking and alcohol
Anxiety/depression	Less physical activity
Large meals just before sleep	High dietary fat intake
Certain medication like NSAIDs, calcium channel blockers	

- **Protective Factors:** *Helicobacter pylori* infection and physical activity seem to play a protective role.

Pathophysiology[4]

GERD is the disease of lower esophageal sphincter (LES). The acid reflux is most commonly caused due to transient relaxation of lower esophageal sphincter (TLESRs), which is a physiological phenomenon and increases in frequency postprandially.

Other factors that contribute to acid reflux include:

- Decreased LES pressure
- Increased intra-abdominal pressure
- Hiatal hernia
- Poor esophageal acid clearance
- Delayed gastric emptying

Non-acid Reflux[5]

- Undoubtedly, acid reflux is the chief cause of symptoms in GERD patients, making gastric acid suppressive therapy (proton pump inhibitor, PPI) the mainstay of treatment.
- In patients with symptoms despite acid suppression, the culprit in more than 80% cases is non-acid reflux (pH>4).
- Three types of refluxes have been defined based on pH:
  - Acid reflux—pH<4
  - Weakly acidic reflux—pH 4–7
  - Weakly alkaline reflux—pH>7
- The proposed mechanisms are:
  - Duodenogastric-esophageal reflux—Regurgitation of duodenal contents, containing biliary and pancreatic secretions into stomach and esophagus.
  - Large volume of refluxate triggering symptoms irrespective of its acidity by mechanical stimulation of esophagus.
  - Greater proximal esophageal extent of reflux resulting in increased likelihood of symptoms.

Clinical Features

- GERD symptoms can be classified into typical and atypical:[3]

Typical symptoms	*Atypical symptoms*	
• Heartburn • Regurgitation • Water brash	• Nausea, vomiting • Belching • Early satiety • Epigastric pain • Hoarseness • Globus sensation • Dental enamel loss	• Chest pain • Nocturnal awakening • Chronic cough • Asthma • Chronic sinusitis • Recurrent sore throat

- Atypical extraesophageal symptoms lead to difficult and delayed diagnosis.
- They have poor response to conventional therapy.

Diagnosis[3,5-8]

The initial diagnosis is usually made on the basis of cardinal symptoms and response to PPI therapy.

In presence of atypical symptoms, it is important to rule out other gastrointestinal disorders (e.g., ulcers, malignancy) and non-gastrointestinal diseases (e.g., ischemic heart disease).

PPI Diagnostic Test

- Patients with typical symptoms can be put on PPI therapy and followed up to 8 weeks.
- Almost 20–40% patients continue to be symptomatic even on adequate PPI treatment.
- The patients with inadequate response and those with alarm symptoms need further evaluation.

Alarm features	
Dysphagia	Early satiety
Odynophagia	Vomiting
Gastrointestinal bleeding	Age > 55 years
Weight loss	Family history of upper GI malignancy
Iron deficiency anemia	

Upper Gastrointestinal (UGI) Endoscopy

- UGI endoscopy should be done in all patients with
  - Alarm features
  - Suboptimal response to PPI therapy.

  - Long standing GERD, endoscopy is necessary to assess for complications.
- Erosive esophagitis should be graded on the basis of endoscopy findings as follows:

Los Angeles classification of erosive esophagitis[3]	
Grade A	One or more mucosal breaks, ≤5 mm, none of which extends between the tops of the mucosal folds
Grade B	One or more mucosal breaks, >5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve <75% of the esophageal circumference
Grade D	Mucosal breaks that involve at least 75% of the esophageal circumference

- Endoscopy guided biopsy is indicated in patients where eosinophilic esophagitis is suspected and in those with Barrett's esophagus.

Ambulatory 24-hour pH Monitoring

- It is the gold standard for diagnosis of GERD
- It is used to quantify:
  - Esophageal acid exposure time (EAT)
  - Number of reflux events (events when pH decreases to <4)
  - Nature of refluxate (acidic/neutral/alkaline)
- An EAT of more than 6% and a total of more than 80 reflux episodes in 24 hours are considered abnormal.
- Normally carried out for 24 hours, the test can be extended up to 96 hours using Bravo esophageal pH recorder capsule.
- It is done:
  - *Off PPI:*
    In patients with unproven GERD (no or LA grade A/B esophagitis)
    Before surgery
    Atypical presentations
  - *On PPI:*
    In proven GERD (LA grade C/D esophagitis) or BE > 1 cm or prior abnormal pH study
    To establish causation of refractory symptoms

Esophageal Manometry

- It does not help in diagnosis of GERD
- It is used to localize LES before placement of capsule in 24-hour pH metry.
- It helps to diagnose motor disorders like achalasia.

Barium Esophagogram

- It has no role in diagnosing GERD
- It helps in detecting achalasia, esophageal stricture, or hiatus hernia.

EndoFLIP (Endoscopic Functional Luminal Imaging Probe) System

- It assesses the distensibility of esophageal body and GE junction at various volume-controlled (usually 20–30 mL) distending pressures
- GERD patients seem to have increased GE junction distensibility
- FLIP can also identify esophageal motility disorders
- It serves as a useful tool in anti-reflux procedures

Multichannel Intraluminal Impedance Monitoring

- To diagnose non-acid reflux, pH monitoring is not quite helpful as it uses acidity as marker of reflux but not the actual reflux.
- Multichannel intraluminal impedance monitoring combined with pH monitoring can reliably identify non-acid reflux.
- The technique uses changes in resistance to electrical currents to detect the presence of intraluminal liquid.

Treatment[3,7]

Lifestyle Modifications

In patients with uncomplicated GERD, the initial step of management is lifestyle modifications which include:

- Elevation of head end of bed by 4–8 inches
- Dietary changes
  - Avoiding fatty, spicy, large meals
  - Avoiding late evening snacks
  - Avoiding chocolate, citrus foods, caffeine, carbonated drinks
- Minimizing smoking and alcohol
- Weight reduction
- Avoid NSAIDs

Medical Management

This comprises of acid-neutralizing (antacids) and acid-suppressing (H2RA, PPI) agents.

- *Antacids:*
  - Mostly used for occasional or short-term symptoms

  - Include sodium, calcium, aluminum, magnesium salts, and alginate containing agents
- *Histamine type-2 receptor antagonists (H2RA):*
  - Better efficacy and prolonged action than antacids
  - However, tachyphylaxis (usually within 2 weeks) is an issue
  - Should not be given at same time as PPI
  - Currently, there are four FDA-approved H2RAs: cimetidine, famotidine, nizatidine, and ranitidine
  - Lavoltidine and lafutidine are under trial
- *Proton pump inhibitors:*
  - Most potent and hence, the mainstay of treatment
  - PPIs have a better, faster, and long-lasting effect in both NERD and EE
  - Most effective when taken 30 minutes before meals

Acid suppression can be achieved in the following three ways:

- *Step-up therapy:*
  - Starting with less potent agent and moving up for response
  - Patient is first started on H2RA
  - If no response is seen for 2 weeks, patient is shifted to PPI followed by double dose of PPI
- *Step-down therapy:*
  - Patient is started with twice daily dose of PPI
  - When response is achieved, he is switched to once daily dose followed by on-demand dose
- *On-demand therapy:*
  - Here patient is given standard dosage of H2RA or PPI as and when needed

Side Effects of PPI

- The efficacy and ease of availability of PPI has led to its misuse
- Patients either self-treat themselves or once prescribed, continue them for prolonged periods without re-evaluation
- This leads to excessive cost of therapy as well as adverse effects
- Most of the side effects are mild and self-limiting like headache, nausea, abdominal pain, and flatulence
- Recent studies, however, reveal association of PPI with some serious adverse effects

Side effects of PPIs	
Pneumonia	Vitamin B_{12} deficiency
C. difficile diarrhea	Iron deficiency
Risk of fractures	Thrombocytopenia
Hypomagnesemia	Rhabdomyolysis
Acute interstitial nephritis	Enteric infections and neoplasms

Refractory GERD[9,10]

Refractory heartburn is defined as symptoms of reflux of gastric content that do not respond to a double dose of a PPI given for at least 8 weeks.

Functional heartburn and reflux hyper-sensitivity are the most common underlying mechanisms. Other less common mechanisms include psychological factors, functional bowel disorders, delayed gastric emptying, bile reflux, rapid PPI metabolism, PPI resistance or improper PPI timing.

Every patient with refractory GERD should also be evaluated for Eosinophilic esophagitis (EoE), achalasia and Zollinger-Ellison syndrome.

The management of refractory GERD includes:

- Optimization of PPI therapy
  - Lifestyle modifications
  - Better compliance
  - Proper dosing time
  - Splitting the dose
  - Shifting to another PPI
- Adding a night-time H2 receptor antagonist.
- Baclofen- A gamma-aminobutyric acid-B agonist (5-20 mg three times a day) reduces gastroesophageal reflux by decreasing TLESR rate.
- Neuro-modulators (like tricyclic-antidepressants, selective serotonin-reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and trazodone) are effective in patients with functional heartburn or reflux hypersensitivity.
- Endoscopic treatment
- Antireflux surgery.

Recent Developments in Medical Management[11]

- *Extended-release PPIs:* In order to increase their potency, PPIs have been modified into enantiomers that undergo slower hepatic metabolism and maximum absorption and thus increased bioavailability.
  - Dexlansoprazole MR:

    - Dual delayed-release formulation of dexlansoprazole (R-enantiomer of lansoprazole)
    - Two peaks of drug release; at 1–2 hours and at 4–5 hours
    - Can be given irrespective of meal timings
  - Tenatoprazole and S-Tenatoprazole:
    - Contain an imidazopyridine molecule (not a benzimidazole molecule like other PPIs)
    - Offer better night-time control, due to prolonged half-life
  - Esomeprazole strontium delayed-release (Esomezol)
  - Ilaprazole
- *PPI combinations:*
  - *PPI-VB101 (Vecam):* Combination of omeprazole and succinic acid that increases activation of proton-pumps in parietal cells
  - *OX-17:* Omeprazole plus famotidine
  - *NMI-826:* Nitric-oxide-enhanced PPI
  - *Secretol:* Omeprazole plus lansoprazole
- *Potassium-competitive acid blockers (P-CABs):*
- Act by reversibly inhibiting gastric H^+/K^+-ATPase by competing with K^+
- Do not need prior proton pump activation
- Have a faster onset of action; hence, useful as on-demand therapy
- Linaprazan, Soraprazan, Revaprazan, and TAK-438 are P-CABs under trials
- Associated with side effects like hepatotoxicity.
- *TLESR reducers:*
- *Cannabinoid Receptor-agonists:* Delta-9-tetrahydrocannabinol (CB1/CB2 receptor agonist), Rimonabant (CB1 receptor antagonist)
- *Cholecystokinin/Gastrin Receptors-antagonist:* Itriglumide, Loxiglumide
- *GABA-B agonists:* Baclofen, Lesogaberan

Endoscopic Management

- Endoluminal procedures offer a less invasive means of treating GERD
- Patients suitable for endotherapy are those with:
  - Typical symptoms of GERD
  - Low-grade EE (Los Angeles Grades A and B)
  - Endoscopy negative with abnormal esophageal acid exposure
  - No or small hiatal hernia (<3 cm)
  - At least a partial response to PPI treatment
  - Preference for nonmedical, nonsurgical therapy
- Contraindications:
  - Morbid obesity
  - Esophageal motility disorder (e.g., achalasia, scleroderma)
  - Prior esophageal/gastric surgery
  - Esophageal stricture or Barrett esophagus
  - Esophageal/gastric varices
  - Pregnant/lactating women
- Basic techniques of endotherapy:
  - Constriction of LES by using thermal energy
  - Augmenting LES pressure by injecting bulking agent
  - Mechanical alteration of gastroesophageal junction (GEJ)
- Currently, three endoluminal methods are in practice:[12]
  - *Stretta procedure:*
    - Here, compliance of LES is reduced by using radiofrequency ablation
    - This decreases frequency of TLESRs and hence, reflux
  - *Transoral incisionless fundoplication (TIF):*
    - Here using the Esophyx Z device, an anterior full thickness fundoplication is done
    - This constructs a valve 3–5 cm in length and greater than 270 degrees circumferential wrap around LES
- *Ultrasonic surgical endostapler*
  - This technique makes use of a modified endoscope that incorporates a miniature camera, an ultrasound probe, and a stapler on its tip
  - With the use of this endoscope, an anterior full-thickness fundoplication is done
- Endoscopic procedures still under development are:
  - Anti-reflux mucosectomy
  - Endoscopic full thickness plication
  - Submucosal injection of a biocompatible substance

Surgical Management[3,7]

- The anti-reflux surgery is said to have only marginal long-term benefit over PPI therapy
- Patients with typical symptoms respond better to surgery than those with atypical or extra-esophageal symptoms

- Approximately half of the patients will still need anti-reflux medications, post-surgery
- Further, postoperative complications like solid food dysphagia, diarrhea, and early satiety have been reported in 7–10% patients
- Surgery does not prevent progression to adeno-carcinoma
- Patients who will be benefitted the most from surgery are those with:
  - No response, non-compliance or intolerance to medical therapy
  - Complications like refractory esophagitis, stricture, and BE
  - Large hiatus hernia (>5 cm)
  - Documented acid reflux with defective anti-reflux barrier
  - Cardiac dysfunction
  - Normal gastric emptying and esophageal motility
- *Linx™ reflux management system:*[13]
  - This device is in the form of a ring made by series of titanium beads with a magnetic core connected with titanium wires
  - This ring is placed, laparoscopically, around the lower end of distal esophagus
  - It prevents reflux by augmenting LES
  - Short-term studies are promising with more than 90% patients reporting improvement in quality of life
  - However, dysphagia was seen in 68% patients

Conclusion

GERD is a common gastrointestinal disorder with significant impact on quality of life. PPIs, though mainstay of treatment, have got serious long-term side-effects and are less promising in patients with non-acid reflux and extra-esophageal manifestations. There may be a rise in patient's interest in anti-reflux surgery and endoluminal therapy in future; thus, highlighting the need to explore beyond the conventional therapy.

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CHAPTER

145 Post-Infectious Irritable Bowel Syndrome

BK Tripathi

Abstract

Post-infectious irritable bowel syndrome (PI-IBS), a subclass of IBS, where this clinical entity has been linked with occurrence of various gastrointestinal infections, bacterial, protozoal, viral, etc. Studies have clearly shown its occurrence in different ethnicity and every part of the world. As it starts after an episode of GI infection, a few studies throw some light toward its mechanism. Its pathophysiology, clinical features, prognosis, and possible treatment have been discussed here.

Introduction

Many patients of IBS, on being enquired, when did their symptom begin, will struggle to give a correct date. But some occasional patients would come out with an answer, suggest a specific date, saying I was fine until.....Such patients who connect onset of their symptoms to an episode of disorder infectious gastroenteritis, appear to be a little different from others. This subset of patients may be labeled as post-infectious irritable bowel syndrome (PI-IBS). However, most patients of PI-IBS cannot recognize their illness by the past events because either they do not remember or they do not give much importance to any such episode. The clinical syndrome, PI-IBS, denotes persistence of abdominal discomfort, bloating, and constipation diarrhea, which continue despite absence of inciting pathogens. A met analysis in the past concluded that the risk of developing PI-IBS increases sixfold after GI infection and remains elevated for next 1–3 years.[1]

Epidemiology

A link between enteric infection and IBS dates back to the Second World War when numerous cases of GI discomfort were seen in British troupes that had earlier suffered from enteric infection. Since then a number of studies in various parts of the world have reported such illnesses. The incidence or prevalence of PI-IBS, 5–32%, in such studies tell us that it is a global phenomenon and not related to a particular ethnic group or environment **(Box 1)**.[2,3] The wide variation in this reported incidence or prevalence may be because of differences in study methodology, inclusion criteria, definition of IBS, etc. **Table 1** describes the prevalence of PI-IBS in some of these countries.[4] The prevalence rate of PI-IBS (11.5%) does not vary much, if we take into account the post-infection period, that is, 3, 6, 12, 13–59, or more than 60 months.[5] But initial infective organisms matter and overall, the rate

BOX 1 Factors involved in PI-IBS

- Genetic susceptibility
- Intestinal inflammation
- Intestinal permeability
- Altered visceral sensitivity
- Severity of infection
- Psychiatric disturbances
- Pathogens involved
- Host factors

TABLE 1 Prevalence of PI-IBS in different areas

Canada	14.9%
US	17.6%
Norway	54.3%
UK	14.9%
Denmark	20.9%
Germany	45.8%
France	4.5%
Italy	4.5–24.0%
Spain	11.4%
Bangladesh	16.5%

of PI-IBS was the highest after protozoa/parasitic infective enteritis, followed by bacterial and the lowest rates were seen with viral infection.[6]

Pathophysiology

IBS is a disease where diagnosis is based on clinical criteria in absence of any organic changes. Though gut mucosa of patients of IBS are endoscopically normal, recently complex alteration in digestive mucosa has been identified in PI-IBS patients. These changes mainly alter the integrity of intestinal epithelial barrier. It results in paracellular permeability, which can encourage exposure and migration of microflora or food borne antigens. This in turn stimulates intestinal mucosal immunity, leading to persistent intestinal microinflammation. The possibility of inflammatory state of intestinal mucosa is substantiated by the occurrence of infiltration of T lymphocytes, mast cells, and enterochromaffin cells. These cells are responsible for release of cytokines and mediators of inflammation. In one study, increased intestinal permeability was associated with increased stool frequency and was proved by demonstrating increased lactulose-mannitol fractional excretion ratio in patients, 2 years after a water borne outbreak of gastroenteritis involving *Campylobacter jejuni* and *Escherichia coli*.[7,8] These changes suggest a pathophysiological model of PI-IBS and genesis of symptoms of IBS, where symptoms start after a bout of infection rather than its absence. An increased number of mast cells in rectal mucosa and mucosal cellularity were significantly higher in patients of PI-IBS as compared to patients of IBS, a fact confirmed by rectal-sigmoid and ileal mucosal biopsy.

Risk Facors for Development of PI-IBS

Female sex is associated with 2.2 times higher risk. Smoking is not considered a risk factor. Prevalent anxiety and depression at the time of infective enteritis is associated with PI-IBS development more often. Similarly, somatization and neuroticism, at the time of infection, are risk factors.[6,9] Host immune status of elderly persons protects against infection and thus lowers risk of its development.[2]

The nature of pathogen too influences the risk of developing IBS, post infection. The hazard ratio is 4.3 for *E. coli*, 2.9 for *C. jeuni*, 2.5 for Salmonella spp, and 2.2 for viral gastroenteritis. The mechanism of low-hazard ratio for viral etiology is poorly understood. It is possible that viral enteritis is associated with less mucosal damage and poor structural and immunological alteration.[10] However, the high incidence of PI-IBS after an attack of protozoal enteritis (Giardiasis) merits attention as it shows the prevalence much higher, i.e. 39–89%.[11]

Clinical Features

The diagnosis of IBS is always symptom based and is mostly challenging. Similarly, there are no definite diagnostic criteria for post-infectious IBS. The element of "new onset IBS after an episode of acute gastroenteritis in patients who never had IBS previously" should always be given significance. There is strong relation between traveler's diarrhea (TD) and PI-IBS. Self reported TD was associated more often than laboratory confirmed TD (1.5-fold rise in RR).

There might be some subtle differences in PI-IBS from IBS, which has greater stool frequency and loose stools as compared to IBS. All different subtypes of IBS are recognized, and the frequency is IBS-mixed, 46%, IBS diarrhea, 39%, and IBS constipation, 15% in some studies.[12,13] Emphasis should be laid before making a diagnosis of PI-IBS to exclude alarm signs and checking for preliminary investigations, that is, CBC, ESR, CRP, stool culture, etc. in one study, PI-IBS was found to be associated with post-infectious malabsorption syndrome (PI-MAS), popularly known as tropical sprue.[14] Small

intestinal bacterial overgrowth (SIBO) has been linked with IBS, particularly IBD-D type.

Other similar conditions like acquired lactase deficiency following gastroenteritis, bile acid malabsorption, inflammatory bowel disease, or lymphocytic colitis should always be taken into account as differential diagnosis.

Prognosis

PI-IBS too lasts for a long time. In one study, the rate of spontaneous remission was 27% in a year. The proportion of patients who improved (as assessed by ROME III criteria) varied across the age group (23% in younger population of 21–30 years and 37.5% in older population if more than 70 years (p=0.18). Other factors responsible for poor recovery are female sex, patients from North America and Europe, and those with history of somatization.[12] Patients with longer history of IBS symptoms exhibited poor recovery. Despite different pathogenesis, surprisingly, prognosis in PI-IBS does not differ much from non PI-IBS with recovery of one in four patients in first year. Still, it is very encouraging to learn that over half of patients of PI-IBS return to their preinfection state. However, it may take years for symptoms to disappear completely.

Treatment

It is legitimate to think that traditional approach of treatment aiming only at attenuating symptoms, must give place to addressing new pathological targets (intestinal permeability, microinflammation, mast cells, serotonin, visceral hypersensitivity, etc.) However, approaches to tackle such anomalies have not met with much success. In a small study, treatment with prednisolone, in PI-IBS, on presumption of immunological genesis has not shown any benefit.[15] Another RCT of an anti-inflammatory agent, mesalazine, showed overall no benefit in IBS patients with IBS with diarrhea, but a post hoc subgroup analysis did suggest some response in PI-IBS.[16] Furthermore, treatment with *E. coli* 0147 infection with mesalazine appeared to reduce the risk of developing PI-IBS.[17] Increased 5HT available in small intestine in PI-IBS patients enhances visceral hypersensitivity which can be blocked by 5HT receptor antagonist, ondansetron. This theory encouraged randomized trial of ondansetron in IBS with diarrhea, which showed relief of symptoms, particularly urgency.[18]

SIBO is seen in rats of PI-IBS after campylobacter infection. A recent study in India suggested that PI-IBS might overlap with tropical sprue in which SIBO is common.[14] Rifaximin is a locally acting antibiotic, which targets SIBO, has shown benefit in IBS-D patients. Bile salt malabsorption may develop following acute gastroenteritis. Several studies have demonstrated that PI-IBS can respond to cholecystokinin. However, intolerance to this drug discourages its use.[19]

Despite all these novel and experimental therapies, treatment of PI-IBS is frequently symptom directed and matches closely with treatment of IBS. **Table 2** summarizes measures, which help treating patients of PI-IBS.

TABLE 2 Major classes of drugs in IBS management

IBS symptom	*Drugs in therapy*
Abdominal pain	• Antispasmodics
Diarrhea	• Loperamide^ • Diphenoxylate^ • Cholestyramine^ • Probiotics^
Constipation	• Bulking agents • Polyethylene glycol • Osmotic or stimulating laxatives^ • Prucalopride^ • Lubiprostone^ • SSRIs^ • Probiotics^
Bloating/abdominal distension/meteorism/ flatulence	• Probiotics^ • Rifaximin^

^Recommended in a few patients based on individual clinical profile
SSRIs, selective serotonin reuptake inhibitors.
Source: Adapted from Tripathi BK, Soni A. Irritable bowel syndrome in patient management. In: Arulrhaj S (Ed). Medicine Update. New Delhi: Jaypee Brothers Medical Publishers; 2020. pp. 633-7.

Diet

Many patients describe a chronological link between onset and worsening of symptoms with a particular food. However, in majority of patients there is no compelling data to recommend an exclusion diet. The knowledge of enhanced intestinal permeability may suggest food allergy on the premise of penetration of food antigens and their contact with immunocompetent cells. Possible exclusion of such items by patients may be helpful rarely.[20] A low fiber diet with soluble fiber will help to some extent. The consumption of poorly absorbed fermentable oligo-, di-, mono-saccharide and polyols (FODMAPs) may be a trigger for symptoms too. FODMAPs and insoluble

TABLE 3 FODMAP (high and low dietary sources)

	High FODMAP foods	*Low FODMAP foods*
Vegetables	Asparagus, onions, garlic, sugar, peas, beetroot, cabbage, cauliflower, celery, sweet corn, and mushrooms	Alfalfa, bean sprouts, green beans, capsicum, carrot, fresh herbs, cucumber, lettuce, tomato, and zucchini
Fruits	Apples, apricots, figs, pears, mango, watermelon, peaches, and plums	Banana, blueberries, strawberries, cherries, kiwi, orange, grapes, and melon
Grains	Rye, wheat containing breads, wheat-based cereals with dried fruit, wheat pasta, and barley	Gluten-free bread, oats, gluten-free pasta, rice, and quinoa
Meat		Meats, fish, and chicken
Dairy	Cow's milk, custard, and ice cream	Lactose-free milk and yoghurt
Alternatives	Legumes/pulses, cashews, and pistachios	Tofu, almonds (<10 nuts) and pumpkin seeds

Source: Adapted from Tripathi BK, Soni A. Irritable bowel syndrome in patient management. In: Arulrhaj S (Ed). Medicine Update. New Delhi: Jaypee Brothers Medical Publishers; 2020. pp. 633-7.

fibers may enhance osmotic pressure in large intestine and provide a substrate for bacterial fermentation. Low FODMAPs can change intestinal microbiota and reduce IBS symptoms **(Table 3)**. More so, different gastrointestinal cell types that produce hormones, which regulate appetite and food intake, show dysfunction too. This, in turn, increase food intake and weight gain. Though, linkage of IBS and obesity is poorly understood, low FODMAPs and insoluble fibers, probiotics, and regular exercise are to be recommended.[21]

Probiotics and Fecal Microbial Transplantation

A number of probiotics are tested in IBS. The results are encouraging, particularly in relieving excessive flatulence. In fact, administration of probiotics during an attack of acute gastroenteritis of bacterial origin has a protective effect on intestinal epithelial barrier. The role of probiotics is seen in animal model of PI-IBS in a favorable manner. Fecal microbial transplantation (FMT) may be, probably, more beneficial as human feces is the ultimate human probiotic. A number of studies have proved its beneficial role in diseases like IBS, IBD, chronic constipation, etc. In one study role of FMT was studied in recurrent *Clostridium difficile* infection (CDI) by Mattila et al.[22] In this study, symptoms resolved in all patients who did not have strain 027 CDI during the first three months Out of 36 patients who had 027 infection, 32 (89.7%) had a favorable response. Unfortunately rest four patients had history of long standing diarrheal disease with comorbidities did not improve and died. However, no human trial of FMT is available in PI-IBS but success in other areas offers legitimacy for using this therapy and conducting a large trial.

Conclusion

Post-infectious IBS represents a frequently occurring new clinical entity which has led to better understanding of the factors involved in pathophysiology of IBS. ROME IV recognizes post-infectious IBS, a multidimensional clinical chronic inflammation triggered by enteric infection. Present literature on IBS is very descriptive and large randomized trials are lacking. Future research is needed to establish a link between hosts and microbes in which participants are subdivided according to underlying mechanisms. The response of each subgroup will provide new tools for prevention and management.

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Section 11

Section Editor: L_pg I bcp N Singh

Nephrology

CHAPTER

146 Management of Hypertension in Chronic Kidney Disease

Mritunjay Kumar Singh

Abstract

The relationship between hypertension and chronic kidney disease is phenomenal hypertension (HTN) which is considered as most important modifiable risk factor for chronic kidney disease (CKD). Personalized and individualized HTN therapy using standardized office BP and home BP monitoring hold great promise. Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), Calcium channel blocker (CCB), appropriate diuretic therapy, dietary salt restriction, and ensuring proper adherence to therapy make up the foundation for the treatment of HTN in CKD.

Introduction

Studies from India and abroad have provided concordant data on high prevalence of chronic kidney disease (CKD) worldwide. Up to 1 in 10 people world wide has CKD. It is a silent killer like other metabolic diseases and engages major human and economical resources. Association of CKD and hypertension (HTN) is bidirectional. There is a cause and effect relationship between them. HTN is considered as most important modifiable risk factor for CKD. Managing HTN effectively not only retards the progression of CKD, but also reduces the cardiovascular risk significantly.

Pathophysiology of HTN in CKD[1-3]

Pathophysiology of HTN in CKD is multifactorial. It contains components of neural and hormonal pathways. The important mechanisms include:

- Impaired sodium excretion—Guyton and his team have shown that HTN can be generated in partially nephrectomized dog (renal mass reduced to 30%) with salt loading.[4] The elevated blood pressure (BP) in this setting is induced by increased cardiac output (volume expansion) initially, and later on sustained by increased peripheral resistance which is due to autoregulatory peripheral vascular bed vasoconstriction in response to increase peripheral perfusion due to extracellular volume expansion. So sodium retention can induce HTN in two ways—at first by volume dependent mechanism (extracellular fluid expansion) and later on mainly through volume independent mechanism like increased peripheral vascular resistance.
- Increased rennin angiotensin aldosterone activity (RAAS)—Hypersecretion of rennin in a sclerosed kidney leads to increased angiotensin II and RAAS activity leading to increased systemic vascular resistance, sodium retention, and high BP.
- Increased activity of systemic nervous system (SNS)—The kidney is richly innervated sensory organ. Several studies from animal and human subjects establish the kidney-brain axis theory. Sensory inputs from kidney transmitted to central nervous system in turn lead to increased activity of SNS leading to vasoconstriction, rennin secretion, sodium retention, and HTN.
- Endothelin dysfunction—CKD is a chronic low-grade inflammatory state and so endothelial dysfunctions are commonly observed in CKD. Endothelial dysfunction leads to impaired nitrous oxide production and

increased endothelin level leading to increased peripheral vasoconstriction and HTN.

- Vascular stiffness—The distensibility of resistance arteries is affected by certain functional and morphological changes. It includes intimae hyperplasia, medial calcification, smooth muscle cell hyperplasia, and endothelial dysfunction. These changes are largely contributed by disturbed calcium-phosphorus balance, secondary hyperparathyroidism and other neurohumoral components discussed above. Vascular stiffness leads to increased systolic BP and wide pulse pressure, which is a strong predictor of cardiovascular mortality in CKD.
- The erythropoietin induced HTN and obstructive sleep apnea (OSA) are important causes of HTN in CKD, especially in dialysis population. The erythropoietin or erythropoietin-stimulating agents used for treatment of anemia in CKD can induce HTN or require change in antihypertensive regimen in approximately 30% of the cases. Besides rapid and over correction of anemia, HTN in this subset is thought to be caused by vasoconstrictor effect of erythropoietin, which is independent of hemoglobin.[5] OSA is common in advanced CKD population. Chronic intermittent nocturnal hypoxemia provoke sympathetic nervous system activity, RAAS activity, and increases nocturnal BP.
- Medications like over-the-counter nonsteroidal anti-inflammatory drugs, herbal supplements, steroids, and decongestants can provoke HTN in the CKD population.
- The worsening of HTN has been reported in CKD patients with the use of potent anti-tuberculosis drug rifampicin. Rifampicin is a potent enzyme inducer and decreases the level of commonly used antihypertensive drugs—amlodipine, metoprolol, and prazosin. So it is advisable to monitor HTN in CKD patients, once they have been put on rifampicin.[6]
- The HTN is the most common complication of CKD as well as major factor responsible for progression of CKD. Renal autoregulatory mechanism protects renal vasculatures from elevated BP. Maintenance of afferent arteriole tone in response to elevated systemic pressure and increased sodium chloride delivery to macula densa are part of this autoregulatory mechanism. However, it is impaired in patients with diabetes and non-diabetics CKD, thus leads to progressive renal damage with even moderate elevation of BP.

Measurement of BP in CKD[3,7-9]

The proper BP measurement is the first step toward the effective BP management in CKD. BP measurement can vary depending on the setting (e.g., casual office, standardized office, or home) and type of device used (e.g., aneroid or Oscillometric). Standardized office BP (SOBP) is 5–10 mm Hg lower than casual office BP. Most of the recent trials on optimum BP goals have used SOBP as a method of measurement. For standardized office BP measurement certain preparations are required—(e.g., 5 minutes of quite rest/no nicotine, caffeine, and exercise 30 minutes prior to measurement/well validated and periodically calibrated device/correct cuff size/middle of the cuff should be placed at the level of right atrium/average of more than two readings obtained on two occasions) as laid down by 2017 ACC/AHA high BP guidelines.

The out of office BP measurement (ambulatory BP and home BP monitoring) is required to diagnose white coat HTN (defined as elevated office BP with controlled out of office BP, prevalence in CKD ranges from 2% to 41%) and masked HTN (defined as controlled office BP and elevated out of office BP, prevalence in CKD ranges from 6% to 51%). Additionally 24 hour ambulatory BP gives clue about the nocturnal BP. Physiological nocturnal dipping is absent in 14–75% of the CKD population. Thus in CKD out of office BP accurately define the clinical problem and predicts more accurately about the cardiovascular and renal outcomes than office BP.

KDOQI (kidney disease outcome quality initiative) US commentary on the 2017 ACC/AHA HTN guideline commented that home BP monitoring can accurately predict target organ damage and better placed than ambulatory BP monitoring and office BP monitoring. HBPM can also help to overcome the therapeutic inertia.

In our limited resource setting we should prefer standardized office BP, because it requires nothing but our little patience (pre-measurement preparation as mentioned above).

Target BP in CKD[2,3,10-14]

The management of HTN in CKD is a dynamic process, as estimated glomerular filtration rate, comorbidities

and risk changes with time. Due to presence of vascular stiffness and wide pulse pressure in CKD, achieving a BP target rapidly may lead to postural hypotension. So a cautious and gradual approach is required to reach a desired BP target.

From 1994 till 2010, there were four landmark trials compared the standard versus intensive BP control in patients with CKD. These were:

- MDRD (modification of diet in renal disease), year 1994
- AASK (Africans American study of kidney disease and hypertension), year 2002
- REIN-2 (Ramipril efficacy in nephropathy-2), year 2005
- ACCORD (Action to control cardiovascular risk in diabetes), year 2010

Results of all these trials favored standard BP control rather than intensive control in most of the CKD patients, exceptions are patients with proteinuria more than 1 g/day, which were benefited from intensive control of BP. On the basis of these trials, KDIGO (kidney disease initiative global outcome) 2012 suggested a lower BP for significant proteinuria.

- Albuminuria (<30 mg/24 hr): ≤140/90 (1B)
- Albuminuria (>30 mg/24 hr): ≤130/80 (2D)

Till year 2015, it was thought that controlling BP to less than 140/90 mm Hg is likely to be beneficial in CKD population. But with the advent of SPRINT (systolic BP intervention trial) study in 2015, intensive control of systolic BP (<120 mm Hg) has gained momentum. SPRINT has included data from 9,361 adults age 50 or older with systolic BP of 130 mm Hg or higher and at least one additional cardiovascular disease risk factor. Around 28% of participants had CKD without significant proteinuria. The highlights of SPRINT study are:

- intensive reduction in SBP reduces cardiovascular events
- intensive reduction in SBP has mortality benefit in CKD population
- the subgroup analysis of older patients with CKD in SPRINT has also favorable outcome
- with adoption of SBP <120 mm Hg in all CKD population, separate BP target for proteinuria is not required

However, it should be noted that more than 50% of participants in intensive arm of SPRINT had not achieved SBP target after 1 year. So targeting and achieving a lower SBP is a big challenge. Additionally the benefit of lower BP is less certain in diabetic CKD and advanced CKD population. The 2017 American College of Cardiology (ACC) has adopted the result of SPRINT and suggested more intensive BP control in CKD population. In light of SPRINT and other newer studies KDIGO controversies conference 2017 has also suggested for revision in BP diagnosis threshold and BP treatment target.

In our setting, we should target lower BP:

- If SOBP/HBPM is the method used for measurement of BP
- If patient is tolerating the target BP well without postural hypotension or other adverse effect
- If patient is having non-diabetic CKD

Secondary HTN in CKD[3]

Secondary causes of HTN are potentially treatable and should be searched in following conditions:

- If the onset of elevated BP occurred before puberty and preceded the development of CKD.
- Severe or malignant HTN that is out of proportion to the degree of CKD is present.
- Acute worsening of BP control occurs in a previously hypertensive patient with good BP control, or resistant HTN is present.
- Persistent hypokalemia off diuretic treatment (primary aldosteronism).
- Development of tremor and palpitation (pheochromocytoma).
- Flash pulmonary edema (renal artery stenosis).

Non-pharmacological Therapy[1-3]

Early institution of non-pharmacological therapy in the form of dietary modification and life style modification is the first step to the treatment of HTN in CKD.

- Dietary salt restriction (sodium intake <1.5 g/day)—Reduce BP and proteinuria; potentiate the action of ACEI/ARB.
- DASH (Dietary approach to stop HTN) Diet—Diet rich in fruits and vegetables, low in saturated and unsaturated fat can lead to modest reduction in BP. But it is not appropriate to use DASH Diet in advanced CKD because of the potential for hyperkalemia.
- Modest physical activity of 150 minutes duration/week is useful for CKD population. It can be modified

depending on the cardiorespiratory fitness status and physical limitation of the individual.
- Other life style interventions include weight loss in obese people, limiting alcohol intake, and avoidance of over the counter medications such as non-steroidal anti-inflammatory drugs.

Choosing Antihypertensive Drugs in CKD[2,3,8,15]

Most of the CKD patients require multiple antihypertensives for adequate control of HTN. Certain classes of antihypertensives are preferred because of their renoprotective, cardioprotective, and diuretics actions apart from antihypertensive effects. Before choosing antihypertensive agents in CKD we should look for comorbidities, risk benefit ratio of individual drug, volume status, and age of the patient.

- Angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs)—
  - ACEI/ARB are the agent of choice to treat HTN in diabetic CKD with severely increased proteinuria (>300 mg/day). But the superiority of ACEI/ARB over other agents (calcium channel blockers, diuretics) is questionable in non-proteinuric CKD. However, as majority of CKD patients require multiple agents to achieve adequate control of HTN, it is reasonable to include ACEI/ARB as add on therapy in non-proteinuric CKD patients.
  - The common side effect of ACEI/ARB is hyperkalemia particularly in advanced CKD hence limiting their use despite their proven benefit. Novel potassium binding agents (patiromer and sodium zirconium cyclosilicate) in combination with ACEI/ARB could change the way of pharmacotherapy in HTN in CKD. But further research is required before their routine clinical use.
  - Another potential problem with the use of ACEI/ARB is acute kidney injury. Recent guidelines suggest that up to 30% increase in serum creatinine in first few weeks and later on stabilization is an acceptable physiological change which confers long-term renoprotection.
  - Combination therapy (ACEI+ARB) has failed to show any cardioprotection and renoprotection in major studies. Additionally this combination is associated with increase risk of hyperkalemia, acute kidney injury, and hypotension.
- Calcium channel blockers (CCB)—dihydropyridine (DHP)-CCB (amlodipine) are frequently prescribed antihypertensives in CKD because:
  - they are the potent antihypertensive agents,
  - can work synergistically with ACEI/ARB,
  - work well in volume expanded states, and
  - minimal side effect (pedal edema).
- Diuretics—
  - Sodium retention and volume overload are the main concerns of the majority of CKD patients. Diuretics act by natriuresis (promote sodium excretion through kidney), thus reduce extracellular volume and has been shown to improve left ventricular mass index (LVMI) and arterial stiffness in CKD patients. Diuretics also enhance the BP lowering effect of ACEI/ARB. Thiazide diuretics (hydrochlorothiazides and chlorthalidone) are less effective at lower glomerular filtration rate so switching to loop diuretics (furosemide and torsemide) with frequent dosing is done in advanced CKD. Some times loop diuretics can be combined with thiazide diuretics to treat refractory edema in advanced CKD.
  - Diuretics should be avoided in end stage renal disease with no residual function and polycystic kidney disease as they can lead to accelerated cyst growth and decreased renal function. The major adverse effects of diuretics are volume depletion and electrolyte imbalance.
  - Mineralocorticoid receptor antagonists (MRA) are effective drugs for resistant HTN but may cause hyperkalemia in patients with low-estimated glomerular filtration rate, so better to avoid at estimated glomerular filtration rate below 45 mL/min/m^2.
- Beta blockers—
  - Although beta blockers has lost credential in treatment of primary HTN in general population, but still they are found to be useful adjunctive therapy in CKD population because they decrease sympathetic over activity and are cardioprotective. A recent trial named HDPAL (HTN in hemodialysis patients treated with atenolol or lisinopril) has concluded that atenolol arm has less cardiovascular

events and better BP control than lisinopril arm in hemodialysis patients.
  - Other antihypertensive agents for patients with CKD include direct vasodilator (minoxidil and hydralazine), centrally acting alpha adrenergic agonist (clonidine), alpha blockers (prazosin), and direct rennin inhibitors (aliskiren).
- Resistant and refractory HTN in CKD[1,3,16]—
  - The prevalence is up to 40% as shown in CRIC Study. It has got poor prognosis—increases the risk of death by 30% and the risk of heart failure by 59%. The selection of complementary medications and ensuring drug adherence often resolve treatment resistance. Thiazide and thiazide-like diuretics in combination with ACE/ARB or MRA can be very effective in treatment of CKD populations with apparent drug resistant HTN.

Adherence[2,9]

Adherence to therapy is poor due to frequent dosing of pills, pill burden, drug interaction, and adverse effects. Strategies to improve adherence include:
- Patients should be communicated regarding treatment and its importance.
- Use of combination pill and whenever possible long acting, once a day medication to be used.

Nocturnal Therapy[2,17,18]

Non-dipping is detected more frequently in later stages of CKD and associated with significant CV death. Multiple clinical trials have shown an improvement in nocturnal dipping of BP by dosing at least one antihypertensive medication at bedtime.

Management of HTN in Patients on Dialysis[2,3,19,20]

The relationship between BP and CVD in this group is more complex. There is U-shaped relationship between 24-hour ambulatory SBP and all cause mortality as noted by Mayer et al. So BP treatment should be individualized in this group keeping in mind of comorbid conditions. Besides pharmacotherapy, these are the novel measures to treat HTN in dialysis patients:
- Dry weight reduction (DRIP trial)
- Dietary sodium restriction
- Dialysate sodium restriction
- Adequate time on dialysis
- Consideration of frequent dialysis

Managing HTN Following Kidney Transplantation[1-3]

HTN is common in post-transplant period. It has been reported that HTN is prevalent in more than 90% of calcineurin inhibitors treated kidney transplant recipient. The higher BP is associated with poor graft survival, increased CVD risk, and most common cause of death post-transplant. KDIGO and the ACC/AHA guidelines currently recommend a BP target <130/80 mm Hg. Some useful tips to manage HTN following kidney transplants are:
- Weight control
- Steroid and CNI dose optimization
- During 1st year after transplant, CCB (DHP) is the preferred antihypertensive agent over ACEI/ARB
- In patient with mild graft dysfunction with proteinuria, ARB are the preferred drug
- In case of post-transplant hyperuricemia losartan is the preferred drug

Future Perspective[21-25]

In recent years, the underlying mechanism and unmet therapeutic needs to halt the progression of CKD and CVD have been better understood. Due to this few promising therapeutic measures have emerged. They are:
- *Sodium glucose transport 2 inhibitor (SGLT-2I):* Interest in molecules of this group has intensified following the result of EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) and CREDENCE (Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy) trials, which demonstrated significant slowing of CKD progression and a reduction in the composite outcome of death from CVD. Combining ACEI/ARB with SGLT2I may further reduce intraglomerular pressure by their synergistic effects.
- The DUET (Dual Endothelin Receptor and Angiotensin Receptor Blocker) trials with sparsentan and irbesartan have shown promising results in control of HTN and proteinuria in IgA nephropathy and focal segmental glomerulosclerosis (FSGS).

- *Renal denervation therapy (RDN):* After initial hiccups this radio frequency energy based therapy for ablation of the networks of nerves around renal arteries has shown promising results in newer trials. However, this strategy is still in experimental stage.

Conclusion

The Prevalence of HTN in CKD is very high, but HTN control rate is far from optimal. When CKD and HTN coexist, CV morbidity and mortality is substantially increased. Personalized and individualized HTN therapy using standardized office BP and home BP monitoring holds great promise. ACEI or ARB, CCB, appropriate diuretic therapy, dietary salt restriction, and ensuring proper adherence to therapy make up the foundation for the treatment of HTN in CKD.

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CHAPTER

147 Prevention of Progression of CKD—What Is New?

Krishnaswamy Sampathkumar

Abstract

Chronic kidney disease (CKD) afflicts approximately 7–10% of adult population of India. It is a silent killer due to its far reaching ill effects on the cardiovascular system. The manifestations of CKD are varied and can mimic a variety of medical and surgical conditions. Early recognition is of paramount importance since preventive strategies are successful only if applied before irreversible renal fibrosis sets in. This article gives an overview of recent evidences. Dietary protein restriction should be applied to meat based diets and not for vegetable proteins. Plant-based protein intake has been shown to be renoprotective due to its alkaline nature and fiber content. RAS blocker therapy, and antihypertensive therapy are the inseparable duo of prevention. A dose escalating strategy of RAS blockade aiming for proteinuria reduction has been successfully applied in the Indian context. However, it requires close serum creatinine and potassium monitoring to prevent harm. Based on well conducted large trials, SGLT2-inhibitors have provided substantial benefits in terms of renal, cardiac, and all cause mortality. Their use is recommended for both diabetic and non-diabetic renal diseases. Sodium bicarbonate and statin usage have shown benefits. However, uric acid lowering therapy has failed to provide beneficial effects in recent trials.

Introduction

Chronic kidney disease (CKD) is a silent killer, which afflicts approximately 7–10% of world's adult population. It means that India which makes up 17% of world population carries a large burden of the disease.[1] It is commonly mistaken for a number of conditions such as nutritional anemia, nutritional rickets, peptic ulcer disease, dysfunctional uterine bleeding, etc. In the absence of a National Registry, the exact prevalence of the disease is open to conjecture. A population based study showed incidence of End Stage Renal Disease (ESRD) to be 159 per million population.[2] Once a patient reaches ESRD the treatment is not only prohibitively expensive but survival rates are worse than advanced malignancy. Thus every physician should update himself with current practice guidelines for optimal prevention of progression of CKD.

Contributors to Accelerated GFR Loss

The glomerular filtration rate (GFR) falls at a rate of approximately 0.5 mL/min/year in the normal adult population. Patients with progressive CKD the loss of GFR may be as steep as 5–15 mL/min/year. In addition to non-alterable factors such as age, gender, and genetics a number of factors which are potentially treatable contribute to the risk of progression. A recent work showed genetic polymorphisms involving intracellular antioxidant systems can accelerate the progression and mortality dramatically.[3] Dietary factors, lack of exercise, albuminuria, hypertension, hyperglycemia, lipids, morbid obesity, and metabolic acidosis, mini AKIs, and gut dysbiosis are some of the modifiable risk factors.

Lifestyle Modifications

Diet

Earlier view—Restricting all forms of proteins in the diet retards the progression of CKD.

Current view—Plant based proteins are renal friendly and should be promoted.

In a community-based study of adults without CKD, higher adherence to a healthy plant-based diet or a provegetarian diet was associated with lower CKD risk.[4] Higher consumption of healthy plant foods (fruits, vegetables, whole grains, nuts, legumes, coffee, tea) was associated with a lower risk and slower eGFR decline in GFR. Dietary red meat contains cardiotoxic metabolites from lecithin and carnitine such as trimethylamines. Plant-based proteins are recommended for a variety of reasons such as higher fiber content, lesser diet acid load, less phosphorus and uric acid generation, enhanced vitamin K (reduction of coronary calcium scores), and promotion of healthy gut microbiome. Dals, lentils, and Soya beans can be substituted for dietary animal proteins such as meat and dairy products. Daily intake of locally available fruits and vegetables are recommended in CKD Stages 3–4. Compensatory potassium excretion from the colon increases when dietary fiber intake is liberalized. Vegetable diet also inhibits the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 in the distal convoluted tubule cells which increase the cortisol induced K excretion in addition to aldosterone effect.

Physical Exercise

Physical deconditioning sets in during progressive CKD, which results in muscle energy dysmetabolism. A reduction in mitochondrial activity develops even in earlier stages of CKD, which is progressive. Oxidative stress, inflammation, erythropoietin, vitamin D, and testosterone deficiencies are possible reasons. The symptoms include easy fatigability and proximal muscle weakness. Later, muscle atrophy sets in. As in general population, the cardiovascular benefits of exercise cannot be ignored in CKD patients. Regular moderate intensity exercises involving all the major core groups of muscles are recommended. Both endurance and weight bearing exercises are indicated in Stage 3 CKD.

Albuminuria

Earlier view—Albuminuria is a marker of severity of renal disease.

Current view—It is both a marker and maker of progression of renal disease.

Albuminuria is both a marker and maker of glomerular injury. A direct quantitative relationship exists between the higher proteinuric CKD and faster progression. Filtered albumin is taken up by the proximal convoluted tubule cells where it is toxic and inflammatory. Tubulointerstitial fibrosis sets in faster when the rates of proteinuria are higher. RAS blockers have shown to reduce proteinuria and prevent progression of renal disease. Highest tolerable doses of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors are recommended to provide optimal renoprotection. Higher doses are accompanied by hyperkalemia. An important advance has been the clinical entry of New K binding agents like zirconium and patiromer, which permit continued and safe use of RAS blockade in the face of hyperkalemia. In the OPAL-HK study involving CKD patients with hyperkalemia, treatment with patiromer reduced the serum potassium levels and enabled significantly more patients to continue RAS blockers without interruption than placebo.[5] The drug was well tolerated.

Hypertension

Earlier target—BP reduction below 130/80.

Current view—More intensive BP reduction below 120–125/<80 in proteinuric CKD.

Long-term follow-up of 15 years in MDRD and AASK trials highlighted that intensive BP control reduced both overall mortality and progression to ESRD. The recently released SPRINT trial data showed that in CKD subgroup the all cause mortality was lower in the intensive arm.[6] However, the incidence of ESRD or a 50% decline in GFR was not altered in the intensive arm. However, a note of caution is that diastolic BP reduction below 70 mm Hg is not recommended in older adults with atheromatous central arteries, which can lead onto coronary insufficiency.

ARBs and ACE inhibitors are the preferred first-line agents. Maximally tolerated doses of these drugs should be given. As an example losartan is started on 50 mg OD and titrated up depending on proteinuria reduction and BP reduction to 50 mg BID. Supra pharmacological doses

can be prescribed with a close, watch on serum K and BP. The dose required to optimize GFR reduction was 150±88 mg/day in an Indian Study.[7] Though combinations of ACEi and ARBs are prohibited by most of the guidelines, individualization of therapy can result in better outcomes.

Since multiple drugs are required in CKD, calcium channel blockers, diuretics (Thiazides in Stage 3 and loop diuretics in Stage 4), are added in a stepwise fashion. Dietary sodium restriction to below 2–3 gm/day is an important adjunct to improve BP control. Due to concerns about hyperkalemia, there is reluctance to start spironolactone therapy in those with resistant hypertension. Recently published AMBER study showed that when patiromer is added to spironolactone more patients could continue the latter drug without developing hyperkalemia.[8]

Canrenone and Finerenone are novel non-steroidal aldosterone receptor antagonists with low risk of hyperkalemia. Current prospective trials are testing their efficacy and safety in CKD patients.

Glucose Control

Earlier view—Insulin therapy for Stage 3 CKD onward.

Recent view—SGLT2 inhibitors are strongly recommended to prevent progression of CKD and reduce cardiovascular morbidity and mortality.

CREDENCE trial on canagliflozin versus placebo on CKD patients has shown remarkable renal and cardiovascular benefits for patients with diabetic nephropathy.[9] All the patients had an estimated GFR of 30 to less than 90 mL/minute and albuminuria and were treated with renin-angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease, or a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Over a 2.6-year period, the relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group (hazard ratio, 0.70). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66) and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68). Cardiovascular events were also significantly less in the treatment arm. Risk of amputations or fractures were not significantly elevated in the treatment arm. Sodium reabsorption is inhibited in the proximal convoluted tubule cells following SGLT2 inhibitor therapy. This results in more sodium ions reaching the DCT and thereby producing afferent arteriolar vasoconstriction. This ultimately results in renal preservation since intraglomerular pressure is lessened.

GLP1 analogs (liraglutide) have also shown both renal and cardiovascular benefits in trials. In the LEADER trial involving liraglutide new onset of persistent macroalbuminuria, occurred in significantly fewer participants in the liraglutide group than in the placebo group (hazard ratio, 0.74).[10] The reduction in GFR in the placebo arm was –5 mL/min/year, which reduced to –0.3 mL/min/year in the treatment group.

In contrast, DPP4 inhibitors have not shown reno- or cardioprotective benefits in trials. But they are still useful agents since the incidence of hypoglycemia is less, which enhances the acceptability of the drug in CKD population.

The recommended target HbA1C level for the prevention of progression of CKD is between 6.5–7%. However, in those with higher comorbidities who are prone for complications of hypoglycemia, one can opt for a compromised target of 7.5–8%.

Acidosis Correction

Recent view—Sodium bicarbonate therapy is nephroprotective.

The serum bicarbonate levels are ideally maintained above 22 meq/L in patients with CKD. Acidosis correction improves bone health and retards progression of renal disease. The latter is due to reduced ammonia generation, which is linked to inflammation by stimulation of alternate complement pathway. A condition called normobicarbonatemic acidosis develops in CKD, which is characterized by reduced urinary excretion of citrate.[11] This can be addressed by providing fruits and vegetables, which are a rich source of citrate.

Sodium bicarbonate is commonly given by oral route in tablet or capsule forms. Adult dose is between 1.5–2.5 gm/day depending on the degree of acidosis. Each gram contains 12 mEq of base. The potential side effects include gastic distension and metabolic alkalosis. Aggravation of hypertension is uncommon. It decreases the absorption of ranitidine and increases the propensity of quinolones for crystalluria. It is contraindicated in hypocalcemia and hypokalemia.

Management of Hyperlipidemia

Earlier view—Statin therapy is beneficial at the earlier stages of CKD. No new data have emerged recently.

Observational studies among apparently healthy individuals or in patients with preexisting cardiovascular disease (CVD) have shown a roughly linear relationship between risk of cardiovascular-related death and serum total and low-density lipoprotein (LDL) cholesterol. Among patients with CKD, however, this relationship is much less obvious. The cardiovascular abnormalities in Stage 4–5 CKD are progressive medial vessel wall calcification, left ventricular hypertrophy (LVH) and diastolic dysfunction. These are poorly responsive to statin therapy. There are no new evidences in the last decade in this field in the aftermath of SHARP trial, which showed a significant, 17% reduction in major atherosclerosis events and a 15% reduction in major cardiovascular events in the entire cohort of 9,000 patients. The earlier the statin therapy is initiated, the better were the cardiovascular protection benefits.

Prevention of AKI

Earlier view—Recovered AKI patients regain normal renal function.

Current view—Up to 30% of patients with comorbidities who develop AKI may progress to CKD.

In CKD patients multiple episodes of AKI are the cause of accelerated decline in GFR.

The downtrending of GFR slope from above 90 mL/min to 10 mL/min does not occur in a straight line if plotted against time. There are periods of flattening interspersed with periods of acute reduction. These "Mini AKIs" due to volume depletion, cardiac failure, UTI, hypotension, and NSAID drug toxicity result in incomplete recovery to original levels. It is critically important that these events are aggressively managed.

Intestinal Microbial Flora

Recent view—It is beneficial to alter the dysbiosis, which is prevalent in CKD patients.

Human gastrointestinal (GI) tract is home to trillions of bacteria, which undergo both a qualitative and quantitative alterations in CKD. Products of bacterial metabolism are linked to inflammation, uremic syndrome, and cardiovascular disease. Oral ingestion of probiotics has been shown to reduce the serum levels of products of protein metabolism like p-cresol and indoxyl sulfate, which induce cardiovascular toxicity.

Obesity

Earlier view—Weight loss should be routinely advised in CKD patients.

Recent view—Mildly overweight category of patients show best survival.

The association between body mass index (BMI) and mortality has shown some surprising findings. In a large observational study from US veterans found that best survival of Stage 3–4 CKD was seen in those with BMI between 25 and 35 kg/m^2. In morbidly obese patients, when bariatric surgery was undertaken, both proteinuria and GFR reduction are attenuated.[12]

Uric Acid

Earlier view—Treatment of hyperuricemia is reno-protective.

Recent view—Hyperuricemia correction does not result in renal benefits.

Uric acid produces inflammation and proliferation of afferent arterioles in mouse models of CKD. Extracellular precipitation in the form of microscopic crystals and macroscopic urate stones can cause structural damage. Intracellular mechanisms show its propensity to precipitate injury relating to its oxidative properties. Humans and other primates are prone to hyperuricemia because enzyme uricase was lost in evolutionary mutation. To lower uric acid levels, xanthine oxidase inhibitors (XOIs) such as allopurinol and febuxostat are commonly used in clinical arena.

Does Reduction of Uric Acid Produce Renal Benefits?

The short answer seems to be no. Based on many observational studies which reported that higher serum uric acid levels heightened the risk for new-onset CKD as well hastened its progression, a commonly held view was that a level above 7 mg% required intervention for renal benefits. However, two large, high-quality trials, which were published recently refuted a causal relationship and revealed that urate-lowering therapy neither prevents CKD nor slows down its progression.

PERL trial randomized over 500 adults with type 1 diabetes and early-to-moderate diabetic kidney disease, with allopurinol versus placebo. At 3 years treatment with allopurinol had no effect on the change in measured GFR compared with placebo; worryingly, allopurinol increased albuminuria, and nonsignificantly increased the rate of fatal or nonfatal cardiovascular events. In the CKD-FIX study of over 350 adults with more advanced CKD, the rate of decline of estimated GFR at 2 years was the same with allopurinol and placebo.

Anemia correction and correction of calcium phosphorus dysmetabolism have not been shown to have any effect on the progression of CKD, and hence they are not discussed at length. But they have to be addressed all the same since cardiovascular and skeletal health are inseparable sufferers from renal dysfunction.

Thus a multipronged strategy implemented with attention to minutiae will be needed. Though the task looks daunting, it is achievable if pursued with dedication as shown by Prof. M. K. Mani at Chennai.

Conclusion

CKD can be termed as An Orphan Disease since awareness levels are low even amongst the physicians. The four most effective strategies for its prevention are RAS Blockade, SGLT2 inhibitor therapy, Hypertension control, and Blood Glucose control. In the years to come personalized medicine looking at the genetic makeup of the patient may become an added tool to decide the therapeutic options.

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CHAPTER

148 Lupus Nephritis—Current Understanding and Management

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Abstract

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease, and lupus nephritis (LN) is associated with increased morbidity and mortality. Kidney biopsy is essential and the "gold standard" for diagnosing LN. Extra-glomerular involvement is seen in up to two-thirds of patients with LN and is associated with poor outcomes. The revised 2018 International Society of Nephrology/Renal Pathology Society classification for LN has changed parameters for activity index and redefined few pathological parameters. Repeat kidney biopsy is done for resistant disease or during flare, usually when atypical features are present. Protocol biopsy is a promising tool to monitor patients with LN and decide maintenance therapy. Newer therapies like multi-targeted therapy and biological agents such as obinutuzumab have shown promise in treating LN.

Introduction

Lupus nephritis (LN) is seen in 25–50% of patients at the outset of systemic lupus erythematosus (SLE) and about 60% of the patients are affected during the disease course, which varies with race and ethnicity.[1-3] The probability of a new renal flare is 20–30% per patient-year of follow-up.[4] Patients with LN, particularly those with proliferative histology, are at 2.28 times higher risk of mortality as compared to those without LN and up to one-third of them progress to end stage renal disease (ESRD) within 15 years.[5,6] The prevalence of SLE and the chances of developing LN vary considerably between different regions of the world, with higher rates in Africans and Hispanics.[7] Most often, LN occurs early (within 5 years) in the disease course of SLE.[8] SLE is more prevalent in women than men across all age groups and populations; the female-to-male ratio is highest at reproductive age, ranging between 8:1 and 15:1, and is lowest in prepubertal children at about 4:3.[9-11]

Pathology of Lupus Nephritis

LN is initiated by deposition of circulating immune complexes and by binding of autoantibodies to antigens in the glomerulus and vessel walls. This interaction activates complement mediated cytotoxicity, macrophage, and natural killer cell-induced cell cytotoxicity along with Fc receptor-based T-cell mediated cell damage. Anti-phospholipid antibodies can result in thrombotic lesions in the glomerulus and in the vessels. In 20–30% of patients with LN, anti-neutrophil cytoplasmic antibody can be positive and may contribute to the development of vasculitic lesions.[12]

Value of Renal Biopsy

Treatment of LN is guided by the histological patterns described in the classification system 2003 International society of Nephrology/Renal Pathology Society (ISN/RPS) classification. Clinical severity does not always correlate with histological severity and is shown in **Table 1**.

TABLE 1 Clinicopathological correlation in lupus nephritis

Lupus nephritis class (ISN/RPS)	*Proteinuria*	*Active urine sediment*	*Increased serum creatinine*	*Active lupus serology*	*Hypertension*
Class I	–*	–	–	+/–	–
Class II	+/– *	–	–	+/–	–
Class III	++ (NS: 30%)	+	+/–	+/–	+/–
Class IV	+++ (NS: 50%)	++	+/–	++/–	++/–
Class V	+++ (NS: 60%)	–	+/–	+/––	+/–
Class VI	++	+/–	+	+/––	+

(+) represents frequent occurrence of symptom/sign, (–) represents infrequent occurrence of symptom/sign, NS: Nephrotic syndrome; * NS is seen in class I/II LN in presence of podocytopathy

Therefore, renal biopsy remains indispensable and the "gold standard" to correctly classify LN. The Kidney Disease Initiative Global Outcomes (KDIGO),[13] American College of Rheumatology (ACR),[14] and European League Against Rheumatism/European Renal Association-European Dialysis and Transplantation Association (EULAR/ERA-EDTA)[15] guidelines recommend that a renal biopsy should be performed to confirm and classify LN in cases of SLE with clinical manifestation of proteinuria (>500 mg/day), urinary red blood cells (>5 per high power field) or cellular casts (any), or unexplained renal dysfunction.

Classification of LN: The classification of LN (based on histology) has been in place for over five decades with the latest modification in 2018.

2003: ISN/RPS[16] proposed a new classification system that would provide better clinical correlation, uniformity in reporting and reproducibility. The classification schema is based on glomerular pathology, which includes assessment by light microscopy (LM) and immunofluorescence (IF). Class IV LN is the commonest pattern seen worldwide. In a study from our center, of total 232 patients, Class II was seen in 21, Class III in 36, Class IV in 130, and Class V in 30 patients.[17]

2018: Changes in the 2018 ISN/RPS[18] revision were: the distinction between class IV-S and IV-G was not evidence based and hence, has been removed; the threshold for defining crescent is lowered and various types of crescents are defined in addition; activity and chronicity scores are modified and are required to be mentioned instead of A (activity) or C (chronicity).

Extraglomerular Involvement

Tubular atrophy and interstitial fibrosis (IFTA) are one of the strongest predictors of renal failure. Various studies reported vascular involvement in LN to indicate increased risk for progression to renal failure. In a study from our center,[9] of total 197 patients, thrombotic microangiopathy (TMA) was found in 25.4% with 10% having concomitant APS. Patients of LN with TMA had significantly higher rates of oliguria (p=0.035), advanced renal injury, that is, serum creatinine more than 3 mg/dL (p=0.002), fibrocellular and fibrous crescents (p=0.01), and tubular atrophy (0.001) compared to non-TMA patients. They also had higher rates of treatment failure (p=0.02) compared to the group without TMA.[9] Another study (unpublished data) from our center included 241 patients with LN with 60% having tubulointerstitial involvement, 32.3% having vascular involvement. Those with tubulointerstitial and vascular involvement had lower rates of remission.

Role of Repeat Biopsy

Repeat biopsy is done during renal flare for refractory LN or as a protocol after induction and/or maintenance therapy for LN. Repeat biopsy is useful as histological transformations are common and may affect treatment decisions. It has also been shown to be predictive of long-term outcomes. Protocol re-biopsies can guide therapeutic decision as 20–50% of patients in clinical complete response after therapy were shown to have histological activity on the biopsy.[19] Furthermore, protocol biopsy after prolonged clinical remission can help in deciding safe withdrawal of maintenance therapy, as

was shown recently in a prospective study on clinically quiescent LN patients.[20] Recently, the **EULAR 2019**[21] guideline has recommended repeat biopsy in those with incomplete renal response defined as 24-hour proteinuria more than 0.8–1 g/day with stable/improved renal function despite at least 1 year of immunosuppressive treatment. In a study from our center, which included 62 patients who underwent repeat biopsy for clinical indications, we found histological transformations in 61.3% of the patients.[22] Class switch from proliferative to non-proliferative occurred in 13.7% and 18.2% of patients with non-proliferative histology switched to proliferative classes. On repeat biopsy, endocapillary proliferation and fibrinoid necrosis decreased whereas glomerulosclerosis and IFTA increased (P<0.001). Presence of IFTA more than 30% and TMA on the second biopsy correlated with worse long-term outcome.[22]

Management of Lupus Nephritis

Treatment of LN involves use of aggressive immunosuppressive therapy in the induction phase to achieve rapid control of inflammation in the kidneys followed by less intense immunosuppression to maintain remission. The initial phase for induction is for a duration of 3–6 months followed by a maintenance phase of 3–5 years usually.

Induction Agents

Corticosteroids: Steroids form the backbone of induction therapy of active LN. However, there is an increasing concern about the side-effects with high and prolonged doses of steroids. Many newer trials have investigated this by trying to compare regimens, which include introduction of lesser toxic novel agents to allow reduction of steroid dose versus the standard induction therapy. Based on these concerns and the existing literature, the 2019 EULAR-ERA/EDTA guideline[23] for LN has recommended the use of methylprednisolone pulse (at doses between 500–2,500 mg) followed by oral prednisolone of 0.3–0.5 mg/kg/day and a rapid taper to reach less than 7.5 mg/day by 3–6 months.

Cyclophosphamide: Intravenous cyclophosphamide (CYC) along with corticosteroids became the standard of care for treatment of LN based on randomized control trials conducted by the National institute of health (NIH). The NIH regimen includes monthly intravenous pulses of CYC at a dose of 500–1,000 mg/m^2 for 6 months followed by maintenance with quarterly infusions at same dose for the next 2 years.[24] Using this protocol, remission could be achieved in 61% of patients at the end of induction phase and there were no relapses in the 2-year follow-up period. A similar study at our center revealed overall response rate of 70% (Complete + Partial remission) and 30% failure rate (Failure 20% + Death 10%).[25] Major side effects associated with CYC such as leukopenia, infections, gonadotoxicity, hemorrhagic cystitis, and risk of malignancies in long-term are associated with cumulative dose received. Fixed low-dose intravenous CYC, that is, six doses of 500 mg every 2 weekly followed by azathioprine (2 mg/kg) as maintenance agent was compared with NIH regimen in the European Lupus Nephritis Trial (ELNT).[26] This trial, which included predominantly Caucasians and excluded severe renal involvement, showed no difference in long-term outcomes like patient survival, renal survival, or doubling of serum creatinine in the two arms. Another trial[27] done at our center comparing CYC given as ELNT protocol with mycophenolate mofetil (MMF) for induction in patients with LN showed similar renal outcomes in both the arms. A total of 100 patients were equally randomized to receive either CYC or MMF. At 24 weeks, 37 patients in each group achieved the primary end point. The complete remission rate was 50% in CYC and 54% in MMF group.

Mycophenolate mofetil: MMF was first used in induction phase in a pilot study conducted in Chinese patients with class IV LN and was shown to be non-inferior to oral CYC.[28] Subsequently, a multiethnic study comparing MMF with intravenous CYC, by Ginzler et al.[29] showed non-inferiority of MMF as compared to CYC. One of the largest multicentric randomized control trials by Appel et al.,[30] Aspreva Lupus Management Study (ALMS) involving 370 patients comparing intravenous monthly CYC with MMF showed similar clinical response rates (53% vs. 56%, respectively) at the end of 6 months in both the arms. MMF had better response rates compared to CYC in Blacks and Hispanics (60% vs. 39%).

Although guidelines for management of LN including ACR, EULAR/ERA-EDTA, and KDIGO recommend CYC or MMF as agents for induction in LN, high dose CYC (NIH regimen) is routinely reserved for severe renal disease (Sr Creatinine >3 mg/dL), crescentic glomerulonephritis, TMA, and in the presence of concomitant extraglomerular

lesions like central nervous system (CNS) lupus or diffuse alveolar hemorrhage.

Calcineurin inhibitors (CNIs): CNIs act by inhibiting T-cell activation and, in turn, decreasing B-cell activation and antibody production. Furthermore, it stabilizes the actin cytoskeleton in podocytes, thus contributing to reduction in the degree of proteinuria. However, long-term uses of CNIs are associated with nephrotoxicity and there is a higher chance of relapse once the drug is withdrawn.

Cyclosporine: Cyclofa-Lune study[31] involved 40 patients of proliferative LN who were randomized to Cyclosporine A and intravenous CYC. Clinical outcomes at the end of induction phase and maintenance phase were similar between two groups; response rates were 52% versus 43% in CYC and Cyclosporine arms, respectively at the end of induction, and they were 38% versus 58% for overall response at the end of maintenance phase. The extended follow-up (median: 7.7 years) of these patients showed similar rates of renal survival, patient survival, and proteinuria in the two arms.[32]

Tacrolimus: Comparison of tacrolimus with MMF for induction in active LN patients showed similar rates of complete remission at the end of 6 months.[33] In those with pure membranous LN, tacrolimus resulted in higher response rates of 100% as compared to 75% in MMF group. However, the rates of relapses by the end of 5 years were higher in those who received tacrolimus (62%) than those who received MMF (42%).[34]

Voclosporin: Voclosporin is a structural analogue (trans-isomer) of cyclosporine which is fourfold more potent than cyclosporine and is associated with lesser off-target side effects such as cosmetic effects and nephrotoxicity. In addition, it does not require drug level monitoring owing to stable pharmacokinetics. In a recently completed phase 2 trial on patients with LN, voclosporin, added to MMF and low-dose steroid achieved complete renal remission in 32.6% patients with 23.7 mg twice a day dosage regimen as compared to 19.3% in placebo group.[34] The phase III AURA-LV trial evaluating the efficacy and safety of voclosporin in patients with active LN is ongoing, with interim analysis showing promising results.

Multitargeted therapy: Combination of tacrolimus (4 mg/day) with MMF (1 g/day) and steroids (intravenous methylprednisolone 500 mg for 3 days followed by 0.6 mg/kg/day of prednisolone), called multitargeted therapy (MTT), as induction therapy was compared with intravenous monthly CYC (0.75 g/m^2) in 368 Chinese patients with active LN. MTT was superior to CYC, with complete remission rates being 46% versus 26% at the end of 6 months. However, rates of serious infections were higher in the MTT group.[35]

Maintenance Therapy

After the induction phase, maintenance immunosuppressive agent is necessary to reduce the risk of flares and further renal damage. NIH trials showed that maintenance with quarterly pulses of intravenous CYC for a period of 2 years had lesser episodes of relapses in comparison to no maintenance.[24] Contreras et al.[36] showed that maintenance with MMF or azathioprine was better than quarterly pulses of CYC in terms of efficacy and side effects.

MAINTAIN trial:[37] It included 105 predominantly white patients induced with intravenous CYC by ELNT regimen and were followed up for 5 years. There was no statistical difference between rates of renal flare between MMF (19%) and azathioprine (25%) maintenance, respectively.

ALMS maintenance trial:[38] It included 227 patients who achieved remission with MMF induction and were randomized to MMF and azathioprine maintenance. At 36 months, composite outcome which included renal flare, ESRD, doubling of serum creatinine, death, or use of rescue therapy was significantly lesser in the MMF group than the azathioprine group (16.4% vs. 32.4%). The ALMS maintenance trial, which included multiethnic patients, larger number of patients, and had compared composite outcomes, favors use of MMF as maintenance agent over azathioprine. The ACR[14] and KDIGO[13] guidelines recommend use of either MMF or azathioprine as maintenance agent; however, 2019 EULAR/ERA-EDTA[23] guideline recommends MMF maintenance specifically for patients induced with MMF. Duration of maintenance immunosuppression is recommended to be at least 3 years in patients who achieve complete remission at the end of induction therapy.[23] In those with high risk of deterioration of renal function such as failure to achieve complete remission after induction therapy, frequent renal flares, and high disease activity index, prolonged immunosuppression is given usually.

Newer Therapies

Biological Agents

Despite the use of conventional immunosuppressive agents, response rates of LN are only 60–70% at the end of induction therapy. High rates of relapses after achieving remission and reduction of drug toxicity have been unmet needs in the management of LN. Hence, there is need for newer drugs which are safer and more effective. Biological agents with specific targets in the immune system have been used as alternative options for conventional drugs for achieving higher rates of remission, managing refractory disease and as steroid sparing agents.

Rituximab: This is a chimeric monoclonal antibody against CD20 on the B-cell surface. Several nonrandomized studies have shown efficacy of rituximab in managing patients with LN. **LUNAR** (Lupus nephritis assessment with Rituximab) trial[39] was a placebo-controlled phase 3 RCT. Those in rituximab arm received 1,000 mg of rituximab 2 weeks apart at the start and it was repeated after 6 months. All the patients received three pulses of intravenous methylprednisolone followed by oral steroids along with MMF at a dose of 2–3 g/day. Renal response at the end of 52 weeks was not different between both the arms (57% vs. 46% in rituximab vs. placebo arms). However, rituximab was shown to be effective in refractory LN.[40] Rituximab has also been proven to be effective as a steroid sparing agent in a pilot trial of 50 patients of active LN who were given two doses of 1 gm/dose rituximab 2 weeks apart along with MMF and single dose of intravenous methyl prednisolone (500 mg). About 86% of patients achieved response (52% complete response and 34% partial response) at the end of 52 weeks.[41] Based on the encouraging results, an open label, multicentric RCT (RITUXILUP) was being carried out using rituximab for steroid sparing effect. Rituximab or any B-cell depleting agent causes B-cell activating factor/B lymphocyte stimulating agent (BAFF/BLyS) to increase, which in turn can lead to early repopulation of remnant B-cells. So, combination of agents to block both would have the maximum effect. To test this hypothesis, CALIBRATE (ClinicalTrials.gov Identifier: NCT02260934) trial was conducted where in patients with resistant active LN were treated with CYC and rituximab followed by belimumab. An interim analysis[42] of data from CALIBRATE shows:

- Anti-BAFF following anti-CD20 for LN did not improve clinical outcome at week 24;
- Anti-BAFF delayed blood B-cell reconstitution following B-cell depletion; and
- Anti-BAFF following anti-CD20 was not associated with hypogammaglobulinemia or an increase in serious infections. Further analyses at 48 weeks and beyond are awaited.

Belimumab: This humanized monoclonal antibody binds to BAFF leading to decreased activation of B-cells. Belimumab is the only biological agent approved for treatment of active SLE. The BLISS-LN (Efficacy and safety of Belimumab in patients with Active Lupus Nephritis) study was recently announced to have favorable findings; although, the results are yet to be published (https://www.clinicaltrialsarena.com/news/gsk-benlysta-sle-phaseiii-data/). It met its primary endpoint demonstrating that a statistically significant greater number of patients achieved Primary Efficacy Renal Response over 2 years when treated with belimumab plus standard therapy compared to placebo plus standard therapy in adults with active LN (43% vs. 32%, odds ratio (95% CI) 1.55 (1.04, 2.32), p=0.0311). Based on the positive post hoc analyses from trials in non LN patients and the benefits of belimumab in observational studies involving LN, it has been suggested to be used as add-on in treating extrarenal flares/disease activity in LN patients by the 2019 EULAR/ERA-EDTA guideline.[23] It can also be used as steroid sparing agent.

Obinutuzumab: NOBILITY trial[43]—In patients with proliferative LN, Obinutuzumab (intravenous) in addition to MMF (2–2.5 g/day) and steroids (0.5 mg/kg/day of prednisone followed by taper) versus placebo in addition to MMF and steroids at same doses as intervention arm—overall renal response was higher than placebo arm at 52 weeks. Obinutuzumab was as safe when compared to placebo. From this trial, it becomes apparent that more effective B-cell depletion results in better clinical outcome, unlike the LUNAR trial. More stringent CD19 B-cell depletion could be achieved with Obinutuzumab as compared to Rituximab as Obinutuzumab is a type II monoclonal antibody known to enhance antibody dependent cytotoxicity of B-cells and therefore, better and deeper response.

Other biological agents that were tested or being tested in clinical trials for Lupus Nephritis are—

Trials which failed or were terminated:

- Abatacept (CTLA4-Ig)—(ACCESS trial)—failed to meet the endpoint
- Bortezomib (plasma cell proteasome inhibitor)—trial terminated
- Rituximab (anti-CD20)—failed to meet endpoint
- Ocrelizumab (anti-CD20)—failed to meet endpoint
- Sirukumab (anti-IL6)—failed to meet endpoint
- Tabalumab (anti-BLyS)—failed to meet endpoint

Trials which showed encouraging results or are ongoing:

- Laquinimod—encouraging phase 2 trial results
- Obinutuzumab: humanized anti-CD20 antibody: NOBILITY—phase 2 clinical trial—encouraging results—show better overall renal response than placebo arm
- Belimumab—anti-BLyS/BAFF antibody: BLISS-LN—phase 3 clinical trial-met the primary endpoint
- Rituximab and cyclophosphamide followed by belimumab: CALIBRATE—phase 2 clinical trial
- Anifrolumab—anti-IFN alpha-R antibody: phase 3 clinical trial—TULIP-LN1-ongoing
- Voclosporin—calcineurin inhibitor: AURA-LV-phase 2 trial—met its primary endpoint; AURORA phase 3 clinical trial (https://www.clinicaltrialsarena.com/news/aurora-trial-lupus-kidney-disease-drug-therapy/): met the primary endpoint

Conclusion

LN is characterized by flares and about 30–40% of patients do not respond to conventional induction therapy. Protocol repeat biopsy is a promising tool to monitor LN. Less toxic and more effective agents are the unmet needs in the management of LN.

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CHAPTER

149 Diagnosis and Management of Nephrotic Syndrome

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Abstract

Nephrotic syndrome is an important presentation of glomerular disease featured by heavy proteinuria, hypoalbuminemia, and edema. The etiology of nephrotic syndrome is more complex and heterogenous in adults compared to children. The renal function is often normal but can progress to chronic renal failure which depends on the duration and amount of proteinuria. Acute renal failure is rare and mostly caused by a precipitating event. Early recognition is possible through urine protein estimation, but a renal biopsy is often recommended. Current treatment recommendations are mostly based on randomized control trials (RCTs) in children, and there are only small RCTs and a few case series studies in adults. Diuretics are required in large doses due to the low-serum albumin levels. Immunosuppressive treatment is often used with little evidence. Prophylactic treatment to prevent infection or thrombosis is not recommended routinely unless indicated.

Introduction

Nephrotic syndrome is a glomerular disease, defined as a pentad of proteinuria more than 3.5 g/day, hypoalbuminemia less than 3.5 g/dL, edema, hypercholesterolemia, and lipiduria.[1] Patients present with edema, typically periorbital or at dependant sites or as a complication of nephrotic state such as thromboembolism.

Etiology

Nephrotic syndrome may be due to a primary glomerulopathy, secondary to systemic diseases or as a result of genetic mutations. The primary disorders are minimal change disease, focal segmental glomerulosclerosis, and membranous nephropathy (MN). Secondary causes are elaborated in **Table 1**.

Pathophysiology and Clinical Manifestation

Proteinuria

Protein loss is due to glomerular proteinuria. Electrical potential differences generated by transglomerular flow may modulate the passage of macromolecules across the glomerular capillary wall.[2] The podocyte appears to be the major target of injury in idiopathic nephrotic syndrome. Adult-onset primary MN and focal segmental glomerulosclerosis (FSGS) may be due to autoantibodies to podocyte or circulating factor that affect the podocyte.

Hypoalbuminemia

Most of albumin loss is due to urinary excretion leading to reduction in total protein and serum albumin with increased $\alpha 2$-globulin and reduced γ-globulin fraction. Hepatic albumin synthesis is increased in response to the albumin loss mediated by an increase in gene expression and the release of an unidentified circulating factor.[3]

Edema

Two major mechanisms have been thought to be responsible for the development of edema. One is "**underfill** hypothesis" where secondary sodium retention due to low plasma oncotic pressure causes shifting of fluid into the interstitium leading to underfilling of the

TABLE 1 Secondary causes of nephrotic syndrome

MCD	*FSGS*	*MN*	*Others*
Drugs • NSAID • Interferon-α • Lithium • Gold **Allergy** • Pollens • House dust • Insect stings • Immunizations • Poison oak **Malignancy** • Hodgkin disease • Mycosis fungoides • CLL	**Virus associated** • HIV-1 • Parvovirus B19 • Simian virus 40 (SV40) CMV **Drug induced** • Heroin • Interferon • Lithium • Pamidronate • Sirolimus • Anabolic steroids • Tyrosine kinase inhibitors **Hyperfiltration injury** • Renal agenesis	**Autoimmune diseases** • Class V lupus nephritis • Rheumatoid arthritis • Sarcoidosis • Sjogren **Infections** • Hepatitis B • Hepatitis C • HIV • Syphilis • Malaria • Schistosomiasis **Malignancy** • Solid tumors (colon, stomach, lung, prostate)	• Diabetes • Plasma cell disorder • Paraprotein deposit disease • AA amyloidosis • Pre-eclampsia

vasculature and activation of the renin–angiotensin–aldosterone system (RAAS) causing further sodium and water retention. Second mechanism is "**Overfill** hypothesis" where primary sodium retention occurs due abnormalities in tubular function like increased activity of the Na-K-ATPase pump, epithelial sodium channel (ENaC),[4] and relative resistance to ANP and urodilatin due to increased phosphodiesterase activity.

Hypercoagulability

Patients with the nephrotic syndrome have an increased incidence of arterial and venous thrombosis, particularly deep vein thrombosis (DVT) and renal vein thrombosis. Thrombotic state occurs mainly due to urinary loss of antithrombin III, plasminogen, protein C and S. Increased platelet activation, thrombocytosis, hyperfibrinogenemia, and inhibition of plasminogen activation also contributes. Renal vein is a common site of thrombosis in nephrotic syndrome, possibly due to stimulation of thrombin production in the glomerular efferent vessels as a result of glomerular injury.

Hyperlipidemia

Hyperlipidemia is triggered by the reduction in plasma oncotic pressure. The severity of the hyperlipidemia is inversely related to the fall in oncotic pressure and resolves with the remission of nephrotic syndrome. Enhanced hepatic synthesis of lipoproteins containing apolipoprotein B and cholesterol and diminished catabolism caused by inhibition of lipoprotein lipase due to elevated levels of sialylated angiopoietin like-4 (especially triglycerides) is thought to be the mechanism behind this. Lipoprotein glomerulopathy is a rare form of glomerular disease that is associated with dyslipidemia and lipoprotein deposits in the glomeruli.

AKI and CKD in Nephrotic Syndrome

Acute kidney injury (AKI) is less common in nephrotic syndrome. Most cases of nephrotic syndrome have a risk of progression to chronic kidney disease (CKD) except minimal change disease (MCD). Greatest risk factor is the degree of proteinuria (>5 g/day). **Table 2** shows various causes for AKI in nephrotic syndrome.

Diagnosis

Urine Analysis

- *Twenty-four hour urine protein estimation:* More than 3.5 g/day is considered nephrotic-range proteinuria.
- *Protein-to-creatinine ratio:* It is only an alternative to the 24-hour urine protein estimation. The total protein-to-creatinine ratio (mg/mmol) on early morning sample of urine is calculated. This ratio correlates closely with daily protein excretion in

TABLE 2 Various causes for AKI in nephrotic syndrome

• AIN secondary to drugs (including diuretics)
• ATN due to volume depletion or sepsis
• Hemodynamic response to NSAIDS, ACEI, ARBs
• Nephrosarca
• Pre-renal failure due to volume depletion
• Renal vein thrombosis
• Transformation of underlying glomerular disease

g/1.73 m^2 of body surface area. A value more than 300 mg/mmol is considered nephrotic range. But this method has limitations and 24-hour urine protein estimation is more preferred.

Serologic Studies

A number of serologic studies often are obtained in the evaluation of patients with the nephrotic syndrome depending upon clinical setting **(Table 3)**.

Renal Biopsy

In adult nephrotic syndrome, biopsy is indicated when the etiology of persistent nephrotic-range proteinuria is in doubt in order to determine management decisions.

Indication for biopsy:
- Adult with nephrotic syndrome
- Children with:
  - age <1 year or >12 years
  - Gross hematuria
  - Marked hypertension
  - Renal failure without severe hypovolemia
  - Low C3 level

Imaging

- *Ultrasound:* It must be done routinely before planning renal biopsy to rule out small kidneys or kidneys with severe cortical thinning, as they indicate chronic irreversible disease. These findings can limit renal biopsy and aggressive immunosuppressive therapy.
- *2D Echocardiography:* When infective endocarditis is suspected.
- *Renal Doppler:* Indicated in patients with flank pain, hematuria, and rapid worsening of renal function to rule out renal vein thrombosis.

TABLE 3 Serologic studies (marker and diagnosis)

Serological marker	*Diagnosis*
Anti-PLA_2R	Primary MN (70–80%)
Anti-THSD7A	Primary MN (5%)
ANA, anti-dsDNA, anti-Ro/La	Lupus nephritis (MN), Sjögren (MN)
HB_sAg, Anti-HCV, HIV, VDRL/FTA-Ab	Secondary MN
PSA	Ca prostates (MN)
CEA	Ca colon (MN)
HIV antibody	FSGS >> MN
Low C3.C4 levels	MPGN Type 1
Plasma-free light chains	Multiple myeloma (MN)
RA factor, Anti-CCP	MN
RBS, HbA1c	Diabetic nephropathy

Histological Patterns

See **Table 4**.

Management

Management of nephrotic syndrome consists of general supportive measures, disease-specific therapy for the underlying cause in secondary nephrotic syndrome, and immunosuppression in case of primary nephrotic syndrome.

General Supportive Treatment

It includes measures to reduce proteinuria, edema, control blood pressure, and to address other metabolic consequences of nephrotic syndrome.

Treating Edema

All patients with nephrotic edema are initially treated with diuretics and dietary sodium and water restriction. It is recommended to restrict salt intake to less than 3 g per/day and water intake less than 1.5 liter/day.[5] Most patients respond well to loop diuretics. They are highly protein-bound but this bonding is reduced with hypoalbuminemia resulting in a slower rate of delivery to the kidneys. Loop of Henle may be relatively resistant to loop diuretics. Gut edema also limits the oral absorption of diuretics. Thus, the effective diuretic dose is usually higher in patients with nephrotic syndrome. Intravenous infusion can also

TABLE 4 Histopathological patterns

	MCD	*FGGS*	*MN*
LM	Normal	Sclerosis in parts (segmental) of some (focal) glomeruli	Homogenus thickening of capillary wall (H&E)
			Spikes in GBM (Silver stain)
EM	Diffuse foot process effacement	Diffuse foot process effacement	Sub-epithelial deposit on surface of GBM
		Wrinkling and retraction of GBM	Foot process effacement
		Hyaline accumulation	
IF	No deposits	IgM, C3, C1q (Classical)	Diffuse global finely granular deposits of IgG along outer surface of all capillary walls
Pathology	Circulating permeability factor	Podocyte injury	Immune complex and complement mediated podocyte injury (Secondary MN)
	Abnormal regulation of T-cell	Nephron loss	Autoantibody mediated podocyte injury

be tried as it increases the diuretic efficacy. Furosemide 40 mg orally twice a day or bumetanide 1 mg twice daily is a reasonable starting dose and may be increased up to a dose of 600 mg/day according to need. Patients who do not respond adequately to loop diuretic require the addition of a thiazide diuretic. Alternatively, amiloride[6] or acetazolamide[7] can be combined with loop diuretics in patients with refractory edema. Prior administration of albumin increases the efficacy of diuretics.[8]

Proteinuria

Progressive loss of renal function can be reduced if proteinuria can be reduced below 0.5 g/day. It can be controlled by either blocking efferent arteriole vasoconstriction or decreasing the preglomerular pressure (antihypertensives). Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are the agents of choice. They reduce proteinuria independent of blood pressure and can be safely used in normotensive patients. If proteinuria persists in spite of ACEI/ARB, aldosterone antagonists can be added. They can raise the serum creatinine by 30–40% as glomerular filtration rate (GFR) is reduced, but should not be stopped unless serum creatinine levels are continuously increasing.

Hypoproteinemia

Adequate dietary protein intake of 0.8–1 g/kg/day with high carbohydrate to maximize the use of that protein is recommended. In heavy proteinuria, add the amount of urinary protein loss to dietary protein intake. As a last resort, nephrectomy and renal artery embolization can be done if protein loss cannot be managed medically.

Hypertension

Hypertension in nephrotic syndrome requires strict control to delay the progression of renal disease and prevent cardiovascular complications. Initially life style modification can be adopted. High dose diuretics and dietary salt restriction are necessary. The KDIGO guideline recommends a target BP <130/80 mm Hg,[9] but recent SPRINT trial suggests a target of 120/80 mm Hg. ACEIs and ARBs are the first choice. DHP-CCBs are not preferred as they increase GFR causing worsening of proteinuria and also add to peripheral edema.

Hyperlipidemia

Control of hyperlipidemia is important in preventing cardiovascular complications. Dietary modification alone has only a moderate effect on hyperlipidemia. Statin alone is preferred in patients more than 50 years of age with early stage CKD and in late stages, addition of ezetimibe is recommended. In young adults, consider statin if having significant comorbidity.

Prophylaxis for Thrombosis

The decision to prescribe prophylactic anticoagulation must be balanced against the risk of bleeding. If the

bleeding risk is unclear, ATRIA Risk score or HAS-BLED risk can be used to take a decision. Prophylactic low-dose heparin is indicated in cases with high risk for thrombosis, like in pregnancy or an immobilized patient, with a serum albumin less than 2.5 g/dL. If albumin is less than 2 g/dL, full anticoagulation with low-molecular-weight heparin (LMWH) or warfarin should be considered.[10] Patients with MN are at high risk for thrombosis, and if the albumin level is very low and even if the risk of bleeding is intermediate, they may benefit from anticoagulation. Warfarin is preferred over LMWH because of low levels of antithrombin III impeding efficacy.

Management and Prevention of Infection

Risk of infection is exacerbated by nephrotic immunodeficiency caused by T-cell transformation dysfunction and urinary loss of immunoglobulins including IgG and alternate pathway complement factors. Patients may develop recurrent respiratory and urinary tract infections, peritonitis, and sepsis; particularly with encapsulated bacteria. Antibiotic with pneumococcal coverage is the mainstay in infections and prophylactic pneumococcal vaccination is recommended. In case of repeated infection, IgG level should be estimated and if low IVIgG should be given to maintain a level above 600 mg/dL.[11]

Treating MCD

Initial Treatment

Low dose oral prednisolone (1 mg/kg/day up to maximum 80 mg/day) should be started according to KDIGO guideline and recommends it to be continued up to 6 months. Initial dose should be maintained for a minimum of 4 weeks if full remission achieved or 16 weeks if full remission not achieved. Once remission has been achieved, dose should be tapered at least within 4 weeks of response. Induction with methylprednisolone pulse therapy may lead to rapid response and fewer relapses. If the patient has not achieved remission even after 12–16 weeks of treatment, consider repeating biopsy, as it can be FSGS which might have been missed due to limited number of nephrons in earlier specimen. If MCD presents with non-nephrotic range proteinuria, it can be managed with ACEIs/ARBs and there is no need for starting steroids.

Steroid Dependent (Table 5), Frequently Relapsing and Resistant MCD

These patients should be started on second-line therapy. This includes:

- *Cyclophosphamide:* 2–2.5 mg/kg/day orally for 12 weeks is given. Due to risk of infertility, banking of sperm and ova is to be considered before starting therapy.
- *Calcineurin inhibitors:*
  - *Cyclosporine:* 4–6 mg/kg/day for at least 12 months is given. Nephrologists prefer calcineurin inhibitors over cyclophosphamide in young adults to prevent infertility.
  - *Tacrolimus:* A dose of 2–4 mg twice daily, adjusted to maintain a target level of 5–10 ng/mL is given. It may be considered as a first line or second line in patient with contraindication for or intolerance to high dose corticosteroid.[12]
- *MMF:* 750–1,000 mg twice daily for 6 months may be used in cyclosporine dependant cases but did not appear as effective as cyclosporine in studies.
- *Rituximab:* It is a B-Lymphocyte depleting agent (anti-CD20) and is used when disease is unresponsive to all

TABLE 5 Terminologies regarding treatment outcomes of nephrotic syndrome

Complete remission	Reduction of proteinuria to ≤0.20 g/day and serum albumin >3.5 g/dL
Partial remission	Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline
No remission	Failure to reduce urine protein excretion by 50% from baseline or persistent excretion uPCR >2000 mg/g (>200 mg/mmol)
Steroid resistance	Persistence of proteinuria despite prednisolone therapy, 1 mg/kg/day for 16 weeks
Relapse	Proteinuria ≥3.5 g/day occurring after complete remission obtained for >1 month
Infrequent relapse	One relapse within 6 month of initial response, or one to three relapses in any 12-month period
Frequent relapse	Two or more relapses within 6 month of initial response, or four or more relapses in any 12-month period
Steroid dependence	Two consecutive relapses during corticosteroid therapy, or within 14 days of completing corticosteroid therapy

Reference: Comprehensive Clinical nephrology - 6th edition

other treatments, but RCT have not been performed. Non RCT studies have shown benefit and reduction in relapse in corticosteroid dependant and frequent relapse cases.[13] A dose of 375 mg/m^2 weekly for 4 weeks.

FSGS

It is very difficult to distinguish between primary and secondary FSGS and most of the times they are treated as primary FSGS. All patients will benefit from good supportive treatment and immunosuppression.

Initial Treatment

It consist of 6 months of continuous corticosteroid (1 mg/kg/day), later tapered over 4–8 weeks.

Steroid Resistant Cases

- *Cyclosporine:* Low dose of 3–6 mg/kg/day is given for 2–6 months. Recent studies show that combination of cyclosporine and corticosteroids has a higher remission rate.[14]
- *Tacrolimus:* Used in cases resistant or intolerant to cyclosporine.
- *MMF and Dexamethasone:* As per KDIGO guidelines, they can be given in corticosteroid resistant cases that are intolerant to calcineurin inhibitors.
- *Rituximab:* Used when all other treatments fail and this drug has shown promising results in steroid-dependent cases.
- *Abatacept (CTLA-4-Ig):* An inhibitor of T-cell costimulatory molecule B7-1(CD-80) showed remission in some patients and further studies are in progress.[15]

Secondary FSGS

Patients with primary FSGS typically present with an **acute onset nephrotic syndrome**, whereas slowly increasing asymptomatic proteinuria and renal insufficiency over a period of time without profound hypoalbuminemia or edema are characteristic of secondary FSGS. Unlike primary FSGS, these patients are less responsive to immunosuppression and the mainstay of the treatment is to correct the primary cause and provide supportive treatment.

Membranous Nephropathy

It is very difficult to treat MN due to its chronic nature, the tendency for spontaneous remission and relapse and the variability in clinical severity. Specific immunosuppressive therapy should not be considered unless the patient has a persistent nephrotic-range proteinuria (>4 g/day) and it has not declined more than 50% from baseline, over a minimum period of 6 months, despite maximum antihypertensive and antiproteinuric therapy.[16] Treatment of secondary MN focuses on cessation of the offending drug or effective treatment of the underlying disease.

Immunosuppression

- *Corticosteroids:* RCTs showed no significant long-term benefit on proteinuria or rate of disease progression. Therefore, use of oral corticosteroids as a single agent is not recommended.
- *Cytotoxic agents with corticosteroids (PONTICELLI REGIMEN):* Benefitted in patients at moderate risk for progression. It starts with methylprednisolone pulses 1 g IV for 3 days at the beginning of months 1, 3, and 5 followed by oral methylprednisolone 0.4 mg/kg/day for 27 days, and each cycle followed by 1 month of cytotoxic agent (cyclophosphamide or chlorambucil).[17] Cyclophosphamide-based regimen is preferred because of a better safety profile.
- *Calcineurin inhibitors:* Given in patients with corticosteroid-resistant MN but has a higher relapse rate.
  - *Cyclosporine:* It is used along with low-dose corticosteroids. It may reduce proteinuria not only through its immunosuppressive effects but also by direct effects on the podocyte.
  - *Tacrolimus:* It can be used as monotherapy, but relapse rate was found to be high.
- *MMF:* Along with steroids, it showed good initial response, but relapse rate was high.[18]
- *Rituximab:* Used in steroid resistant cases. Decline in anti-PLA2R antibody and proteinuria was achieved, subsequently resulting in a partial or complete remission.

Plasma Exchange

It may be useful in resistant MN, severe nephrotic syndrome, and high anti-PLA2R antibody titer cases. A

study in such type of patients, treated with a "rescue" regimen consisting of four plasma exchanges, 20 g of intravenous (IV) immunoglobulin, and 375 mg/m^2 of rituximab showed shorter remission time compared to previous regimens.[19]

Adrenocorticotropic Hormone (ACTH)

ACTH acts via melanocortin 1 receptor expressed on podocytes. Synthetic form of ACTH, 1–2 mg weekly intramuscularly for 1 year showed prolonged remission in the majority of patients with MN.[20]

Conclusion

Nephrotic syndrome includes a wide spectrum of primary glomerular disorders and secondary diseases. Early recognition through urine protein estimation and bringing out the histological variant through renal biopsy aids in planning treatment properly in order to prevent progression into renal failure. At present, reducing proteinuria and immunosuppression remains the mainstay in most of the cases and larger RCTs are lacking. Many new treatment targets have been identified, which needs further studies. A proper recommendation for management of nephrotic syndrome needs to be postulated.

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CHAPTER

150 Dietary Salt and Hypertension

PP Varma

Abstract

Epidemiological data suggests that dietary salt is a modifiable risk factor for hypertension; especially in those with salt consumption in the highest tertile. WHO recommends 5 gm of salt intake per day but we in India are consuming 9–12 gm of salt per day. Besides hypertension, salt is also incriminated for CV mortality, stroke, and obesity. Hence, there is need to restrict salt consumption to check the menace of hypertension. Here we bring the update on association of salt and hypertension.

Introduction

Today over 30% of world's adult population has hypertension (HT). Over 60% of the cerebrovascular diseases and about half of ischemic heart diseases are attributable to HT. Dietary salt is one of the modifiable culprits in causation of HT. Present commentary is about data on dietary salt and its association with HT.

Historical Perspective

During paleolithic times, hunter gathering man was dependent on raw meat and his dietary salt intake was less than 1 gm a day. Around 5,000 years back, Chinese learnt that food can be preserved with the help of salt and Egyptian used this knowledge for preservation of mummies. Civilizations started developing along the salt routes, which was considered a precious entity. In Libya, salt was exchanged for equivalent amount of gold. French salt tax "gabellee" probably incited French revolution. In India, Britishers did not allow Indians to make their own salt and wanted them to buy expensive salt brought from England. This was the genesis of famous Dandi March, an important event in the freedom struggle of India. Salt (NaCl) crystals are white in color and readily dissolve in water. The molar mass is 58.5 g/mol.

With agricultural revolution our food habits changed, and from 100% animal food, now plant based food formed 50% of our diet; however, salt intake remained less than a gram per day. Earliest comment relating to dietary salt and HT came from Chinese doctor, Huang Ti Nei Ching Su Wen, who wrote in The Yellow Emperor's Classic of Internal Medicine—"therefore, if large amounts of salt are taken, the pulse will stiffen or harden." However, over the years with civilization and changing food habits our dietary salt intake has increased and this is being correlated with increasing prevalence of HT. Today average Indian salt intake is 9–12 gm/day against WHO recommendation of 5 gm.[4] In this article we shall review the available data showing correlation between salt intake and HT.

Consumption and Its Source

A study reported by George Institute from India found that average Indian is taking 10.98 gm of salt per day. Salt consumption is higher in south Indians than north Indians. If one looks at the source of consumed salt, there

are three sources: our natural food (cereals, vegetables, fruits, non-vegetables) contains less than a gm of salt and makes 10% of daily intake. Another 2–3 gm (20–30%) is added as cooking salt in our food and vegetables. However, 70% of our consumed salt comes from processed food—snacks, bread and bread products, pizza, French fries, pasta, pickles, sauces, etc. It may be interesting to know that each large slice of bread has 500 mg of salt in it. Twenty-four hour urinary sodium estimation is the best marker of salt consumption.

Data on Salt Studies and Hypertension

- *Epidemiologically:* It is known that areas with low salt consumption have lower incidence of HT. Solomon islanders consume less than 2 gm of salt per day and have an HT prevalence of 1%. Among Yanomamo Indians from Brazilian amazon, 84% have urinary sodium excretion of 1 mmol/24 hours. Their mean BP is 96/60.0 mm Hg (78/37–128/86 mm Hg) and there is no change in BP with age. In tribes with salt intake of 3 gm/day, prevalence of HT is 3%. Interestingly in Newfoundland average salt intake is of 6.7–7.3 gm and HT prevalence is 15%. Its coastal area where salt consumption is of 8.4–8.8 gm/day, HT prevalence is 27%. This data suggests that with increasing salt intake prevalence of BP increases.
- The effect of life style change and migration is exemplified by Yi community living in southwestern China. Those still living in mountainous environment and eating sodium-poor diet had yearly rise of systolic and diastolic BP by 0.13 and 0.23 mm Hg, respectively. In contrast, Yi community who had migrated in urban areas and consumed sodium-rich diet had a yearly rise of 0.33 mm Hg for both systolic and diastolic BP, stressing the importance of life-style change on BP.
- First good animal study about salt and its correlation with HT came from chimpanzees that are phylogenetically similar to humans. Normally chimpanzees eat diet rich in fruits/vegetables with dietary salt content of 0.5 gm/day. Study was done on 26 chimpanzees.[1] To their normal diet ~15 gm of salt was added. BP started rising and after 84 weeks BP rose by 33/10 mm Hg. Again chimpanzees were reverted back to their original diet, without added salt. BP reverted back to normal 6 months later. Study shows the effect of salt on BP in chimpanzees.
- The first double-blind controlled study of moderate salt restriction on human was from MacGregor et al.[3] They recruited 19 patients with mild to moderate HT (average supine BP of 156/98 mm Hg). Patients were advised not to take sodium laden food. After 2 weeks of dietary salt restriction, patients entered an 8-week double-blind randomized crossover study. One group was given "Slow Sodium Ciba" (Ciba-10 mmol of sodium per tablet) and other group received "Slow Sodium Placebo." In fourth week, the mean supine BP was 7.1 mm Hg (6.1%) lower in slow sodium placebo group ($p<0.001$). Urinary sodium excretion in the fourth week of slow sodium ciba was 162±9 mmol/24 hours and that in the fourth week of slow sodium placebo was 86±9 mmol/24 hours ($p<0.001$). They suggested that moderate sodium restriction should become part of the management of essential HT and one should avoid sodium-laden foods.
- First large international study on salt and HT was "Intersalt study."[2] The study was conducted in 52 centers from 22 countries; each with sample size of 200 with a total of 10,079 participants. Four of these 52 centers, were tribal belts with very low salt consumption. Data from 48 centers showed an insignificant trend but pooled data from 52 centers showed that higher salt consumption was associated with age-related rise in BP. This study prompted lot of debate whether to reduce salt consumption or not. A revisit of study inferred that 100 mmol of extra salt intake (70 mmol vs. 170 mmol) was associated with higher BP by 5–7/2–4 mm, stressing the need to reduce salt intake.
- A community trial was done to study the effect of salt on HT in Portugal. Two communities with 800 persons each were selected. Both had salt intake of 21 gm/day and HT prevalence of 30%. In one of the two communities with extensive health education, salt intake could be reduced to 12 gm/day. By the end of second year BP dropped in intervention community by 13/6 mm Hg. BP drop was across all age groups and in both normotensives and hypertensives alike. Those with greatest fall in salt excretion had the largest fall in BP.
- *Trials of hypertension prevention (TOHP I & II):* TOHP I was conducted over 18 months' duration and TOHP II for over 36 months. Lower salt intake (lower by 44 mmol and 33 mmol/day) in intervention group was

associated with 25% lower CV events. So, besides lowering BP, lower salt intake is associated with lower CV events also.[6] A metanalysis of 13 studies, with 177 025 participants (FU 3.5–19 years) showed that higher salt intake was associated with greater risk of stroke (RR1.23) and cardiovascular disease (RR 1.14). A Finnish study on impact of salt and CV events, comprising of 1,173 men and 1,263 women found that increased sodium intake by 100 mmol/day increased the hazard ratio for coronary artery disease, CV disease, and all-cause mortality by 50% (HR of 1.51).

- *INTERMAP study:* A recent study (Hypertension 2018;71:631-37)[9] included 4,680 persons from China, Japan, UK, and the USA. This study addressed the effect of dietary salt intake on BP and its possible modulation with other dietary factors. Study found that group with two SD higher sodium excretion was associated with rise in BP by 3.5/1.7 mm Hg (p<0.001) and most other 26 micro- or macronutrients in diet had only a modest countervailing effects on Na-BP relationship. The study again emphasized the need for salt restriction as other micro- or macronutrients did not make much difference.
- Prospective urban rural epidemiology (PURE) study (Mente et al., 2018)[10] was conducted in 18 countries on a population of 1,68,000, in the age group of 35–70 years. The 664 communities from low, middle, and high income countries were selected. A 24-hour sodium excretion was divided into three tertiles: low—4.04, middle—4.70, and high tertile—5.75 gm. The study found that mean systolic BP increased by 2.86 mm Hg per 1 gm increase in salt intake. Sodium intake was also associated with cardiovascular disease and strokes. This association was however significant only in those falling in highest tertile of salt intake (p<0.0001). Study suggested that those in highest tertile of salt consumption had significant detrimental effect.
- *Dietary approaches to stop hypertension (DASH):* In this study 412 normotensive and hypertensive participants were assigned to eat either typical American diet (control diet) or DASH diet. DASH diet is rich in fruits, vegetables, and has low-fat dairy products. Aim of the study was to test if DASH diet reduced BP and if salt reduction in patients on DASH diet had an additional advantage. Study population was divided in three groups:
  - high salt intake—150,
  - intermediate salt intake—100, and
  - low salt intake—50 mmol/day.

In control group, reduction of sodium intake from the "high to the intermediate level" over 30 days, resulted in reduction of systolic BP by 2.1 mm Hg (p<0.001) and in the "from intermediate to the low level" by 4.6 mm Hg (p<0.001). In DASH group salt reduction resulted in drop of BP by 1.3 mm Hg (p=0.03) and 1.7 mm Hg (p<0.01) "from high to intermediate" and "intermediate to low salt" group respectively. Benefit of salt reduction was observed in both sexes, all races and in normotensives also. The study inferred that participants in DASH diet had a significantly lower systolic BP at each sodium level. If one compares control diet group with high salt intake and DASH diet group with low salt intake, there is a BP difference of 7.1 mm Hg in normotensives and 11.5 mm Hg in hypertensives.

Few important points emerge from these studies:

- Epidemiological data clearly shows low prevalence of HT in areas with low salt intake.
- Animal and human trials show drop in BP with reducing salt intake and increase in BP with increased salt intake.
- Cardiovascular mortality also increases with increase in salt intake.

An important inference is that prevalence of HT and risk of CV mortality is prominent and significant in group with highest tertile of salt intake.

- *Salt intake and obesity:* It has been observed that excessive salt intake is associated with obesity. As small as 1 gm of extra salt consumption per day by children and adolescents has been found to be associated with consumption of 27 gm of sugar-sweetened soft drink. There has been controversy, if obesity is due to consumption of extra sugar or processed food or due to extra salt. However, increasing evidence suggests that there is direct link between salt intake and obesity independent of total energy intake. Even after adjusting variables like ethnic group, social status, energy intake, educational status, smoking, alcohol consumption, etc., 1 gram a day of extra salt increases the risk of obesity by 28% (p=0.0002) in children and 26% (p<0.0001) in adults.
- *Is very low salt intake detrimental:* In the "Framingham Offspring study"—a 16-year follow-up data, of 2,632

men and women between 30–64 years, showed that very low intake of salt (<2.5 gm) is associated with increased BP. This is in line with many workers who feel that there is J-shaped curve between salt consumption and hypertension **(Fig. 1)**.

Salt Sensitive Hypertension

An important and debatable issue is that should salt restriction advise be universal or only for those having inappropriately high consumption/salt sensitive population. Luft et al studied 14 subjects (7 white and 7 black) and gave them increasing doses of salt, 10-1500 meq/day. He found mean rise in blood pressure in both groups but rise in blood pressure was higher in blacks **(Fig. 2)**; showing the racial difference. Salt sensitivity can be studied by giving high and then low salt—1 week of 200 mmol and another week of 30 mmol of salt and then seeing the BP response. A 24-hour urinary sodium is collected on last day of the week to see compliance. However, long 29 days compliance for this test is an issue, so an abbreviated version (7 day test) has been suggested. Rise and drop in BP by 5–10% is taken as positive test.[7] Castiglioni et

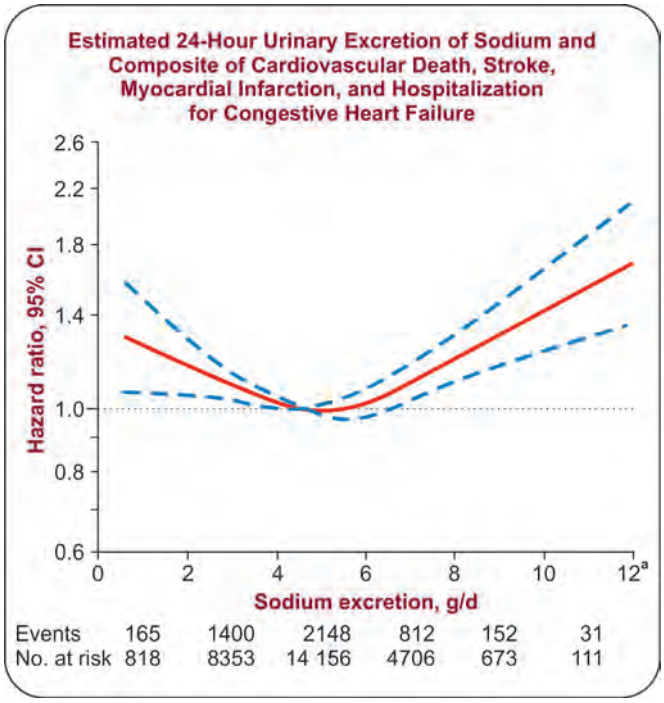

Fig. 1: Graph shows J-shaped relationship between salt and hypertension

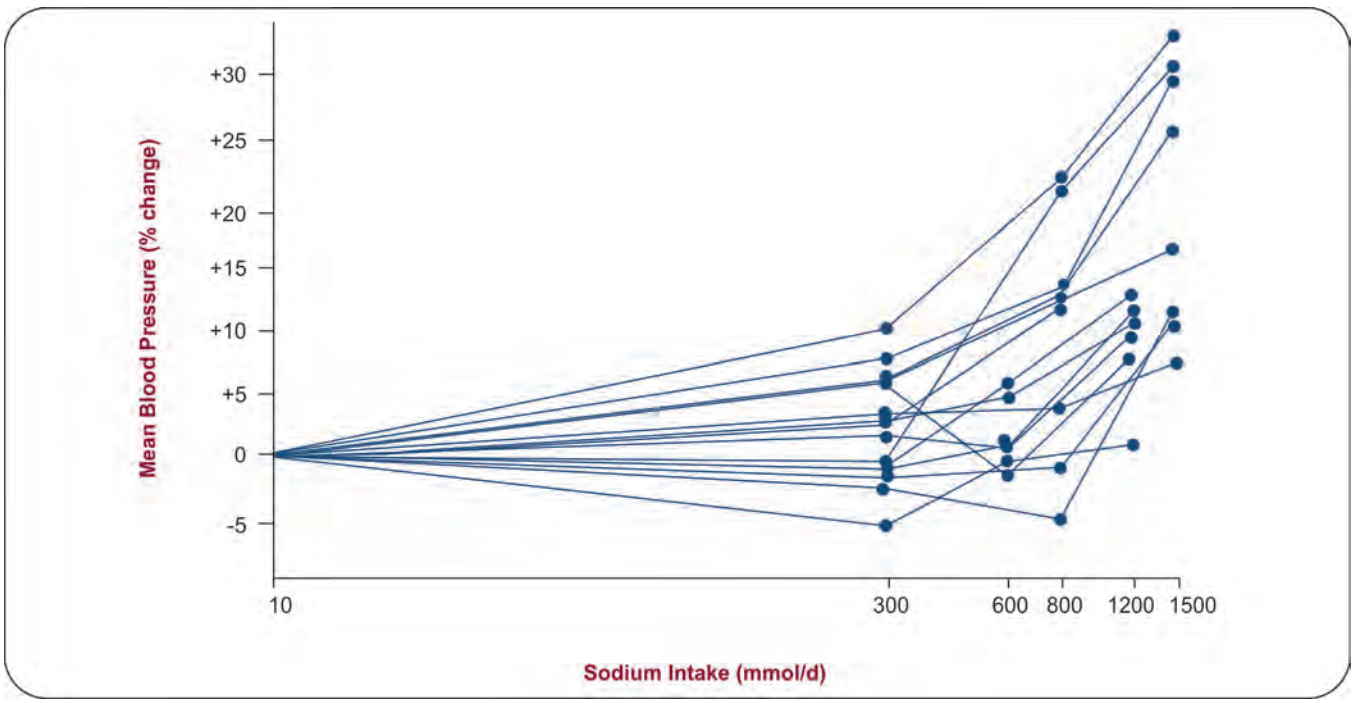

Fig. 2: Percentage change in mean arterial pressure in normotensive subjects receiving incremental increases in sodium. Blood pressure at the end of 7 days of low (10 mmol/d) salt intake was taken as baseline. All subjects demonstrated an increase in blood pressure with salt loading

al.[8] suggested that ambulatory BP monitoring (ABPM) is a better option and more practical. It is assumed that patients who are salt sensitive retain salt and water with resultant loss of circadian nocturnal dip of BP and higher mean heart rate. No salt restriction is required in this test. Based on these two parameters Indices have been devised and patients have been divided into mild, moderate, or highly salt sensitive. Most workers believe that 25% of general population and 50% of hypertensive population is salt sensitive. Salt sensitivity is largely genetic.

Conclusion

In India, average salt intake is between 9–12 gm/day, against recommended 5 gm by WHO. Most of the epidemiological animal and human data show that high sodium intake in both normotensive and hypertensive individuals is associated with age related HT. Excessive salt intake is also associated with increased cardiovascular mortality and obesity. Reduction of salt intake reduces BP and CV mortality. Some limited data also suggests that very low salt intake (<3 gm) may be detrimental. It is recommended to consume salt in moderation (approx. 5 gm per day). Maximum benefit of salt restriction occurs in population consuming high/very high amount of salt.

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CHAPTER

151 Newer Avenues in Management of CKD Anemia

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Abstract

Anemia remains one of the challenging aspects in the management of chronic kidney disease (CKD) till date. Oral/intravenous iron and erythropoietin stimulating agents (ESAs) remain the key modalities in the management of anemia in CKD. Traditional forms of oral iron therapy are limited by poor oral tolerance and insufficient absorption from the gut in dialysis population. Newer forms of oral iron such as sucrosomial iron and ferric citrate offer advantages such as alternate mechanism of absorption from the gut, relatively better oral tolerance, and additional properties such as phosphorous binding. Newer forms of intravenous iron preparations have the advantage of higher stability, lesser risk of infusion reactions, and bolus dosing. ESAs are being used for the treatment of anemia in dialysis patients since the 1980s. Although they are effective, higher doses, and higher hemoglobin targets are associated with significant risk of adverse cardiovascular events such as myocardial infarction and stroke. Studies have shown that though anemia predisposes to a poor quality of life and high cardiovascular risk in CKD, correction of anemia does not reduce the cardiovascular risk in these patients. This could be because of the limited options of therapeutic agents available at present and higher doses of both intravenous iron and ESAs have been shown to predispose to higher cardiovascular risk. Thus, there is a need for agents which can not only correct anemia but also not contribute to the pre-existing cardiovascular risk in CKD patients. Hypoxia inducible factor (HIF) stabilizers are one of the newer agents being studied at present in various trials. Studies have shown that these agents can not only reduce the dosages of intravenous iron and ESAs needed to maintain hemoglobin levels in dialysis patients but can also reduce cardiovascular risk. They also have beneficial effect on iron profile such as reduction of hepcidin levels, thus enabling better iron absorption. Thus, research for newer modalities of anemia management in CKD aims to address not only the hemoglobin levels but also improving the quality of life and longevity of CKD patients.

Introduction

Anemia in Chronic Kidney Disease (CKD) predisposes to low quality of life, increased mortality, and cardiovascular disease risk.[1] The incidence of iron deficiency anemia increases with the progression of CKD. Cornerstone of anemia management in CKD so far has been iron therapy and use of erythropoietin stimulating agents (ESAs). Traditional oral iron therapy is limited by poor tolerability, gastrointestinal adverse event, and poor absorption in dialysis dependent patients.[2] Intravenous iron although rapidly restores iron stores is limited by infusion reactions, infections, oxidative stress, iron overload, and increased cardiovascular risk.[3] ESAs, though they reduce the need for blood transfusions, are associated with increased cardiovascular risk when hemoglobin levels exceed 13 g/dL.[4] Thus, at present, search is ongoing for agents which not only increase hemoglobin levels, but also reduces the risk of adverse cardiovascular events seen with the present agents.

Erythropoietin-stimulating Agents

Traditionally used ESAs include epoetin alfa (half-live, $t_{1/2}$ 6.8–19.4 hours, 50–100 u/kg/week dosing), darbepoetin alfa ($t_{1/2}$ 25.3–48.8 hours, 0.45 µg/kg per week to every 2–4 weeks dosing), and methoxypolyethylene glycol-epoetin beta ($t_{1/2}$ 130 hours, 0.6 µg/kg every 2–4 weeks). Longer half-live are achieved through subcutaneous route for epoetin and darbepoetin preparations. Dose escalations beyond double the initial weight based dose are discouraged by KDIGO due to risk of adverse cardiovascular events as observed from the TREAT study. Recently the MIRCERA PASS trial,[5] a multicentre randomized non-inferiority trial, randomized 2818 CKD patients to methoxypolyethylene glycol-epoetin beta (MIRCERA) and reference erythropoiesis stimulating agents. The primary outcome of the study was composite of time to occurrence of death, non-fatal myocardial infarction, or nonfatal stroke. This occurred in 45.4% in the MIRCERA group and 45.7% in the reference group. Higher dose of ESAs was associated with higher risk of primary outcome.

Iron Deficiency Anemia in Chronic Kidney Disease

Iron deficiency is one of the important causes of anemia in CKD. The NHANES (National Health and Nutrition Examination Survey) 1988 to 2004 data of non-dialysis dependent CKD showed that low iron stores defined as TSAT less than 20% or serum ferritin less than 100 ng/mL were present in 57.8–58.8% of men and 69.9–72.8% of women.[6] Causes of iron deficiency in CKD include gastrointestinal bleeding, retention of blood in dialyzers and blood lines, repeated sampling, surgical procedures such as arteriovenous fistula creation, drugs such as proton pump inhibitors and phosphate binders and reduced absorption.[7]

Transferrin saturation (TSAT) and serum ferritin are widely used as indicators of iron status in CKD population. KDOQI 2006 guidelines recommend maintaining serum ferritin more than 200 ng/mL with TSAT more than 20% in dialysis dependent CKD population and serum ferritin more than 100 ng/mL and TSAT more than 20% in non-dialysis dependent CKD population.[8] ERBP (European renal best practice)[9] and NICE guidelines[10] recommend iron therapy when serum ferritin is less than 100 ng/mL and TSAT less than 20%. KDIGO 2012 guidelines recommend iron therapy if TSAT less than or equal to 30% and serum ferritin is less than or equal to 500 ng/mL.[7]

However, TSAT is not an ideal marker of iron status. Levels can increase in the setting of inflammation and decrease in the setting of malnutrition predisposing to low and high TSAT respectively if the circulating iron levels are constant. Transferrin levels also exhibit diurnal variation.[11] Serum ferritin being an acute phase reactant can be increased in later stages of CKD because of systemic inflammation and by itself may not reflect true iron status at high levels.[12] As a result of these variations NICE guidelines in 2015[10] recommend not to use TSAT or ferritin levels alone to assess iron deficiency status in CKD. The guidelines recommend the use of percentage of hypochromic red cells (<6%) and reticulocyte hemoglobin content (CHr, <29 pg), if possible, in the place of TSAT and ferritin levels.

Newer Forms of Oral Iron Therapy

KDIGO 2012 guidelines recommend that 1–3 months trial of oral iron therapy can be considered in non-dialysis dependent CKD population with anemia and TSAT less than or equal to 30% and serum ferritin less than or equal to 500 ng/mL.[7] Elemental iron (200 mg) per day is the recommended daily dosage for these patients. In a normal individual 1–2 mg of dietary iron is absorbed per day and with oral iron supplementation. The maximum absorption of iron per day during oral iron supplementation is around 25–30 mg/day.[13] This is impaired in patients with uremia[14] due to rising hepcidin levels,[15] hence oral iron therapy is not very effective in dialysis dependent CKD population.

Oral iron supplementation comes in ferric and ferrous forms. The bioavailability of ferrous form is 10–15% whereas that of ferric forms of iron is three to four times lower due to reduced solubility of ferric iron in the alkaline media of the gut.[16] Several forms of oral iron are available with wide variations in their extent of absorption and adverse effects **(Table 1)**.

The most common forms of side effects with oral iron therapy are gastrointestinal like nausea, heartburn, pain, constipation, and diarrhea. This is seen in 30–70% of the cases. Among all the oral iron formulations, this risk is highest with ferrous fumarate.[10]

Ferric Citrate

Ferric citrate is ferric iron preparation, which was approved as a phosphate binder by US FDA in 2014 for

TABLE 1 Different forms of available oral iron preparations[17]

Agent	*Elemental iron per tablet*	*Salt content per tablet*
Ferric sulfate	65 mg	325 mg
Ferrous fumarate	106 mg	325 mg
Ferrous gluconate	37.5 mg	325 mg
Ferric citrate	210 mg	1 g
Ferric citrate hydrate	45 mg	250 mg
Liposomal iron	30 mg	30 mg

dialysis dependent CKD patients. The formation of ferric citrate coordination inhibits the precipitation of ferric iron and enables better absorption. Formation of oligomeric complexes in acidic pH enables phosphate binding and monomeric complex formation in alkaline pH of duodenum enables ferric iron absorption.[17] Ferric citrate is always administered with meals.

Non-Dialysis Dependent CKD (ND-CKD) Population

Phase 3 multicenter double-blind randomized placebo-controlled trial with primary end point as change in serum phosphate showed significant reduction of serum phosphate and FGF23 level and significant increase in serum iron, ferritin, and TSAT compared to placebo.[18] Placebo controlled phase 2 (n=149)[19] and phase 3 (n=233)[20] trials with primary end point as mean change in TSAT/phosphorous and more than or equal to 1 g/dL hemoglobin rise showed positive results for patients in ferric citrate arm with similar rate of adverse events between the two groups. Mean drug doses used in the two studies were 5.4 g and 5.7 g/day. Pooled analysis of both the trials showed that the percentage of adverse events were not different from that seen with older conventional forms of oral iron with gastrointestinal events being the commonest.[21] To our knowledge trials with head to head comparison with other oral forms of iron do not exist. Ferric citrate was approved for the treatment of iron deficiency anemia in ND-CKD patients in 2017.

Dialysis Dependent-CKD (DD-CKD) Population

In a randomized trial of 441 patients, ferric citrate was compared with active control (sevelamer and calcium acetate). The trial showed ferric citrate significantly raised hemoglobin levels, TSAT, and serum ferritin and had a comparable phosphate binding ability when compared with active control. Those in ferric citrate arm received less intravenous iron and dose of erythropoietin also significantly reduced with similar adverse events between the two groups.[22] Median daily dose was 1680 mg of elemental iron per day. Similar results were shown in 2019 by the ASTRIO study which compared ferric citrate with non-iron based phosphate binders in 93 hemodialysis dependent patients.[23]

Ferric Maltol

Ferric maltol is novel preparation consisting of ferric iron complexed with maltol (3-hydroxy-2-methyl-4-pyrone). Its hydrophilic and lipophilic properties enable higher bioavailability and better absorption of ferric iron. Since it is not a salt-based formulation, iron is directly absorbed from the complex, and the adverse effects due to free iron seen in salt-based formulations are reduced. Although this compound was described as early as 1980s, it was approved by US FDA for the treatment of iron deficiency anemia in CKD in 2019.

AEGIS-CKD study[24] is a placebo controlled double blind randomized trial conducted in non-dialysis dependent CKD patients, which showed that the compound was well tolerated and produced a significant rise in hemoglobin at week 16. The dose used was 30 mg twice daily.

Sucrosomial Iron

Sucrosomial iron consists of a ferric pyrophosphate core surrounded by a phospholipid bilayer consisting of lecithin and sucrester matrix. Ingredients such as starch and tricalcium phosphate further the coat the structure forming the sucrosome. The phospholipids allow the iron to be absorbed in a vesicular form through transcellular and paracellular routes. The absorption is mediated by 'M' cells of the Peyer patches.[25] Thus, bioavailability of iron is high with less free iron mediated gastrointestinal adverse effects. Cell culture studies using the Caco-2 cell lines showed threefold higher absorption rates for sucrosomial iron when compared to ferrous sulfate.[26] Animal studies with iron deficient mice have shown that increase in hepcidin that is seen with other oral iron formulations is not seen with sucrosomial iron.[27] An open label randomized control of 99 ND-CKD patients[28] compared sucrosomial iron (30 mg/day for 3 months) and IV ferrous

gluconate (1 g) in a 2:1 ratio. The study found that at the end of 1 month, greater number of patients in the IV iron group had increase in hemoglobin, but this difference was absent at the end of 3 months. On discontinuation, hemoglobin levels were stable in IV iron group whereas it fell to baseline in sucrosomial iron group. Adverse events such as hypotension, headache, and infusion reaction were more common in IV iron group. Only 5% of patients experienced gastrointestinal side effects in the sucrosomial group. Thus, although sucrosomial iron is a safer formulation and high bioavailability, iron stores repletion may be slower when compared to conventional iron formulations.

Dialysate Iron (Ferric Pyrophosphate Citrate)

This water-soluble preparation consists of ferric iron tightly complexed to citrate and pyrophosphate to reduce the amount of free iron released into the circulation.[29] This form of iron is administered via the bicarbonate component of the dialysate. On entering the circulation, the iron component is directly transferred thus raising TSAT levels. The advantage of this preparation is that it reduces risk of iron overload. For an individual patient 5 mL (5.44 mg/mL) is added to 9.46 liters of bicarbonate concentrate, which gives a concentration 110 µg/L of iron in the dialysate. The drug is administered in each HD session with TSAT and ferritin levels being done every 3 months. Doses are held if TSAT more than 50% or serum ferritin more than 1000 ng/mL. PRIME,[30] a phase 2 prospective randomized double blind trial with primary end point as change in ESA dose showed that dialysate iron significantly reduced the need for IV iron and increase in ESA dose. Phase 3 CRUISE 1 and 2 studies[31] showed that dialysate iron significantly raised hemoglobin when compared to placebo. The study had three stages: Stage 1—run in period, Stage 2—randomization without change in ESA dose (no IV iron), and Stage 3—open label. Hypotension, headache, and muscle spasms were commonly reported side effects.

Intravenous Iron

Intravenous iron preparations contain an iron hydroxide core surrounded by a carbohydrate shell.[10] The stability of this determines how much iron is released into the circulation at a time. In older preparations such as iron sucrose, adverse effects like infusion reactions and oxidative stress frequent due to low stability of the core and higher release of free iron. Newer preparations **(Table 2)** have a more stable core and thus relatively fewer adverse effects.[10] **Table 2** shows the different intravenous iron preparations used over the years.

KDIGO guidelines 2012 suggests that a trial of intravenous iron may be considered in adult CKD patients with anemia and TSAT less than or equal to 30% and serum ferritin less than or equal to 500 ng/mL, who are not on ESAs or in those who are on ESA and increase in hemoglobin or reduction in ESA dose is desired.[6] The guidelines were based on short-term studies with small number of patients and there were very few trials which looked at the safety of giving IV iron in patients with TSAT more than 30% and ferritin more than 500 ng/mL. In 2007, DRIVE[33] study randomized 134 hemodialysis patients

TABLE 2 Properties of different intravenous iron preparations[32]

	Iron gluconate	*Iron sucrose*	*Low molecular weight dextran*	*Iron isomaltoside*	*Iron carboxymaltose*	*Ferumoxytol*
Carbohydrate shell	Gluconate	Sucrose	Dextran polysaccharide	Isomaltoside	Carboxymaltose	Polyglucose sorbitol carboxymethylether
Stability of complex	Low	Medium	High	High	High	High
Labile iron release	High	High	Medium	Low	Low	Low
Plasma half-life (hrs)	1	6	5–20	20	7–12	15
Maximum single dose	125 mg	200 mg	20 mg/kg	20 mg/kg	1000 mg	510 mg
Minimum infusion time (min)	30–60	60	60	15	15	15

TABLE 3 HIF alpha stabilizers and their related trials

Drug	*Dosage used in studies*	*Trials*	*Primary end point*	*Results*	*Other observations*
Roxadustat	20–250 mg	• Phase 3[41] (n=154) multicentre, double blind trial comparing roxadustat with placebo in non-dialysis dependent CKD • Phase 3[42] (n=305) study comparing roxadustat and epoetin alfa in dialysis dependent CKD	Mean change in hemoglobin over week 7 through 9. Mean change in hemoglobin level from baseline during weeks 23–27	1.9±1.2 g/dL raise in hemoglobin in roxadustat group (p<0.001) Greater mean change in hemoglobin in roxadustat group	• Significant reduction in hepcidin and cholesterol levels in roxadustat group. Hyperkalemia and metabolic acidosis seen more in roxadustat group • Significant reduction in mean hepcidin and cholesterol levels in roxadustat group. Hyperkalemia and upper respiratory tract infection seen more in roxadustat group. Greater rise in Hemoglobin in those with higher CRP
Molidustat	25–200 mg DIALOGUE 1: 25, 50, or 75 mg once daily/25 or 50 mg twice daily DIALOGUE 2: 25, 50, or 75 mg once daily (plus additional 15, 100, or 150 mg) DIALOGUE 3: 25, 50, 75, or 150 mg once daily (plus additional 15, 100, and 200 mg once daily)	• Phase 2b trial[43] (16 weeks) • DIALOGUE 1(n=121): randomized double-blind control trial comparing molidustat and placebo for patients not in dialysis • DIALOGUE 2(n=124): open label molidustat in previously darbepoetin treated patients versus continuing darbepoetin for patients not on dialysis • DIALOGUE 3 (n=199): open label molidustat in previously epoetin alfa or beta treated patients versus continuing epoetin for patients on dialysis • DIALOGUE EXTENSION STUDIES: – DIALOGUE 4[44] (<36 months): all patients from DIALOGUE 1 and 2 who achieved their mean Hb targets were made to continue their respective treatment for 36 months – DIALOGUE 5:[44] patients from DAILOGUE 4 who achieved mean Hb targets were continued on their treatments for 36 months	Change in hemoglobin level between baseline and the mean value from the last 4 weeks of the treatment period Change in hemoglobin from baseline to each post-baseline visit	DIALOGUE 1: Significant number of patients achieved the estimated mean hemoglobin in the molidustat group DIALOGUE 2: Mean hemoglobin was maintained in the target range for each dose in molidustat group DIALOGUE 3: Mean hemoglobin levels were maintained for 75 mg–150 mg daily as a starting dose Mean hemoglobin concentration during study were 11.10±0.508 g/dL in molidustat group and 10.98±0.571 g/dL in darbepoetin group Mean hemoglobin concentration during study were 10.37±0.56 g/dL in molidustat group and 10.52±0.47 g/dL in epoetin group	Estimated difference in mean change in hemoglobin between molidustat and darbepoetin was 0.6 g/dL Lower starting doses were associated with a fall below target range in hemoglobin in the first week. Small increase in hemoglobin was seen with starting dose of 150 mg/day *Side effects:* Adverse effects were comparable between both the groups and were mild to moderate in intensity in all three trials. Numerically more number of patients had hypertension and nasopharyngitis in molidustat group Mean hemoglobin levels were maintained from baseline and throughout the study period in both the groups. Similar percentage of adverse events in both the group (85.6% vs. 85.7%). 21% discontinued drug in molidustat arm when compared to 10% in darbepoetin arm Mean hemoglobin levels were maintained from baseline and throughout the study period in both the groups. Similar percentage of adverse events in both the groups (91.25% vs. 92.2%). More number of patients experienced severe adverse events in molidustat arm (51% vs. 37%). More number of patients discontinued in molidustat arm (23% vs. 7%)

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Drug	Dosage used in studies	Trials	Primary end point	Results	Other observations
Vadadustat	450–600 mg 300 mg OD, 450 mg OD and 450 mg thrice weekly	1) Phase 2b study (non-dialysis dependent CKD, n=210)[45] 2) Open label phase 2 trial (n=94)[46] comparing vadadustat and epoetin alfa	Percentage of patients who in the last 2 weeks achieved Hb ≥11 g/dL or an increase in Hb ≥1.2 g/dL over the predose average Mean change in hemoglobin concentration	54.9% patients in vadadustat arm achieved primary endpoint compared to 10.3% in placebo No statistically significant in hemoglobin from pre-baseline average was observed for all three doses	More number of patients had serious adverse events in the vadadustat arm compared to placebo (23.9% vs. 15.3%). Three deaths occurred in vadadustat arm Nausea, diarrhea, and vomiting were the common adverse effects noted in the vadadustat group. No serious adverse event was noted in the same
Daprodustat	10, 25, 50, and 100 mg 0.5, 2, and 5 mg	1) Multicenter, single blind, placebo-controlled study (n=70, NDD-CKD and 37, DD-CKD)[47] 2) Phase 2a placebo-controlled study (n=73, NDD-CKD and n=83, DD-CKD)[48]	Increase and response rates in achieving target hemoglobin, plasma Erythropoietin level and reticulocyte count Change in hemoglobin over 4 weeks of treatment	Both non dialysis and dialysis dependent population showed a dose dependent increase in hemoglobin, plasma EPO concentrations and reticulocyte count compared to placebo NDD-CKD group: Dose dependent increase in hemoglobin DD-CKD group: 5 mg once daily dose maintained mean hemoglobin levels after switch from erythropoietin	Treatment was discontinued in 33% in the ND-CKD group and 22% in DD-CKD group due to high rate of hemoglobin rise (≥1 g/dL in any 2 week period) or high absolute Hb value (≥13 g/dL). Hepcidin level decreased and TIBC and unsaturated iron binding capacity increased significantly in the daprodustat group Hemoglobin rise occurred with concurrent rise in endogenous erythropoietin levels in daprodustat group. The drug was well tolerated
Enarodustat	2 ,4, and 6 mg	1) Phase 2 study placebo controlled randomized trial in nondialysis dependent CKD (n=94, ESA naïve group and n=103, who previously received ESA)[49]	Rate of rise in hemoglobin per week in ESA naïve group and proportion of patients who maintained change in hemoglobin in previously ESA treated group	ESA naïve group: Dose dependent increase in hemoglobin in enarodustat group Previously ESA treated group: 70% of subjects in enarodustat arm maintained their hemoglobin levels over 24 weeks	Ferritin and hepcidin levels decreased TIBC increased in enarodustat group

with ferritin 500–1200 ng/mL and TSAT less than or equal to 25% to intravenous ferric gluconate and no iron. The study found that hemoglobin increased significantly in the IV iron group with similar side effects between both the groups. FIND-CKD study in 2014 found that hemoglobin rise was significant in ND-CKD patients randomized to high ferritin targets (400–600 µg/L) when compared to lower targets. REVOKE[34] trial in 2015 which randomized patients to oral ferrous sulfate and IV iron sucrose found similar results but with increased serious adverse events in the Intravenous group. PIVOTAL,[35] an open label multicenter trial in 2019 randomized 2141 patients on maintenance hemodialysis less than 1 year to IV iron sucrose in a proactive fashion (400 mg monthly, unless TSAT ≥40% or ferritin ≥700 µg/L) or reactive fashion (400 mg if ferritin ≤200µg/L or TSAT <20%). The primary end point was composite of nonfatal MI, stroke, death, and hospitalization for heart failure. The study found that hemoglobin rise was rapid, blood transfusion, and ESA dosage was reduced in the proactive group. Adverse effects were similar between the groups and the most common adverse event was infection. Thus, higher ferritin targets than that proposed by 2012 KDIGO guidelines, may reduce the need for blood transfusion and higher ESA exposure.

HIF Stabilizers

Hypoxia inducible factors (HIFs) are transcription factors made of α (1α, 2α, and 3α) and β subunits.[36] HIF 1α is widely expressed across all normal tissues whereas HIF 2α expression is restricted to endothelium, selected cells in the kidney, gut, lung, liver, and carotid body. During normoxia, the enzyme prolyl hydroxylase (PHD1, PHD2, and PHD3) hydroxylate prolyl residues in the alpha subunit of HIF. Hydroxylation leads to recognition by von Hippel Lindau (VHL) ubiquitin E3 ligase and subsequent proteosomal degradation of HIF. During hypoxic conditions, the PHDs are inactive and this leads to dimerization of α and β subunits of HIF and target gene expression. HIF 2α regulates erythropoiesis. HIF 2 binds to hypoxia response elements of genes encoding proteins such as duodenal cytochrome B and ferroportin and enables iron absorption.[37] HIF 2α also suppresses hepcidin levels which are elevated in chronic inflammatory states such as ESRD.[38] HIF alpha stabilizers which are currently under study are mentioned in **Table 3**. Most of the trials related to HIF stabilizers are phase 2 in nature **(Table 3)**. Phase 3 studies are ongoing. So far, phase 2 studies have shown that these drugs are well tolerated in both dialysis dependent and dialysis independent CKD population. Apart from correction of anemia, other effects such as reduction in cholesterol levels have been documented in studies.[38] Preliminary data from phase 3 trials (DOLOMITES study, NCT02021318) of Roxadustat has shown that it reduces major adverse cardiac events by 30%. Despite their beneficial effects shown in the studies, other proposed harmful effects such as promotion of tumor growth[39] by increasing VEGF levels are yet to be studied. Long-term studies with large numbers of patients are required to enable safe introduction of these drugs into clinical practice.

Other Upcoming Therapeutic Strategies

Lexaptepid pegol is a pegylated L-oligo-ribonucleotide, which inactivated hepcidin. Phase 1 studies[40] of the compound have shown good safety profile and dose dependent reduction of hepcidin levels in healthy volunteers and in hemodialysis patients. Activins are dimmers, which belong to transforming growth factor beta (TGF-β) family which influence erythropoiesis. *Sotatercept* is a fusion protein of Fc domain of human IgG1 and activin receptor IIa. Phase 2 studies in hemodialysis patients have shown acceptable safety profiles, stable hemoglobin levels, and lower rates of rescue with ESAs.

Conclusion

Newer modalities of management of anemia in CKD patients are aimed at development of agents, which can reduce the need for blood transfusion, need for escalation of dose of ESAs and maintain stable hemoglobin levels for prolonged periods of time without increasing the risk for adverse cardiovascular events associated with the current available agents.

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CHAPTER

152 SGLT2 Inhibitors—Mechanisms of Cardiorenal Protection

Ashwini Balasaheb Gadde, Vijay Kher

Abstract

Sodium Glucose co-transporter-2 (SGLT2) inhibitors are a class antihyperglycemic agents, which act by selectively inhibiting SGLT2 present in the proximal tubules in the kidney causing glucosuria and to some extent natriuresis. Though originally invented as one of the oral hypoglycemic agent (OHA), many randomized controlled trials have confirmed their role far beyond this, in cardiovascular (CV) and renoprotection. This is in sharp contrast to other OHAs which were associated with either mild CV benefits or rather harm. The benefit possibly extends to nondiabetic population as well.

Though SGLT2 inhibitors act mainly by causing glucosuria, natriuresis, and by inhibiting tubuloglomerular feedback (TGF), these effects are insufficient to explain the impressive CV and renal outcomes. In this review we aim to explain the possible mechanisms of cardiorenal protection of SGLT2 inhibitors.

Introduction

Sodium Glucose co-transporter-2 (SGLT2) inhibitors (-gliflozins) are a class antihyperglycemic agents, which act by selectively inhibiting SGLT2 present in the proximal tubules in the kidney, leading to increased glucosuria and thereby decreasing blood glucose levels. Though initially approved in 2013 as one of the oral antihyperglycemic agents for type 2 diabetes, the outcomes in EMPA-REG OUTCOME trial opened a window to its role far beyond glycemic control.[1] This study established a remarkable and unexpected cardiovascular (CV) and renal benefits of empagliflozin in patients with type 2 diabetes with clinical cardiovascular disease (CVD). Later many studies supported and strengthened their role in wide class of patients, including those without established CVD proving their beneficial effects in diabetes mellitus as primary as well as secondary prevention for CV & renal endpoints.[2-7] **Table 1** summarizes the CV and renal outcomes in major trials. These trials have established SGLT2 inhibitors as a paradigm shift in the management of CV and renal complications of type 2 diabetic patients[2-5] and may be in nondiabetic CKD patients as well.[6]

Basic Mechanism of Action of SGLT2 Inhibitors[9]

Approximately 90% filtered glucose reabsorption is mediated by SGLT2 channels located on S1 segment of proximal convoluted tubules (PCT). These channels are also responsible for 5–14% of Sodium reabsorption depending upon the glycemic status. Thus, the physiological effects of SGLT2 inhibitors are a consequence of both glucosuria and natriuresis.

Before going in detail, let's concentrate on the glucose absorption in diabetes mellitus and effects of SGLT2 inhibitors on tubuloglomerular feedback (TGF)—an important mechanism for glomerular hemodynamic alteration of in type 2 diabetes and diabetic nephropathy **(Fig. 1)**.

TABLE 1 Cardiovascular and renal outcomes of SGLT2 inhibitors in trials

Trial	*Population*	*Cardiac end point Hazard ratio (confidence interval)*	*Renal end points Hazard ratio (confidence interval)*
EMPA-REG OUTCOME[1] N=7020	T2D+CVD eGFR>/30	3-point MACE* 0.86 (0.74–0.99)	Doubling of serum creatinine with eGFR<45, initiation of RRT or kidney-related death 0.54 (0.40–0.75)
CANVAS program[2] n=10,142	T2D+CVD (if>/30 yrs) or >2 CV risk factors if >/50 yrs	3-point MACE* 0.86 (0.75–0.97)	Progression of albuminuria 0.73 (0.67–0.79) 40% reduction in eGFR, RRT, or renal-related death 0.60 (0.47–0.77)
DECLARE -TIMI58[4] N=17,160	T2D+CVD/>2 CV risk factors	3-point MACE* 0.93 (0.0.84–1.03) non-significant. Composite of CV death or HHF 0.83 (0.73–0.95)	>40% decrease in eGFR to <60, ESRD or renal-related death 0.53 (0.43–0.66)
CREDENCE [3] N=4401	T2D+ eGFRof 30 to <90, albuminuria and on stable dose of ACEi/ARBs for >/4 weeks 3	Composites of CV death or HHF 0.69 (0.57–0.83) 3-point MACE 0.80 (0.67–0.95) HHF 0.61(0.47–0.80)	Relative risk of the primary outcome composite of ESRD, doubling of the serum creatinine level from baseline or death from renal or cardiovascular disease. Was 30% lower (hazard ratio, 0.70 (0.59–0.82)*
DAPA-HF[5] N=4744	Heart failure and an ejection fraction of 40% or less (irrespective of the diabetes status)	The primary composite outcome of worsening heart failure or CV death 0.74 (0.65–0.85)	A composite of worsening renal function 0.71 (0.44–1.16) [§]
DAPA-CKD[6] N=4304	Adults with CKD with an eGFR ≥25 but ≤75 mL/min/1.73 m^2 and a UACR ≥200 mg/g but ≤5000 mg/g on stable dose of ACEi/ARBs for >/4 weeks	The composite of CV death or HHF 0.71 (0.55 to 0.92).	Primary composite endpoint • Time to ≥50% eGFR decline from baseline (confirmed by ≥28-day serum creatinine) • Time to ESRD defined as eGFR <15 mL/min/1.73 m^2, need for chronic dialysis (both confirmed after ≥28 days) and renal transplantation • Time to renal or cardiovascular death 0.61 (0.51 to 0.72)

*Primary outcome, §Not significant

3-point MACE, major adverse cardiac events (composite of nonfatal stroke, nonfatal MI, cardiovascular death); ACEi/ARB, angiotensin converting enzyme inhibitors/aldosteron receptor blockers; CKD, chronic kidney disease; CVD-cardiovascular disease; ESRD, end stage renal disease; HHF, hospitalization for heart failure; RRT, renal replacement therapy; T2D, type two diabetes; UACR, urine albumin creatinine ratio

In hyperglycemic state, filtered glucose load is increased. To handle that load, there is increased expression of SGLT2 on PCT. Along with glucose, sodium reabsorption also increases. This increased work of Na and glucose reabsorption leads to increased cortical oxygen consumption and also tubular hypertrophy, resulting in renal cortical ischemia, which promotes interstitial fibrosis.[8] As more glucose and sodium are absorbed in PCT, less sodium will be delivered to distal convoluted tubules (DCT), which is sensed by macula densa. This causes increase in single nephron glomerular filtration rate (SNGFR) via TGF. Due to the decreased sodium in DCT (TGF), there is afferent arteriolar dilatation and efferent arteriolar vasoconstriction due to increase in renin secretion and increased renin–angiotensin–aldosterone system (RAAS) activation.[8] High SNGFR further increases the work of reabsorption continuing this vicious cycle. Hyperfiltration and increase in intraglomerular pressure also causes proteinuria which is nephrotoxic and contributes to progression of diabetic nephropathy.

SGLT2 inhibitors interfere with these essential pathophysiological effects in a diabetic kidney **(Fig. 2)**. By inhibiting SGLT2 channels, hyper-reabsorption of Na and glucose reabsorption is inhibited thus decreasing the tubular work load and oxygen consumption avoiding cortical ischemia. Because of the inhibited Na and

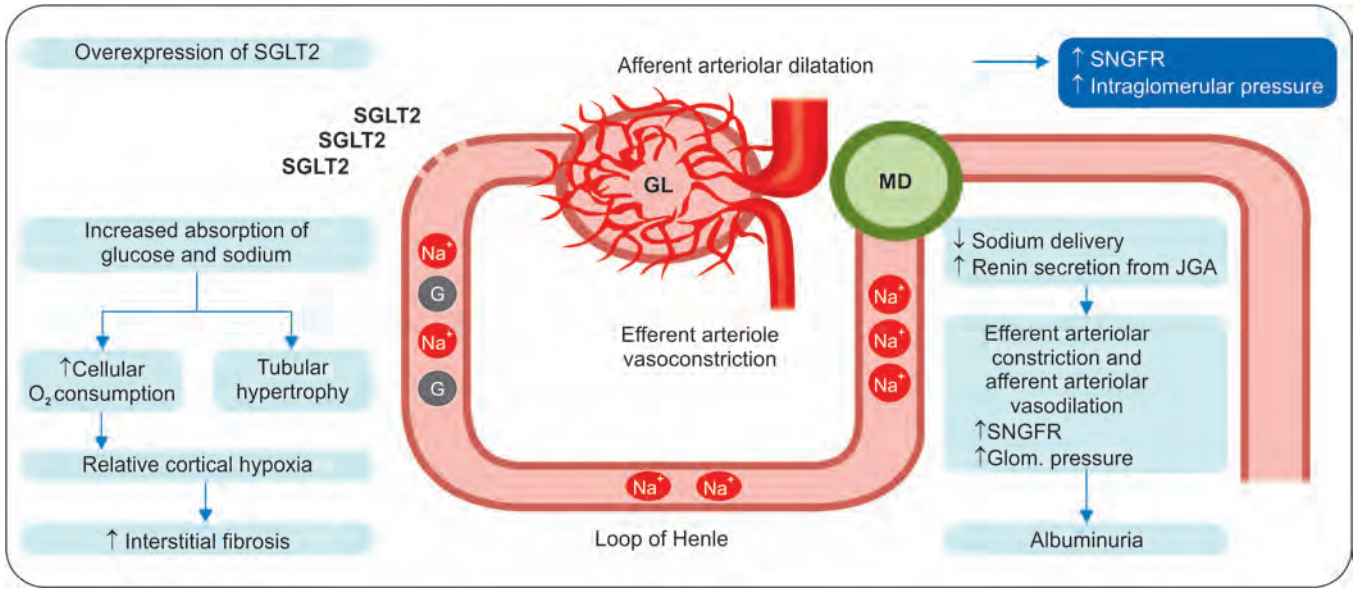

Fig. 1: Glucose absorption in diabetes mellitus and effects of SGLT2 on tubuloglomerular feedback and in evolution of diabetic nephropathy
JGA, juxtaglomerular apparatus; SNGFR, single nephron glomerular filtration rate; MD, macula densa

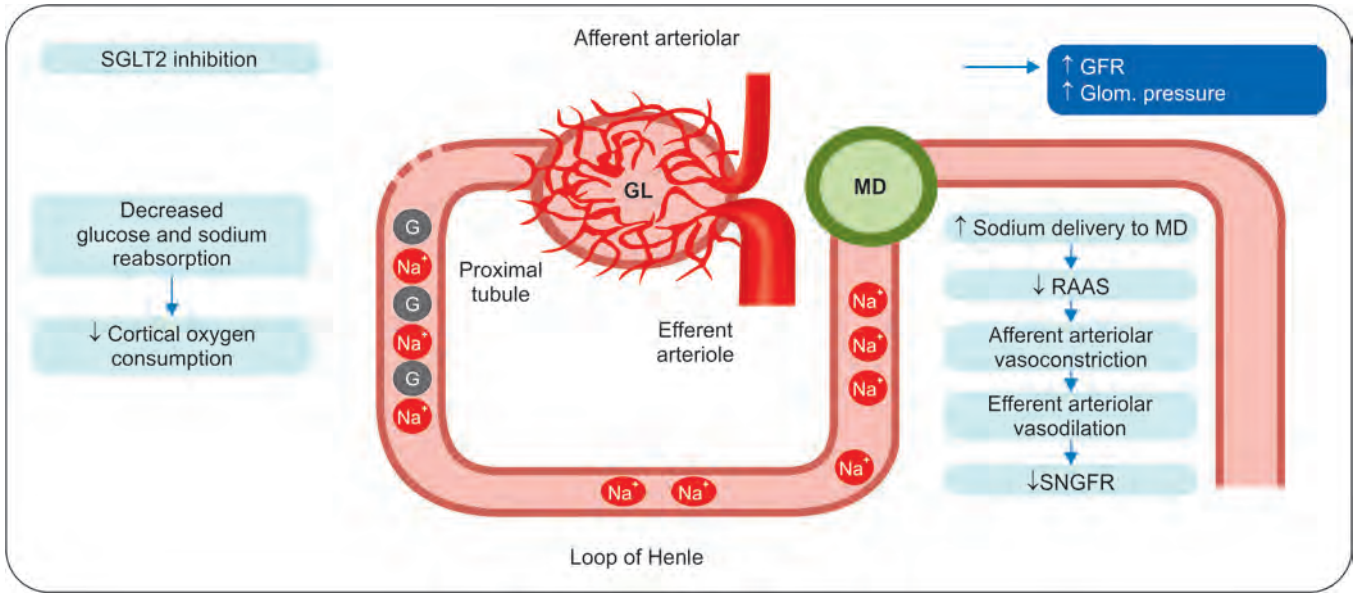

Fig. 2: Effect of SGLT2 inhibitors on pathophysiological mechanisms on diabetic nephropathy

glucose reabsorption in PCT, more is delivered the DCT. This causes afferent arteriolar constriction and decreases SNGFR via TGF mechanism. Also because of increased load of sodium and potassium in DCT, tubular backpressure in the Bowman's capsule increases, leading to decrease in SNGFR. These effects together lead to decrease in intraglomerular hypertension, glomerular blood flow leading to decrease in proteinuria.

These effects to some extent do explain the renal benefits of SGLT2 inhibitors but may be inadequate to explain the mechanism for CV benefits. Although the glucose lowering efficacy of SGLT2 inhibitors declines at

the lower eGFR range, the CV benefits are persistent across wide spectrum kidney disease (eGFRs of 30–60 mL min–1 [1.73 m]–2, 60–90 mL min–1 [1.73 m]–2 and >90 mL min–1 [1.73 m]–2).[10] Also, beneficial effects of SGLT2 inhibitors extend to nondiabetic population as well **(Table 1)**.[6] This implies that many "extrarenal" effects might play a role.

Metabolic Effects Secondary to Glucosuria

Reduction in HbA1c

Placebo substracted HbA1c difference in EMPA-REG was mild (0.4%) but it showed impressive 38% reduction in CV death, 35% reduction in heart failure, and 46% risk reduction was seen in composite renal outcome. This is in sharp contrast with other oral hypoglycemic agents (OHAs), which were associated with either mild CV benefits or sometimes even harm.[11-13] So, mechanisms other than this need to looked into.

It is important to note that SGLT2 inhibitors do not cause hypoglycemia. This is due to intact counter-regulatory mechanisms including upregulation of hepatic gluconeogenesis. Also, SGLT1 downstream prevents glucose excretion during SGLT2 inhibition when the filtered glucose falls below the transport capacity of SGLT1.[7]

Weight Loss

SGLT2 inhibitors reduce body weight and fat mass, especially epicardial fat which is important for leptin (a proinflammatory adipokine) secretion. In a 52-week study comparing canagliflozin with glimepiride, canagliflozin reduced serum leptin levels by 25% and increased the levels of the anti-inflammatory adipokine adiponectin by 17%.[14] The antinatriuretic, anti-inflammatory and antifibrotic effects of SGLT2 inhibitors (discussed further) antagonise the deleterious effects of leptin on heart and kidneys.[14]

Decrease in Uric Acid[15]

Though benefit of this effect on CV protection is unclear.

Hemodynamic Effects Secondary to Natriuresis

Blood Pressure Reduction

Along with SGLT2 inhibition, direct inhibition of the cardiac sodium-hydrogen exchanger (NHE)1 by SGLT2 inhibitors is another pathway hypothesized in natriuresis and reduction in BP.

In EMPA-REG trial, SGLT2 inhibitors reduced systolic/diastolic BP by around 5/2 mm Hg.[1] A recent meta-analysis of 43 randomized controlled trials with 22,528 patients assessed the seated clinic blood pressure effects of SGLT2 inhibitors in patients with type 2 diabetes mellitus. The reduction in blood pressure was over and above the already receiving antihypertensive therapy.[16]

Diuretic Effect

SGLT2 inhibitors decrease preload by both natriuresis and osmotic diuresis secondary to glucosuria. But those are different from other conventional loop/thiazide diuretics. They do not cause reflex sympathetic activity thus causing no compensatory tachycardia.[17] It is postulated that as opposed to diuretics, SGLT2 inhibitors promote a greater decrease in interstitial fluid relative to blood volume.[18] This may have significant benefits in reducing neurohormonal activation via their effects on RAAS. Also, thiazide/loop diuretics are known to cause hyperuricemia and sometimes hyperglycemia, but these parameters are positively affected by SGLT2 inhibitors.

Decrease in Intraglomerular Hypertension

As explained earlier, natriuresis also causes increased delivery of sodium to macula dense which will lead to afferent arteriolar constriction via TGF mechanism. This decreases the intraglomerular hypertension and hyperfilteration occurring in early diabetic nephropathy. This will also decrease proteinuria but at the cost of initial dip in eGFR (around 4–6 mL/min) in initial 3–4 weeks,[1] which is reversible either after stopping medication or sometimes even after continuous prolonged treatment. This suggests that it's related to a functional change rather than structural changes, similar to angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blockers (ARBs).

Currently, ACEi/ARBs are the standard treatment for this purpose, which dilates efferent arteriole. In EMPA-REG as well as other studies related to SGLT2i, most of the patient population (almost 80%) was already on ACEi/ARBs. Benefits of SGLT2i are additive to current optimal therapy. RAAS blockers are active through neurohormonal pathways of hyperfiltration whereas SGLT2 inhibitors work via tubular pathway.

Though above mentioned hemodynamic and metabolic effects have positive impact on CV outcome, in practice, this impact is unexpectedly strong. Previously it was thought that these CV benefits are because of the effect on atherosclerosis, but benefits are seen as early as 3 months from the start of treatment. It is very unlikely that atherosclerosis-related effect will show impact so early. So, more possible mechanisms have been proposed and are getting tested.

Cardiac Fuel Energetics

So to explain these remarkable cardiac and renal benefits, Ferrannini et al. came up with a "Thrifty substrate" hypothesis.[19] Glycosuria lowers insulin levels and raises fasting and post-meal glucagon concentrations. This causes restriction of glucose utilization and increase in lipid mobilization. Increased delivery of free fatty acids (FFAs) to the liver stimulates *ketogenesis*. In conditions of prolonged hyperketonemia, b-hydroxybutyrate is freely taken up by the heart and oxidized in preference to fatty acids. The benefit of preferential fuel selection was demonstrated in a study of 3-hydroxybutyrate versus placebo in humans with chronic HF in which ketone infusion increased *stroke volume, cardiac output,* and LVEF in a dose responsive fashion.[20] This fuel selection improves work efficiency with respect to oxygen consumption especially, in failing heart and also in kidneys.[21] But recently this theory has been challenged. Animal studies to prove this change in cardiac energetics have been inconclusive. Also, the stressed heart already preferentially utilizes ketone bodies, and the diabetic kidney is a ketogenic organ[21,22] so what difference does SGLT2 inhibitors do? It needs to be delineated and explored further.

Cellular Reprogramming to "Dormancy State"

Another theory seems to be that instead of postulating a drug-induced enhancement of fuel supply, Avogaro et al. suggest that SGLT2 inhibitors induce a "dormancy state" that mimics starvation.[23] When cells are stressed by starvation or by hypoxia or reactive oxygen species, injured organelles, and misfolded proteins, they activate a transcriptional program to adapt to this low-nutrient conditions. Sirtuin 1 (SIRT1) and adenosine monophosphate–activated protein kinase (AMPK) are the key enzymes in this respect. SIRT1 decreases oxidative stress by enhancing antioxidant activity, AMPK reduces the formation of reactive oxygen species, In addition, both enzymes inhibit energy storage (glycogen synthesis and lipogenesis) while promoting energy utilization (fatty acid oxidation leading to ketonemia). Coordinated activation of two signaling stimulates autophagy which is a lysosome mediated pathway that removes potentially dangerous constituents and recycles cellular components. Since type 2 diabetes is perceived by cells as a state of nutrient excess, it is accompanied by suppression of SIRT1 and AMPK. SGLT2 acts as a sensor of energy overabundance in this situation. SGTL2 inhibitors block this sensing mechanism and inhibits suppression of this SIRT1/AMPK pathway.

Hemoconcentration/Erythropoietin Activation

SGLT2 inhibitors may not only deceive cells into believing that they are fasting but also that they are hypoxic, which activate hypoxia-inducible factor-2α (HIF-2α) via this SIRT1/AMPK pathway. Also, decreased reabsorption in early PCT causes compensatory increased transport work in late PCT and medullary thick ascending loop. This leads to relative medullary hypoxia and stimulation of HIF 1&2 which cause increase in erythropoietin secretion. Elevated hematocrit is also a surrogate marker of reduced plasma volume as well as of recovery of tubulointerstitial function associated with SGLT2 inhibitor therapy. In mediation analysis of EMPA-REG, changes in hematocrit contributed 51.8% of the effect of empagliflozin versus placebo on the risk of CV death, maximum of all the effect of SGLT2 inhibitors.[24]

Direct Effect on LV Mass

Along with decreasing preload and afterload, it is possible that SGLT2 inhibitors have direct beneficial impact of cardiac remodeling. The EMPA-Heart trial which included patients with T2D and coronary artery disease demonstrated a reduction in LV mass indexed to body surface area in patients treated with empagliflozin. This was thought to be in part due to a reduction in wall stress.[25]

Effect on NLRP3 Inflammasome

Activation of the NLR family, pyrin domain-containing 3 (NLRP3) inflammasome in the innate immune cells and

subsequent interleukin (IL)-1β release has been proposed as one of the pathogenic mechanisms in diabetes, atherosclerosis, and heart failure. SGLT2 inhibitors have been shown to inhibit this effect with respect to sulfonylureas.[26]

Effect on Arterial Stiffness

A post-hoc analysis of trials and study comparing dapagliflozin with hydrochlorothiazide demonstrated that empagliflozin was associated with not only decreased BP, but showed positive effects on markers of arterial stiffness and vascular resistance, that is, aortic pulse wave velocity, brachial flow mediated dilation, and shear rates.[27,28]

In addition to these mechanism, many others are being considered and getting investigated in animal/human-inhibition of sodium-hydrogen exchanger 1 on cardiac myocytes,[29] increase in Circulating Pro-Vascular Progenitor Cells.[30]

Conclusion

To conclude, though the exact mechanism of cardiorenal protection is still unclear, one thing is clear that we need to expand the horizon of SGLT2 inhibitors from a "glucose lowering agent" to "organ protective" agent. Studies are underway trying to find its use in nondiabetic population (DAPA CKD, EMPA-KIDNEY, TRANSLATE). Results of DAPA-HF trial have shown positive results in nondiabetic heart failure patients.[5] There were initial safety concerns with respect to acute kidney injury, diabetic ketoacidosis, amputations, urinary and genital tract infections, bladder cancer, and bone fractures. However, recent trials have downplayed these risks, and benefits are found to outweigh risks.

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CHAPTER

153 Optimizing Renal Care in Elderly

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Abstract

The global burden of chronic kidney disease (CKD) is increasing particularly among elderly. Aging itself increases vulnerability for poor renal health. High cost of management and poor outcomes of CKD necessitate optimization of renal care to be started early in the course of the disease. Collaborative involvement of patient, caregiver, primary care provider and multidisciplinary clinics is required to achieve optimal conservative care and renal replacement modality. Dietary changes, lifestyle modification, managing the pill-burden, appropriate nutrient supplementation, and vaccination to take care of risks and complications of CKD are key steps as per latest evidences available. For those progressing to end-stage renal disease (ESRD), an approach, taking into consideration of patient's perspectives and functional and cognitive status, to decide appropriateness of renal replacement therapy (RRT) or end-of-life care is a very essential particularly for elderly patients. There is need of progressive work for optimizing various facets of renal care in elderly patients particularly in economically constrained regions where most of the CKD patients fail to receive appropriate care.

Introduction

The global burden of kidney disease, which has been rising consistently, poses a major challenge to the primary care physician. Recent GBD reported that out of 697.5 million worldwide CKD patients, India harbored 115.1 million.[1] As per latest census in India (2011), around 104 million people were 60 years or above and by 2021 this number is predicted to reach 133.32 million. So, the likely CKD burden among elderly is expected to rise proportionately. Indian CKD registry[2] reported that diabetic nephropathy was most common cause (31%) for CKD and mean age of CKD patient was 50 years. Prevalence of CKD and its risk factors like diabetes, hypertension, obesity, and cardiovascular disease increases with age. Age-related changes in kidney include structural changes like macrostructure changes (decrease in cortical volume, increase in surface roughness, and size of simple renal cysts), microstructure changes (nephrosclerosis-arteriosclerosis, glomerulosclerosis, interstitial fibrosis, tubular atrophy), and functional decline in total-kidney GFR due to decrease in total nephron count.[3] Optimal care of CKD risk factors can delay or even prevent this progression of healthy aging of kidneys into CKD. Elderly population needs special attention to their physical and functional deficits including multiple co-morbidities (hypertension, diabetes), cognitive impairment, frailty and progressive sensory impairment. Owing to high cost and poor outcomes of CKD management, there is a definitive need for optimization of care in elderly CKD patients on individual basis. Optimal care goals include best outcomes at individual, population and society levels for betterment of survival and quality of life. The management of advanced CKD in the elderly can be challenging in regards to prediction of disease progression to ESRD, selection of RRT modality, and choice of optimal vascular access (VA) for hemodialysis (HD). There is a

need for collaborative efforts between patient, caregiver, primary care provider, and interaction of multidisciplinary clinics. Current review will focus on optimizing renal care including conservative medical management and selection of RRT modalities such as HD, peritoneal dialysis (PD) and kidney transplant (KT) for elderly to maximize functional status and minimize treatment-associated morbidity.

Pre-RRT Phase: Elderly Focused Conservative Care

In India, a country with 1.3 billion people and around two thousand nephrologists, practices that promote renal health and prevent renal disease progression are important. Optimal care for elderly involves mix of pharmacological and non-pharmacological interventions. Diet may be important in deciding course of CKD before dialysis. Moderate intake of protein, especially dietary strategies that increase plant protein, low sodium, dietary fiber, vitamin D, and reduction in obesity may limit worsening of CKD.[4] Renoprotective effects of maintaining muscle health, especially among elderly who have high prevalence of sarcopenia, are documented and they must be stressed upon in routine care.[5] Life style changes can be recommended based on specific comorbidity of CKD patients, for example, increasing the aerobic exercise capacity in those with cardiovascular disease, high dietary fiber and moderate intensity exercise for patients with chronic lung disease or rheumatoid arthritis and weight reduction for diabetic patients.[6] CKD patients are likely to encounter polypharmacy risks, potential drug-drug interactions (pDDI) and inappropriate prescriptions. Incorporating procedures and pharmacists to determine pDDI into the kidney care model could help dealing these challenges.[7,8] Non-adherence is a possible outcome of multiple pill burden among CKD patients. Whenever possible during clinical management, tapering thereafter deprescription strategies should be planned. Recommendations have been made on approach to deprescribe PPIs, statins and oral hypoglycemic agents in CKD patients to reduce pill burden.[9] Practices involving identification and avoidance of agents like nephrotoxic antimicrobials, radio-contrast exposure, combining ACEI and ARBs, NSAIDs and diuretics that might precipitate AKI should be promoted.[10] Providing recommended vaccinations—hepatitis B, pneumococcal, influenza, and other routine vaccines are essential for optimum care of CKD patients.[11] Focus should be laid upon patient's values and perspectives about the disease, as deficiency about health literacy is widespread in CKD population.[12,13] Information should be provided using simple terms and techniques like "teach back" to ensure attention and understanding.[14] Routine screening for anxiety, depression, and cognitive impairment may be important because CKD is associated with increased risk for dementia in elderly and poor functional status (including poor overall cognition, language, and memory). Various mediators accounted for cognitive derangement like anemia, increased oxidative stress, inflammatory markers, and changes in lipid and homocysteine metabolism are found in CKD patients.[15] Identifying functional changes is important in order to optimize the management outcome, as studies have shown association of cognitive impairment with negative outcome and increased risk of 1-year mortality among elderly severe CKD patients who were in-hospital.[16-18] The conservative pharmacological management is sometimes the only choice in elderly patients who are declining or not fit for RRT **(Flowchart 1)**.

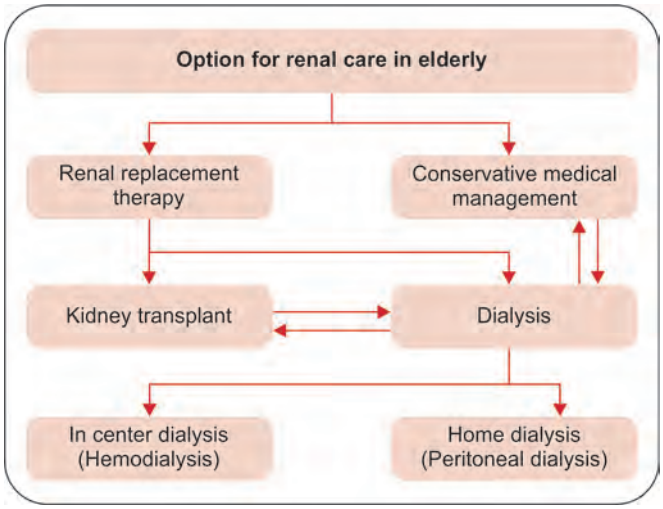
Risks and Complications of CKD

CKD, due to any cause, can progress through I to V stages. Complications and their management begin usually by stage III onward, and by stage IV aim is to prepare the patient for dialysis with suitable measures like VA to be needed during stage V. Appropriate timely management is required, particularly in elderly patients who may have multiple modifiable risk factors that could prevent or delay this progression.

Diabetes Mellitus

Diabetes mellitus is the most common cause of CKD and this holds true for both the developed and the developing world. Diabetic glomerulopathy might be contributing to over half of the ESRD cases. Bringing down of blood glucose levels (to preserve average HbA1c 7%) reflects as delay in urinary albumin excretion, GFR decline, and requirement for dialysis. The use of ACEI/ARBs can further prevent kidney damage in normotensive diabetics with proteinuria.[19] In the elderly, frail, and CKD patients,

Flowchart 1: Options for renal care in elderly



the consequences of hypoglycemia are very serious including injury, myocardial infarction, stroke, and death. Therefore, a tailored approach for target HbA1c levels should be followed for elderly CKD patients to avoid risk of hypoglycemia.[20] Metformin is usually the first antidiabetic to begin with. For reducing risk of lactic acidosis, a rare event, FDA recommends avoiding its use if creatinine in men >1.5 mg/dL and women >1.4 mg/dL. Sulfonylureas undergo renal clearance; therefore, risk of hypoglycemia is more in advanced CKD patients and their use should be avoided if GFR <30 mL/min/1.73 m^2. Among meglitinides, repaglinide is safe to use in CKD. Thiazolidinediones are hepatically metabolized so can be used in CKD with caveat that fluid retention and increased risk of fracture rates in women especially with underlying renal osteodystrophy could be concerning. Insulin is safe for all CKD patients and long acting single dose can be used when oral agents fail to obtain target sugar levels. However, more complicated regimens with multiple insulin dosing may increase chances of error and hypoglycemia, especially among elderly with cognitive impairment. Among GLP1 agonists, no dose adjustments are needed for dulaglutide or albiglutide in CKD while exenatide and liraglutide should be avoided with eGFR <30 mL/min/1.73 m^2 due to poor renal clearance. DPP4 inhibitors (sitagliptin, saxagliptin, linagliptin, vildagliptin) are well tolerated and have some renal clearance and require dosage adjustment.[21] Cardioprotective and renoprotective effect of SGLT2 inhibitors (Empagliflozin, Canagliflozin, Dapagliflozin) have been demonstrated in diabetic kidney disease.[22]

Hypertension

With regards to CKD, hypertension is related as both the cause and effect. Hypertension is a major risk factor that increases the risk of progression of kidney disease and increase the risk of cardiovascular complications. The KDIGO (2012) guidelines have described the general management strategies for controlling blood pressure in non-dialysis-dependent CKD patients. A combination of lifestyle changes and pharmacological management are the key approach to achieve target BP goal in CKD patient. Gradually lowering of blood pressure should be recommended. Blood pressure readings based upon ambulatory and self-measurements better reflect hypertension compared to office blood pressure readings and allow individualizing of antihypertensive treatment. Blood pressure targets need to be individualized and medical management should be based on the age, presence of illness and end-organ damage (cardiovascular and retinopathy), progression of renal disease, and tolerance to treatment. Vascular stiffness necessitates periodic monitoring for postural hypotension as it causes higher systolic blood pressure whereas the diastolic blood pressure could still decline. Slowing of the progression of kidney disease and reduction in CVD risk are the goals of antihypertensive therapy and target BP, as suggested by KDIGO guidelines for non-dialysis patients, 140/90 mm Hg in nondiabetics/diabetics without proteinuria and 130/80 mm Hg in patients with proteinuria, is a key strategy to prevent further renal function decline. Initial fixed dose RAAS inhibitor (ACEI/ARBs) based combination therapy (coadministration of CCB, diuretic, α-blocker, or β-blocker) is more effective and efficient than sequential monotherapy for achieving target blood pressure and reduces risk of adverse events by allowing use of lower doses of each drug.

Anemia

In the elderly especially frail elderly with CKD, anemia is related to poor function and quality of life, increased frequency and duration of hospital stays and mortality.[23] Normocytic normochromic anemia a common complication seen in CKD patients. A thorough assessment of other causes of anemia starting with

complete blood count, peripheral smear, iron studies, B12 and folate levels should be performed before labeling anemia of CKD. As per KDOQI 2012 guidelines, target hemoglobin between 10–11.5 gm/dL is desired in all CKD patients. Consider ESA in pre-dialysis and dialysis patients with Hb below 10 g/dL and between 9–10 g/dL, respectively.[24] KDOQI Anemia Work Group recommends sufficient iron supplementation to maintain serum ferritin concentration >200 ng/mL in HD patients and >100 ng/mL in non-dialysis or on peritoneal dialysis CKD patients for optimal erythropoiesis.[24]

Vitamin and Electrolyte Abnormality

Vitamins and minerals supplementation is critical for elderly care. For CKD patients who are already deficient (S.vit. D <20 ng/mL) or insufficient (S.vit. D = 20–29 ng/mL) in vitamin D, adequate vitamin D is absolute requirement for preventing secondary hyperparathyroidism (SHPT) and its complications. Supplementation with ergocalciferol or cholecalciferol should be done as per individual needs. However, once SHPT develops, vitamin D receptor agonists and/or calcimimetics are required. Ensuring normal reference levels of electrolytes like calcium and phosphorous is essential for prevention of bone disorders among CKD patients. Dyselectrolytemias including hypo- and hypernatremia and hyperkalemia are well associated with aging kidneys.[25] Caution with use of potassium sparing drugs among CKD patients is required to avoid serious adverse events. Metabolic acidosis in CKD patients is often due to impaired ammonia excretion and its management, for example using sodium bicarbonate, improves nutritional parameters as well as CKD progression.[26]

Renal Replacement Therapy

CKD patients are prone to progress to ESRD. Options of RRT include HD, which can be provided in-center or at home, PD, and KT. Economic constraint limits RRT availability to majority of ESRD patients in India. Elderly patient on HD are physically frail with multiple comorbidities and functional dependencies. Initiation of dialysis in elderly should use multidisciplinary approach taking into account various factors including life expectancy, pros and cons of each dialysis modality, quality of life, and patient and caregiver preferences. Possibility of survival benefit for elderly patients on dialysis as compared to those with no RRT patients cannot be ruled out; however, they tend to spend lot of time around health-care facility and may not get life satisfaction.[27] Assessing HD accessibility for each elderly patient opting for RRT is necessary as caregivers and patients feel overwhelmed and burdensome about frequent multiple visits (at least thrice weekly) to a faraway located dialysis center. The approach of incremental dialysis in elderly may assist them in adjusting to dialysis and sustaining residual kidney function.[28] Suggested incremental dialysis approach involves 1–2 dialysis session weekly, each around 1.5–2.5 hours duration until worsening of renal function necessitates further modification. Home dialysis can be suitable for those able to perform it by themselves or with a family member support. However, it may not be preferred choice for elderly with multiple comorbidity, frailty, and lack of support. Exploration of ideal RRT has led to understanding that diverse modalities are used by patients during the entire course of CKD. A term coined as "Integrated Care" has been popularized.[29,30] Originally, it suggested starting with PD and then changing to in-center HD (CHD). The centers pursuing this approach had reported survival benefits and cost optimization.[31,32] PD needs assistance and can be preferred as home based dialysis modality in presence of an assistant. However, PD may not be suitable for elderly having poor functional status and declining vision. PD is relatively contraindicated among those with severe pulmonary disease, irreducible hernias, active inflammatory bowel disease, significant scar from previous abdominal surgery, colostomy, ileostomy, or gastric tubes.[33] Decision about choice of dialysis modality should also match patient's values with treatment characteristics in order to maximize achievable quality of life in elderly.

Vascular Access

An effective VA is very essential for carrying out HD and comprises of arteriovenous fistula (AVF), arteriovenous graft (AVG), and central venous catheter (CVC). For long, as first choice, AVF has been created in the non-dominant hand. Procedure began at a distal site to safeguard proximal blood vessels for future use, thus radiocephalic fistulas became initial choice.[34] This site also reported to have higher failure rate because of thrombosis and inability to mature, requiring more surgeries and use of tunneled catheter for dialysis. Moreover, preserving a venous

location in a frail elderly may not be prudent due to fixed life anticipation, so, the most appropriate AVF, utilizing the most excellent vessels should be created first.[35,36] Complications such as stenosis, thrombosis, and distal hypoperfusion ischemic syndrome (DHIS) are concerning and add to heavy cost and morbidity with access. Therefore, varying views arise stating creation of upper arm AVFs in elderly as standard care or preferring AVGs and CVCs as more suitable options depending on individual patient. De Silva et al. found similar survival for elderly aged >80 years using either AVFs or AVGs, though, that could be attributed to lesser number of patients receiving AVG (25.4%) as compared to AVF (43.2%) that were chosen for tunneled dialysis.[37] Risk of death is more than risk of progression to ESRD in most elderly CKD, especially if age >85 years, so benefits of an invasive procedure should be weighed against associated complication and additional cost arising out of any potential unnecessary procedure.[27] O'Hare et al. demonstrated that only about 25% and 33% of patients started dialysis within 6 month and 1 year, respectively, after access creation in 85–100 year old patients with eGFR <15 mL/min/1.73 m^2.[38] Therefore, life expectancy and rate of deterioration of disease should form basis for timing and type of access creation in elderly. For example, a tunneled catheter usually not the most appropriate access choice, could be considered for those with a life very limited life expectancy (e.g., <6 months). CVCs are preferred in IJV and femoral vein since subclavian vein has high risk of thrombosis. Infections, as the complication, amount to about 30–60% of HD CVCs removal and also, hospitalization rates are higher with CVCs than AVF.[39] Active surveillance and monitoring of AVF is recommended. Physical examination of VA is very useful tool to assess inconvenience during cannulation or clot aspiration, bleeding at cannulation sites post dialysis or failure to attain target blood flows while dialysis. If any such sign present, further evaluation with direct flow rate [using Doppler US and magnetic resonance angiography (MRA)], or indirect flow rate measurement modality [UD (Transonic), timed ultrafiltration methods, ionic dialysance, differential conductivity, and glucose infusion] should be considered.[40] A low-cost method using hemoglobin dilution test was described by Tiranathanagul et al. which can be used in the resource limited areas where ultrasound dilution test (UDT) is costly and unavailable.[41]

Kidney Transplant—An Option in Elderly?

Although, age itself is not a contraindication to KT, but poor accessibility and associated comorbidities could make elderly ineligible for getting a transplant organ. There is lower 5-year survival probability among KT recipients aged >65 years compared to aged 35–49 years (61% vs. 75% respectively).[42] Though Kaul et al. reported, in a retrospective study of ESRD patients, that after adjusting for albumin and BMI, KT group had better short-term and long-term survival as compared to PD group.[43] So, despite increased age, in the absence of other significant factor limiting the life expectancy, KT could be beneficial for elderly.[44] Factors that reduce KT rate in elderly may be strict selection criteria, health-care providers' apprehensions and decreased willingness among older patients for kidney transplantation.[45] Thus, instead of kidney transplantation, most of the elderly with ESRD undergo dialysis.

Social Support and End-of-Life Care

Like most non-communicable diseases, the treatment for CKD is non-curative, thus patient has to learn living with it. This creates functional restrain thereby limiting social involvement and a feeling of being isolated. Increased requirement of assistance for executive functions, dependency for care including dialysis, adjusting to new pattern of daily routine and cognitive changes of ageing may cause a lot of stress, resulting in a feeling of helplessness. Social support including emotional and instrumental is essential for overcoming. Instrumental support helps patient carrying out all routine and financial activities while emotional support enables person to feel loved and cared.[46] Ultimately, terminal patient-care needs interdisciplinary management. End-of-life care discussion involving patient and family members, taking care of their preferences to reach a consensus regarding accepting any intervention or simply withdrawing dialysis for palliative care and reviewing goals of advance care should be considered. Kirchhoff et al. observed that after intervening with patient-centered advance care planning, a significant percentage of ESRD patients withdrew dialysis as compared to those without intervention.[47] Informed choice about all available options, including their pros and cons, can augment decision-making especially for patients on HD among whom 9–13% succumb within 1 year.[48]

Conclusion

Optimization of renal care in a developing country, where health-care infrastructure is already struggling, is challenging. Regardless, perpetual efforts for active care, prevention from and preparation for deteriorating CKD stages and befitting RRT are needed. Optimal care of elderly patients with CKD may be rewarding by decelerating fall in renal functioning, better care of complications, and enabling a rational choice of RRT with well-timed carried out VA.

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CHAPTER

154 Understanding the Role of Vitamin D in Diabetic Nephropathy

Srinath KM, Spoorthy Raj, Manjunath S Shetty

Abstract

Diabetes mellitus includes a group of metabolic disorders which share the common phenotype of hyperglycemia. Diabetes mellitus is the leading cause of end stage renal disease. With the prevalence of diabetes mellitus increasing enormously in present times, the burden of end stage renal disease caused by diabetes mellitus assumes significance.

Three major pathways are implicated in the development of DKD (Diabetic Kidney Disease) initiated by hyperglycemia. They are Activation of Protein Kinase C and polyol pathways, formation of advanced glycation end products, and glomerular hyperfiltration leading to glomerular hypertension.

Vitamin D is known to prevent beta cell apoptosis, increase insulin synthesis and enhance peripheral insulin sensitivity. Also, it is known to suppress RAS (Renin Angiotensin Aldosterone System), prevent podocyte loss and structural derangement of slit diaphragm, suppress inflammation and prevent glomerulosclerosis.

Hence, addition of Vitamin D supplements to ACE inhibitors/ARBs is proposed as a novel mechanism to prevent and halt the progression of Diabetic Kidney disease.

Introduction

Diabetes mellitus (DM) poses a major global public health problem with ever increasing incidence and prevalence in recent years.

At present, diabetes is the most common cause of end stage renal disease (ESRD).

Increasing burden of diabetic kidney disease (DKD) is secondary to widespread prevalence of diabetes.

According to International Diabetic Federation, the number of diabetics is expected to exceed 435 million by 2030, with more than 90% having type 2 diabetes.[1]

The increased risk of all cause and cardiovascular mortality in patients with diabetes is due to the presence of DKD.[2]

Approximately, 25–40% of type 1 DM patients and 5–40% of patients with type 2 diabetes develop this microvascular complication.[3]

Over 20% of the newly diagnosed T2DM have concurrent DKD and a further 20–40% develop diabetic nephropathy mostly within 10 years of diagnosis.[4]

Several genetic and environmental factors lead to pathogenesis of DN.

Hyperglycemic state of diabetes leads to various hemodynamic, biochemical, metabolic changes in kidneys including inflammation and oxidative stress.[5]

Considering the burden imposed by diabetes and DKD, extensive research is done in search of therapeutic agent, which can reduce or stop the progression of diabetic kidney disease. One such novel therapeutic agent for diabetic nephropathy is vitamin D and its analogues.

Risk Factors Associated with DKD

Multiple factors are responsible for the development of diabetic nephropathy and its progression.

These factors can be categorized as susceptibility factors—which predispose patients to the risk of developing DKD and are considered as non-modifiable factors. Acute kidney injury (AKI), dietary factors, hyperglycemia, and hypertension which initiate kidney damage and worsen the DKD are considered as modifiable factors.[6]

Hence, the risk factors for DKD are summarized as:

- *Susceptibility factors:* Old age, male sex, African-American race, and significant family history
- *Initiation factors:* Hyperglycemia and AKI
- *Progression factors:* Hypertension, obesity, dietary factors, and smoking[7]

Among the various risk factors hyperglycemia and hypertension are the most predominant risk factors.

Natural History of DKD[8]

The progressive model of the natural history of DKD has been shown in **Figure 1**.

Pathogenesis of Diabetic Nephropathy

Hyperglycemia is the necessary factor in the initiation of renal injury. Abnormal intracellular metabolism, involving three major pathways that are associated with the development of diabetic nephropathy shown in **Flowchart 1**.[9]

- Activation of protein kinase C and polyol pathways
- Advanced glycation end-products formation
- Glomerular hyperfiltration leading to intra-glomerular hypertension

It is also implicated that there is an excessive production of mitochondrial reactive oxygen species. Interactions between metabolic changes induced by hyperglycemia with hemodynamic factors, including vasoactive hormones such as angiotensin II, play a critical role in inducing renal injury. These mechanisms result in cell injury and activate inflammatory cascade which further perpetuates cell injury and results in vicious

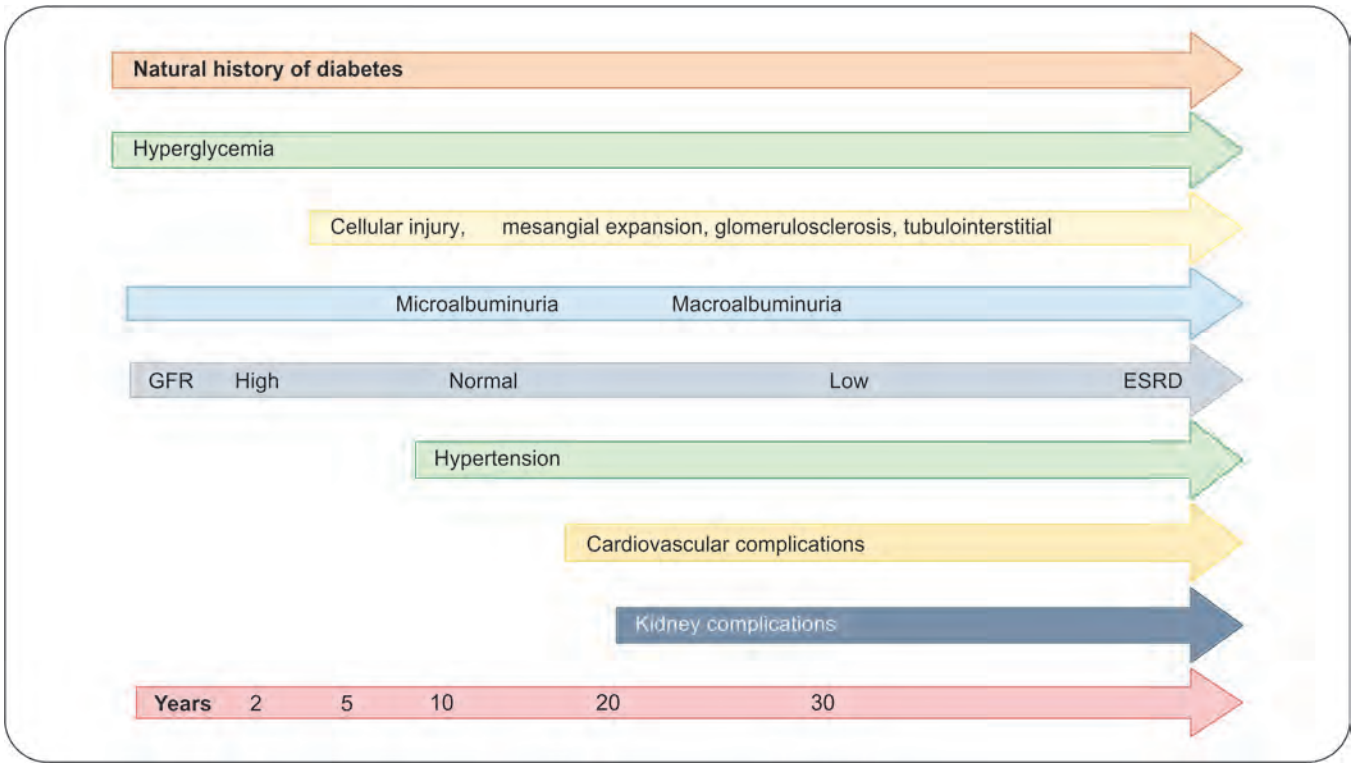
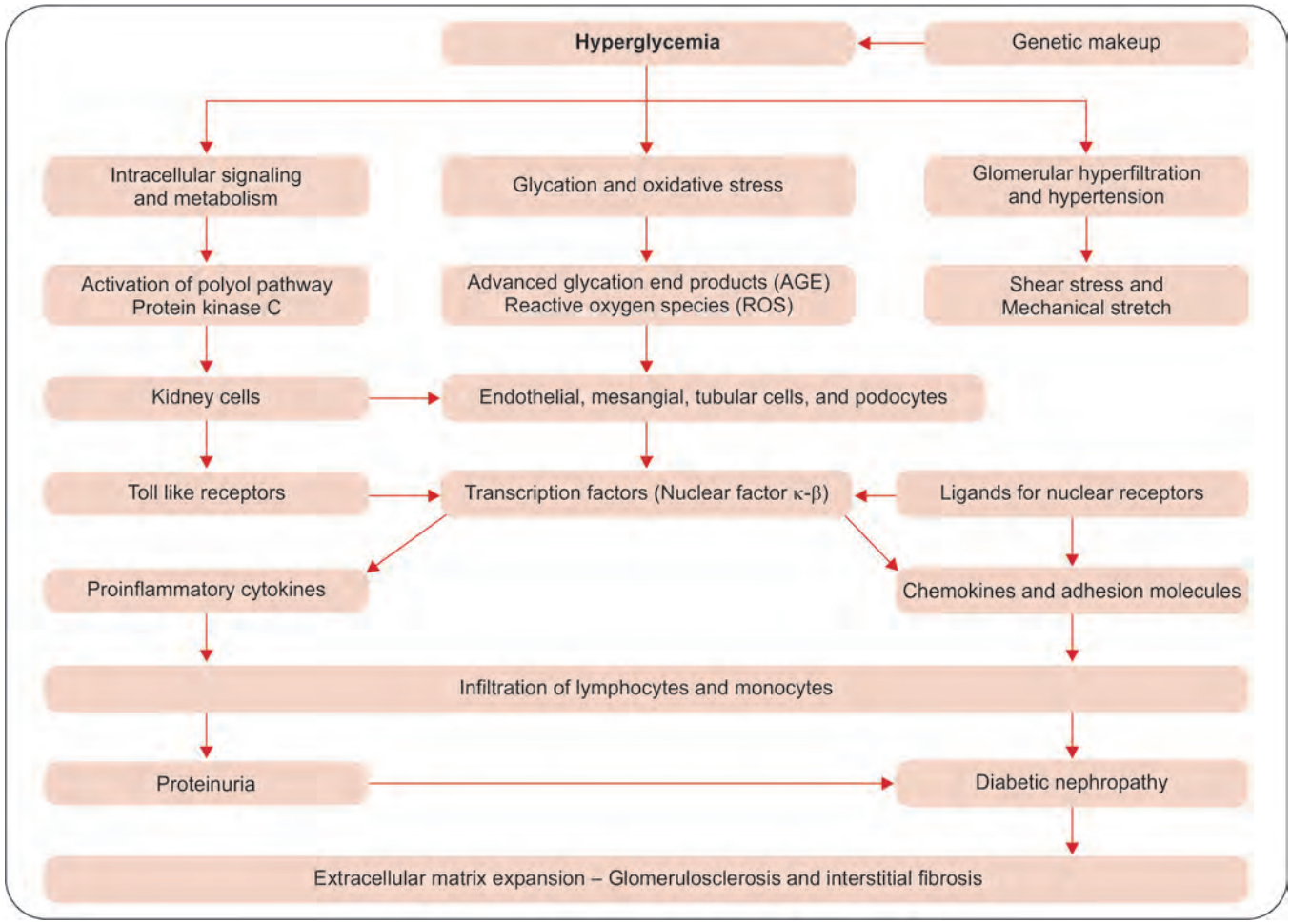


Fig. 1: The progressive model of the natural history of diabetic kidney disease. Duration of diabetes, in years, is presented on the horizontal axis. Timeline is well characterized for type 1 diabetes mellitus; for type 2 diabetes mellitus, timeline may depart from the illustration due to the variable timing of the onset of hyperglycemia

Flowchart 1: Pathophysiology of diabetic nephropathy



Source: Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. Clinical science. 2013 Feb 1;124(3):139-52.

cycle of cell injury—inflammation—further cell injury—fibrosis.[9]

The molecules responsible for inflammation in diabetic nephropathy include:

- Transcription factors, NF-κB
- Proinflammatory cytokines & signaling molecules—IL-6, IL-18, IL-1, TNF, JAK2, & STAT 1&3
- *Chemokines* CCL2 (MCP-1) and CCR2, CXCL12 (stromal-cell-derived factor-1), CX3CL1
- Fractalkine and CX3CR1
- *Adhesion molecules:* Intercellular adhesion molecule 1 (ICAM1), Vascular cell adhesion protein 1 (VCAM1), E-selectin (SELE); Toll like receptors—(TLR2, TLR4)
- *Adipokines:* Adiponectin, Leptin; Nuclear receptors—VDR, NR1H4 (FXR) PPARα PPARγ, PPARδ
- TGF-β1 (transforming growth factor-β1) is a well determined molecule for the accumulation of ECM glycoproteins and subsequent glomerulosclerosis[10]

Pathology of Diabetic Nephropathy

Diabetic nephropathy was first described as glomerulopathy, mainly affecting mesangial cells; however, with further research it is found that glomerular epithelial cell abnormalities like podocyte dysfunction (angiotensin II mediated reduced expression of Nephrin), apoptosis, ultimately resulting in depletion of podocytes is central to development of proteinuria which is a hallmark feature of diabetic nephropathy. Also identified are the important changes in other sites like tubules, interstitium, medulla, and papilla. Renal function and prognosis correlate better

with structural lesions in tubules and cortical interstitium than with classic glomerular changes.[11]

The steps resulting in diabetic nephropathy are:[12]

- Hypertrophy of glomerulus and hyperfiltration
- Glomerular and tubulo-interstitial inflammation
- Decrease in number of cells by apoptosis and accumulation of ECM.

Vitamin D

Fat soluble vitamin D exists in two major forms, namely ergocalciferol (D2) and cholecalciferol (D3).

The main source of vitamin D for human body is endogenously biosynthesized in the skin. Vitamin D absorbed from diet and synthesized endogenously is biologically inert. Vitamin D in liver is converted into 25-hydroxyvitamin D (25(OH) D3) by liver enzyme 25-hydroxylase, which can be measured clinically. 25(OH) D3 is further hydroxylated to 1, 25(OH)2 D3 by kidney-derived 1-alpha-hydroxylase which is an active form of Vitamin D.

The activated form of vitamin D (1,25(OH)2D3) further binds with vitamin D receptors (VDRs) and activates various transcription factors. It is now found that, VDRs and 1-alpha-hydroxylase is expressed in tissues like islets of pancreas, hepatocytes, vascular smooth muscle cells, macrophages, mesangial cells, and podocytes. Vitamin D acts in autocrine manner and exerts multiple non-calcemic effects through VDRs. This includes vascular, immunomodulatory, anti-inflammatory effects, suppression of RAS, and control of glucose homeostasis.[13]

Role of Vitamin D in Insulin Synthesis and Regulating Insulin Sensitivity

Hyperglycemia results in endoplasmic reticulum stress, inflammation (lipotoxicity) and loss of insulin sensitivity.

Thus, hyperglycemia plays a key role in causation of resistance to insulin and β-cell failure.[14-16] Diet induced hypovitaminosis D in animal mice models revealed this hypovitaminosis D is a result of impaired glucose tolerance, decreased islet function related gene transcription, and increased RAS expression.[17]

The postulated molecular mechanism behind regulation of insulin homeostasis by Vitamin D includes:

- Promoter regions of insulin receptor genes have VDR response elements (VDREs).[18]

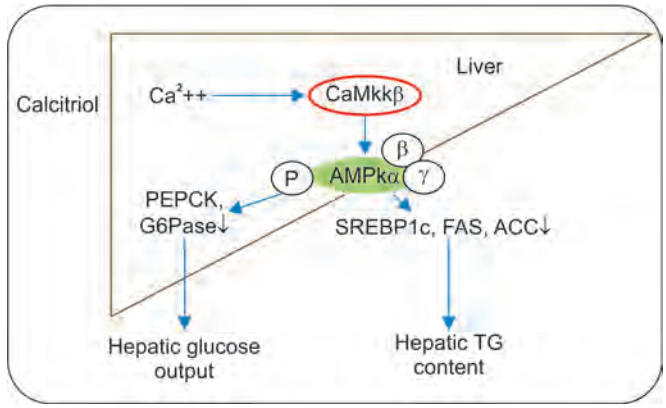


Fig. 2: Role of vitamin D in hepatic glucose homeostasis

- Calcitriol in liver is known to induce calcium flux and activate calcium/calmodulin dependent protein kinase (CaMkkB), which further activates 5' AMP (Adenosine monophosphate) activated protein kinase (AMPK). This results in down regulation of Phosphoenol pyruvate carboxy kinase (PEPCK) and Glucose 6 phosphatase (G6Pase) and thus reduce hepatic glucose output. AMPKa activation can also downregulate sterol regulatory element binding protein 1 (SREBP1c),FAS and Acetyl co-A carboxylase (ACC) which further reduces the hepatic triglyceride content shown in **Figure 2**.
- Increased intracellular ionized calcium and subsequent downstream signaling mediated by vitamin D is known to enhance glucose and arginine mediated insulin release from β-cells of pancreas.[19]
- Suppress the transcription of renin, angiotensin receptors and serve to inhibit local RAS mediated beta cell injury.
- Hyperglycemia and increased free fatty acids result in endoplasmic reticulum stress and reduced activity of Akt pathway, which ultimately results in β-cell apoptosis.

  Vitamin D helps in beta cell survival and also increases compensatory beta cell growth in insulin resistant states by enhancing activity of Akt pathway.[20]
- Vitamin D also reduces accumulation of hepatic triglyceride and glucose output through Ca^{2+}/CaMKK/AMPK signaling activation.
- Vitamin D also inhibits VDR mediated PPAR activity thus inhibits adipogenesis.[21]

Vitamin D Role in Inflammation

Activation of NF-kB pathway results in increased transcription and production of proinflammatory cytokines like TNF-α, IL-1, and IL-6. This proinflammatory milieu leads to leukocyte infiltration of pancreas resulting in reduced β-cell mass, reduced insulin synthesis, islet amyloid deposition, altered downstream insulin signaling through IRS/AKT/PI3K resulting in insulin resistance and also affects the maintenance of energy and blood sugar balance in hypothalamus.[22]

VDD promotes inflammation through NF-kB pathway as evidenced by animal model, whereas vitamin D supplementation has shown beneficial effects in preventing the same.[22]

Vitamin D Role in Diabetic Nephropathy

Diabetic nephropathy is associated with increased incidence of vitamin D deficiency. Probable explanation for the same includes reduced sunlight exposure (e.g., in elderly, sick, dark-skinned people, people wearing veil, losses of vitamin D-binding protein in proteinuric states).

Vitamin D is known to ameliorate the harmful effects of hyperglycemia on kidney by following mechanism:[23]

- Vitamin D inhibits RAS by downregulating renin, angiotensinogen and angiotensin II receptor expression.
- Enhances the expression of nephrin and prevents structural derangement of slit diaphragm.
- Inhibits activation of ERKs, p38-MAPK, Wnt-b catenin pathway, and down regulates proapoptotic signals Bad, Bak, and upregulate anti-apoptotic signal Bcl2 and prevent podocyte apoptosis and podocyte loss.
- Inhibits the expression of Smad 3 protein or by the physical interaction of VDR with Smad 3 protein downregulates the intracellular level of Smad 3 and thus, reduce the expression of TGF-β, and prevent glomerulosclerosis.
- Inhibits the expression of fibronectin and extracellular matrix proteins from mesangial cells and protect against glomerulosclerosis.
- Inhibits the expression of MCP-1 (Monocyte Chemotactic Protein 1) which results in decreased leukocyte recruitment to kidneys and reduces the renal inflammation.

Evidence from Clinical Studies

Clinical trial evidence indicates that combined treatment with losartan and paricalcitol completely prevented albuminuria as well as markedly reduced glomerulosclerosis while restoring glomerular filtration barrier structure.[2] The vitamin D receptor activator (paricalcitol) in albuminuria lowering (VITAL) study showed that addition of two micrograms of paricalcitol to RAS inhibitors safely lowers albuminuria in patients with diabetic nephropathy and can be a novel approach to reduce residual renal risk in patients with diabetic nephropathy who are already on treatment with optimal doses of RAS inhibitors.[24]

Conclusion

Diabetic nephropathy is a common renal complication of DM and a major cause of ESRD. RAS is the predominant mediator of progressive injury to renal system in DN. Hence, RAS inhibitors are being used as the mainstay of treatment for DN; however, RAS inhibition leads to compensatory rise in the renin due to the disruption of renin feedback inhibition. Vitamin D plays a renal protective role in DM by suppressing rennin expression by negative regulation of RAS. Combination therapy with RAS inhibitors and active vitamin D and its analogue markedly ameliorates renal injury.

However, Vitamin D is currently only recommended in treatment of patients with moderate CKD associated with secondary hyperparathyroidism and vitamin D insufficiency. Hence, further study is required to answer many questions and thereby uncover the potential renoprotective role of vitamin D and its analogues in treatment of patients with CKD.

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Section 12

Section Editor: **Shyam Sundar**

Infectious Disease

CHAPTER

155

Anti-malarial Drug Resistance

Neha Agrawal, Anup Singh, Shyam Sundar

Abstract

Anti-malarial drug resistance is a major public health problem which hinders the control of malaria. In India, resistance of *Plasmodium falciparum* (Pf) to chloroquine, the cheapest and the most used drug was first reported in the year 1973. Resistance to commonly used antimalarial drugs like choloquine (CQ), mefloquine (MQ), sulfadoxine/pyrimethamine (SP) have been reported across the country. Emergence of artemisinin resistance in *P. falciparum* strains from Combodia and neighboring countries is a major setback to the antimalarial program of these countries and an ominous sign.

Various drug-resistant genetic markers identified for *P. falciparum* and *P. vivax* antimalarial drugs, like Plasmodium falciparum Multidrug Resistance Protein 1 (PfMDR1), Plasmodium falciparum Chloroquine Resistance Transporter (PfCRT), The K76T mutation in PfCRT protein is a potent molecular marker of CQ resistance and susceptibility. Antimalarial drug susceptibility and resistance to quinine, amodiaquine (AQ), piperaquine, and lumefantrine is affected by variation in the PfCRT protein mutation. Mutation in C-terminal region of K13 protein is associated with the artemisinin resistance. Detection of drug-resistant parasites in *P. vivax* malaria is also prevalent worldwide. Prolonged courses of artemisinin-based combination therapies for 6 days are currently efficacious in areas where standard 3-day treatments are failing.

Introduction

Malaria is a major cause of morbidity and mortality in the tropical countries. Malaria cases in India have reduced from 2 million annually in the 1990s to 1 million in 2012, with a declining trend since 2002. However, the *Plasmodium falciparum* (Pf) cases reported has increased to 50.01% in 2012 from 39% in 1995.[1] Notably, antimalarial drug resistance is becoming a major public health problem throughout the globe. In India, chloroquine-resistance in *P. falciparum* was first reported in 1973 from Assam. The National Vector Borne Disease Control Programme (NVBDCP) has been monitoring the response of antimalarial drugs in *P. falciparum* malaria since 1978 throughout India. This helps in formulation of National Drug Policy and recommends necessary changes in the control strategy including treatment policy to contain resistant *P. falciparum* foci.[1] National Drug Policy recommends the use of ACT as first-line of treatment for *P. falciparum* since 2010 as resistance to commonly used antimalarial drugs like chloroquine (CQ), Mefloquine (MQ), sulfadoxine/pyrimethamine (SP) has been reported across the country.[2,3]

Tools for Monitoring

Drug sensitivity status in India was being assessed following conventional WHO in-vivo protocol till 2002. This is changed in 2003 since when WHO protocol on "Therapeutic efficacy of antimalarial drugs in uncomplicated *P. falciparum* malaria" is being used. The criteria classify response in three categories:

- Adequate Clinical and Parasitological Response (ACPR),
- Early Treatment Failure (ETF), and
- Late Treatment Failure (LTF).[1]

Criteria for Change of Drug Policy

The treatment drug policy is changed for the area/Block PHC, which reports ≥10% total treatment failure (ETF+LTF) to the tested drug, that is, the currently used antimalarials in a sample of minimum 30 *P. falciparum* test cases. To reduce emergence of drug resistance, the National Drug Policy on Malaria recommends use of combination therapy in chloroquine-resistant areas, that is, Artesunate plus Sulfadoxine-Pyrimethamine (AS+SP) for treatment of *P. falcipuram* cases.[1]

Genetic Markers of Drug Resistance

The various drug-resistant markers identified for *P. falciparum* and *P. vivax* antimalarial drugs are discussed here.

Plasmodium falciparum Multidrug Resistance Protein 1 (PfMDR1)

The PfMDR1 gene located on chromosome 5, encodes for P-glycoprotein homolog 1 protein,[4,5] which belongs to the ATP-binding cassette (ABC) superfamily. Resistance to antimalarials is believed to be due to polymorphism, amplification, or variation in mRNA expression level of the PfMDR1 gene.[5]

Drug susceptibility to chloroquine, quinine, mefloquine, halofantrine, lumefantrine, and artemisinin are affected by mutations in Pfmdr1 gene at the following positions (N86Y, Y184F, S1034C, N1042D, and D1246Y). Amodiaquin resistance is associated with PfMDR1 mutations at N86Y and N1042D position. Chloroquine resistance is associated with K76T and A220S mutation in the Pf chloroquine resistance transporter (PfCRT) gene and N86Y mutation in the PfMDR1 gene.[6-10]

Plasmodium falciparum Chloroquine Resistance Transporter

As discussed, PfCRT gene mutation has potential role in chloroquine resistance. This gene is localized to chromosome 7 and PfCRT protein belongs to the drug/metabolite transporter superfamily and chloroquine resistance transporter-like transporter family with ten putative transmembrane domains spanning the digestive vacuole membrane of the parasite.

The K76T mutation in PfCRT protein is a potent molecular marker of CQ resistance and susceptibility.[11] K76T mutation located in the first transmembrane domain of PfCRT protein, allows the efflux of diprotonated chloroquine out of the digestive vacuole by active transport.[12] Other mutations cause resistance only in association with K76T mutation and include C72S, M74I, N75E, A220S, Q271E, N326S, I356T, and R371I.[12]

Antimalarial drug susceptibility and resistance to quinine, amodiaquine (AQ), piperaquine, and lumefantrine is affected by variation in the PfCRT protein mutation.[13-16] There is cross-resistance of chloroquine with AQ and quinine mainly mediated by 76T, and lumefantrine has an inverse cross-resistance having reduced susceptibility in association with wild-type K76.[17]

Plasmodium falciparum Multidrug Resistance-Associated Protein (PfMRP)

PfMRP is a transmembrane protein produced by PfMRP gene located on chromosome 1. This multidrug resistance-associated protein aids the parasite in transporting out of drug and organic anionic substrates like oxidized glucuronate, glutathione, etc. from its inside, thus effecting resistance.[18,19]

Chloroquine and quinine resistance are associated with two mutations in PfMRP at position Y191H and A437S. High sensitivity to various antimalarial drugs such as chloroquine, quinine, primaquine, piperaquine, and artemisinin can be demonstrated by genetic knocking out of PfMRP gene in the resistant parasite, and more accumulation of chloroquine and quinine is observed in the sensitive parasite. Thus, PfMRP is not only involved in determining the drug resistance but has role in varying the antimalarial response to resistance.[19]

Plasmodium falciparum Sodium Hydrogen Exchanger (PfNHE)

This gene on chromosome 13 codes for a protein associated with quinine resistance in Pf, and is involved in active efflux of protons in the parasite to maintain pH at 7.4, in response to acidification by anaerobic glycolysis, the primary energy source for the parasite.[20] Polymorphism in the microsatellite ms470 region exhibited a decrease in quinine susceptibility with an increase in DNNND repeat motif, whereas increase in quinine susceptibility is observed with a rise in NHNDNHNNDDD motif. Three mutations at 790, 894, and 950 codons and polymorphism in the microsatellite region (msR1 and ms3580) showed

no association with quinine resistance.[21] Thus, repeat polymorphism in PfNHE gene may be used as a valid genetic marker to determine quinine resistance in some regions.

Plasmodium falciparum Bifunctional Dihydrofolate Reductase-Thymidylate Synthase (PfDHFR-TS)

The PfDHFR-TS gene has one exon located on chromosome 4 encoding for PfDHFR protein and is a bifunctional enzyme involved in two main folate metabolic activities—biosynthesis of dTMP by thymidylate synthase activity and the reduction of dihydrofolate to tetrahydrofolate by dihydrofolate reductase (DHFR) activity. The folate mechanism of PfDHFR-TS enzyme is inhibited by the action of antifolate drugs such as pyrimethamine and cycloguanil, thus reducing the production of pyrimidine for DNA replication.[22]

Pyrimethamine resistance is mainly associated with point mutation in the PfDHFR protein at S108D codon, and further mutation at N51I, C59N, and I164L positions strengthens the resistance besides amplification of gene.[23,24]

Plasmodium falciparum Dihydropteroate Synthase (PfDHPS)

The PfDHPS gene is located on chromosome 8 and encodes for PfDHPS protein. PfDHPS synthesizes dihydrofolate, a folate precursor that is essential for the synthesis of pyrimidine in the parasite by catalyzing the reaction of pterin derivative and p-aminobenzoic acid (PABA).[25] This catalytic enzyme action to synthesize dihydrofolate is inhibited by sulfa drugs (sulfadoxine and dapsone), which act as an analog to PABA.[25]

Resistance to sulfadoxine in *P. falciparum* is due to S436A/F, A437G, L540E, A581G, and A613T/S mutations in the PfDHPS protein.[24] Sulfadoxine is always provided in combination with pyrimethamine (SP) as monotherapy is associated with antimalarial drug resistance. Point mutation in both PfDHFR and PfDHPS gene is associated with resistance to SP.[23]

Cytochrome B

Cytochrome b (Cytb) gene is a subunit of cytochrome bc1 complex present in mitochondrial inner membrane of the parasite. It catalyses the transfer of electrons across the inner mitochondrial membrane to maintain the electrochemical potential of the membrane. The antimalarial drug atovaquone disrupts the electrochemical potential by binding to the ubiquinol binding site of cytb, and hence is lethal for the parasite. Mutation at the ubiquinol binding site confers atovaquone resistance.[26,27] Single mutation at Y268N/S/C codon in the cytb gene leads to resistance to atovaquone in *P. falciparum* field isolates.

Kelch

Kelch-13 (K13) protein has one exon located on chromosome 13. Mutation in C-terminal region of K13 protein in this region is associated with artemisinin resistance in both clinical and field isolates by disrupting the domain scaffold. However, the exact function of K13 protein, and the effect of various mutations on the protein will only be known after several studies are conducted to ascertain its nature completely.

Nonsynonymous polymorphism at Y493H, R539T, I543T, and C580Y positions observed in the kelch repeat region of K13 propeller domain is associated with higher artemisinin resistance. Mutations at codons F446I, Y493H, P574L, R539T, and C580Y confer a higher degree of resistance to artemisinin, and the frequency of C580Y allele mutation is higher and takes longer time for parasite clearance when compared to variation in other sites. Therefore, K13 propeller protein polymorphism can serve as a potent molecular marker indicating emergence and spread of artemisinin-resistant *P. falciparum*.[28]

Drug Resistance in Vivax Malaria

Drug-resistant *Plasmodium vivax* malaria is also prevalent worldwide. Its treatment primarily consists of two drugs: Chloroquine (blood schizonticide) targeting the asexual blood stages of the parasite, and Primaquine (tissue schizonticide), which targets the dormant live stage (hypnozoites) of the parasite, responsible for relapse.

P. vivax is also associated with molecular markers of drug-resistance, like *P. falciparum*. Increased susceptibility to chloroquine in *P. vivax* is strongly associated with the Y976F mutation in PvMDR1 gene, which is a homolog of PfMDR1. However, the PfCRT gene homolog in *P. vivax*, that is, the PvCRT gene, is not associated with chloroquine-resistance (unlike in *P. falciparum*). Mefloquine resistance

in *P. vivax* is associated with amplification of PvMDR1 gene. Mutation at Y976F position of PvMRD1 *in vitro* has been shown to be associated with resistance to mefloquine and artesunate, in addition to chloroquine.[29,30]

Point mutations at F57L/I, S58R, T61M, and S117T/N codons of PvDHFR gene are linked to pyrimethamine resistance and consequently treatment failure with pyrimethamine in *P. vivax*. The wild type residue V585 in PvDHPS gene has shown innate resistance to sulfadoxine and is enhanced by the mutation in A383G and A553G codons in PvDHPS, which is similar to PfDHPS mutation at codons A347G and A581G.[31,32]

Conclusion

Antimalarial drug resistance poses a major hurdle to our victory over the malarial parasite and contributes to failure in treatment of malaria. Combination therapies targeting different mechanisms of action can delay the emergence and spread of drug-resistant parasites. Molecular markers of drug resistance play a vital role in the detection of resistance in clinical and field isolates when compared to the *in vivo* efficacy studies and *in vitro* tests. Thus, earlier clinical isolates will aid in employing immediate and appropriate treatment that in turn reduces treatment failure and thereby mortality, and also prevents the spread of resistance. Hence, continuous monitoring and surveillance of drug-resistant molecular markers in malaria endemic regions is important in determining and assisting an effective national drug policy for malaria treatment. Therefore, more research is necessary to find new antimalarial drugs/vaccines for multidrug resistance parasites.

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CHAPTER

156 Controversy in Vaccination

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Abstract

Ever since the advent of vaccination against communicable diseases there has been concern in the mind of certain people about its adverse outcome. While there is no doubt about efficacy of the time-tested vaccines which have been able to either eradicate or minimize many dangerous communicable diseases but the apprehension remains there, which were not unfounded. There was apprehension of increased incidences of Autism (MMR Vaccine), GBS (DPT, Influenza vaccine) which later on proved wrong. Dengvaxia saga (2015 with Dengue vaccination), Cutter polio incident (1955), and currently Covid vaccine related adverse effects are few examples which were highlighted out of proportion despite their numbers were few and statistically insignificant. In this article we highlight the various aspects of various controversies revolving around the vaccinations and their scientific explanations which would help us to overcome these apprehensions for future vaccination strategies.

Introduction

Ever since Edward Jenner had introduced the first vaccine in 1796, the global use of vaccines has been detrimental in reducing or eradicated the incidence and spread of childhood diseases.[1,2] Despite the fact that there are a lot of evidences behind the benefits of vaccines, to provide immunity against diseases, there has been opposition in certain quarter against the use of vaccines.[3] Some of these biased views are based on perception of personal, religious, or cultural beliefs that vaccines can be more harmful than good in people who receive them. The Controversy of vaccination is about:

- Safety
- Efficacy
- Dosing
- Availability of different vaccines for different region. This can be attributed to lack of awareness, political and vested interests. However, this fear was not without reasons. Following is the historical facts of various concerns against the vaccinations.

The Cutter Incident:[4] In 1955 Cutter Laboratories produced 120,000 polio vaccines (in which the process of inactivating the live virus proved to be defective), which caused 40,000 cases of polio, 53 cases of paralysis, and 5 deaths. This in turn also infected the family members of the recipients leading to additional 113 cases of paralytic polio and another 5 deaths. It has been rightly described as the worst Pharmaceutical incident.

Other historical facts are given below which created doubts and suspicion in the mind of people regarding efficacy and side effects of vaccinations **(Table 1).**

Despite all the rebuffs to the Antivax (Anti-vaccination) lobby the concerns raised were not without reasons due to the emergence of certain adverse effects in the ensuing

TABLE 1 History of controversies in vaccination and evidences for and against them[5]

Issue	*Allegation*	*Evidence*
MMR vaccine and autism[6]	MMR vaccine can cause autism	• Initial report suggesting an association between vaccination and autism was drawn back • Autism usually occurs in early age group than before recommended age of MMR vaccination (12 months) and is genetically determined • In studies conducted by the epidemiologists there is no increased risk of autism associated with MMR vaccine
DPT	Neurological conditions following immunization[7,8]	• Commission on Vaccination and Immunization (JCVI) confirmed that the risks or neurological problems due to DPT were quite low • With universal childhood immunization, the number of reported cases fell by >95%, and mortality rates decreased even more dramatically[9]
Thimerosal[10]	Increases risk of autism and other neurodevelopmental disabilities may be increased by Thimerosal	• Ethyl mercury (an active ingredient of thimerosal) does not accumulate in the body to harmful levels with consecutive vaccinations • Even after removal of thimerosal from childhood vaccines, incidence of autism continued to increase • Studies have not found an increased risk of autism or other neurodevelopmental disabilities associated with thimerosal-containing vaccines in epidemiological studies[11]
Influenza vaccines may cause GBS[12]	GBS (1978)	It is observed that risk of GBS is greater following natural influenza infection than possible vaccination
Meningococcal vaccine and can cause GBS[12]	GBS (2005–2008)	A large study proved there was no link between Menactra and GBS
Autoimmunity[13]	Vaccines may be responsible for chronic diseases of autoimmune etiology	There is no established mechanism to explain how vaccinations cause autoimmune disease and epidemiologic studies have failed to supported the hypothesis that vaccines cause autoimmune diseases
HPV vaccine: Safety	Risk of autoimmune and other disorders may be increased with HPV vaccination	• Several large studies have not established increased risks of autoimmune or neurologic diseases • Other studies failed to establish increased risks of POI, POTS, or CRPS
Aluminum	Autoimmune diseases and a variety of other disorders, including Macrophagic Myofasciitis can be attributed to aluminum in vaccines[14]	• The serum levels of aluminum are well below the toxic range due to aluminum containing vaccines • There is hardly any correlation between infant blood or hair aluminum concentrations and vaccine history • There were lower incidence of autoimmune disease with higher quantities of injected aluminum adjuvants • Systemic symptoms of MMF secondary to aluminum salts at injection sites have never been established[15]
Too many too soon	Too many vaccines given early in life might interfere with the immune system	• Infants can handle as many as 10,000 vaccines at one time • Long-lasting, gross alterations of the immune system has been found with childhood vaccinations • The number of vaccines or vaccine antigens received in early childhood did not increase risk of disease or developmental delay as per many epidemiological studies
Hepatitis vaccine 1998[26]	Multiple sclerosis	The IOM committee concluded that there is no link between MS and hepatitis B vaccination

CRPS, complex regional pain syndrome; GBS, Guillain-Barré syndrome; HPV, human papillomavirus; IOM, Institute of Medicine; MMR, measles, mumps, and rubella; POI, primary ovarian insufficiency; POTS, postural orthostatic tachycardia syndrome

years. To highlight these concerns, few following events throw insight into the safety and concerns about the vaccination.

Dengue Vaccine Controversy[16,17]

About 400 million people are infected with Dengue every year, out of which almost 25000 people die of dengue hemorrhagic fever (DHF). Due to lack of cure for Dengue and high mortality rate in the countries with less advanced medical system, scientists have since long been on a quest to develop a vaccine. Recently, Dengvaxia (Vaccine against Dengue) was approved by Food and Drug Administration (FDA) to prevent dengue. Despite the fact that this vaccine has the capability to save millions of lives , its approval was not without controversy.

Philippines in 2015 launched a massive campaign to immunize children against the dreaded disease. After about 1 million children were vaccinated, the controversy was raised as the vaccine was associated with the deaths of three children in the Philippines. However, before addressing this issue it is imperative, we understand how the immune system reacts to dengue virus. There are two types of antibodies generated against any pathogen—neutralizing and non-neutralizing. The dengue virus has four serotypes and the antibodies generated against one serotype while it may react with another serotype as well, it does not always neutralize the antigen. This may be acceptable for other pathogens since the antibody-pathogen complex reach the macrophage and is eventually destroyed. However, dengue virus is unique as it primarily infects the macrophage. Thus, antibodies that have developed against one variant of dengue can make subsequent infections far more lethal. The preexisting non neutralizing antibodies bind to dengue virus antigen and attract macrophages facilitating spread. In this manner the non-neutralizing antibodies allow the virus to infect multiple cells with ease, thus causing the severity of the second infection with respect to the first one. This phenomenon is referred as antibody enhancement.[18]

Now, though dengvaxia was indeed engineered to protect against all four serotypes of dengue, many people did not develop neutralizing antibodies against all the serotypes. In this unfortunate people, the vaccine acted as a primary infection thus making the second infection far more lethal **(Fig. 1)**.

Current recommendations of dengue vaccine: Despite these shortcomings, dengvaxia has been approved by FDA for use in the following conditions—

- Children 9–16 years old in endemic areas
- Laboratory confirmed previous infection

Controversies Surrounding HPV Vaccination

The controversy surrounding HPV Vaccine is about its—

- Safety concerns
- Dose scheduling
- Two strains/four strains vaccine
- Whether males should be vaccinated
- Till what age one should be vaccinated

Safety concerns: The main adverse reactions reported with HPV vaccination were: headaches (70%), general fatigue (53%), coldness of the legs (53%), limb pain (50%), limb weakness (48%), difficulty in getting up (48%), fainting (43%), decreased capability to learn (43%), arthralgia (43%), tremulousness (40%), gait disturbances (40%), disturbed menstruation (35%), and dizziness (30%). Besides this, it was associated with enhance autoimmune response and CNS side effects including syncope. Possibility of presence of the active aluminum adjuvant might be contributing to these side effects.[19]

In India, with regards to HPV vaccine, Program for Appropriate Technology in Health (PATH),[20] a nonprofit based in Seattle, in 2009 launched a $3.6 million HPV trial, funded by the Bill & Melinda Gates Foundation, in 24,777 adolescent girls in Andhra Pradesh and Gujarat states; however, it was prematurely terminated by the government when news outlets reported the death of seven girls. However, on further analysis it was found that five of those deaths were evidently unrelated to the vaccine itself. The causes attributed to their death were drowning (1 girl), snake bite (1 girl), suicide (2 girls), malaria (1 girl). The other two deaths were still uncertain.

Dosing of vaccine and cost: Another dilemma with respect to the HPV vaccine is the dosing schedule.[21] While one dose by itself is quite immunogenic so as to provide lasting protection from HPV 16 and 18, data regarding long-term protection after 7 years and protection from HPV and cervical precancerous lesions is lacking. Conversely the immunogenicity produced by two-dose and three-dose HPV vaccine schedules, measured using antibody responses in young females, is comparable.[21]

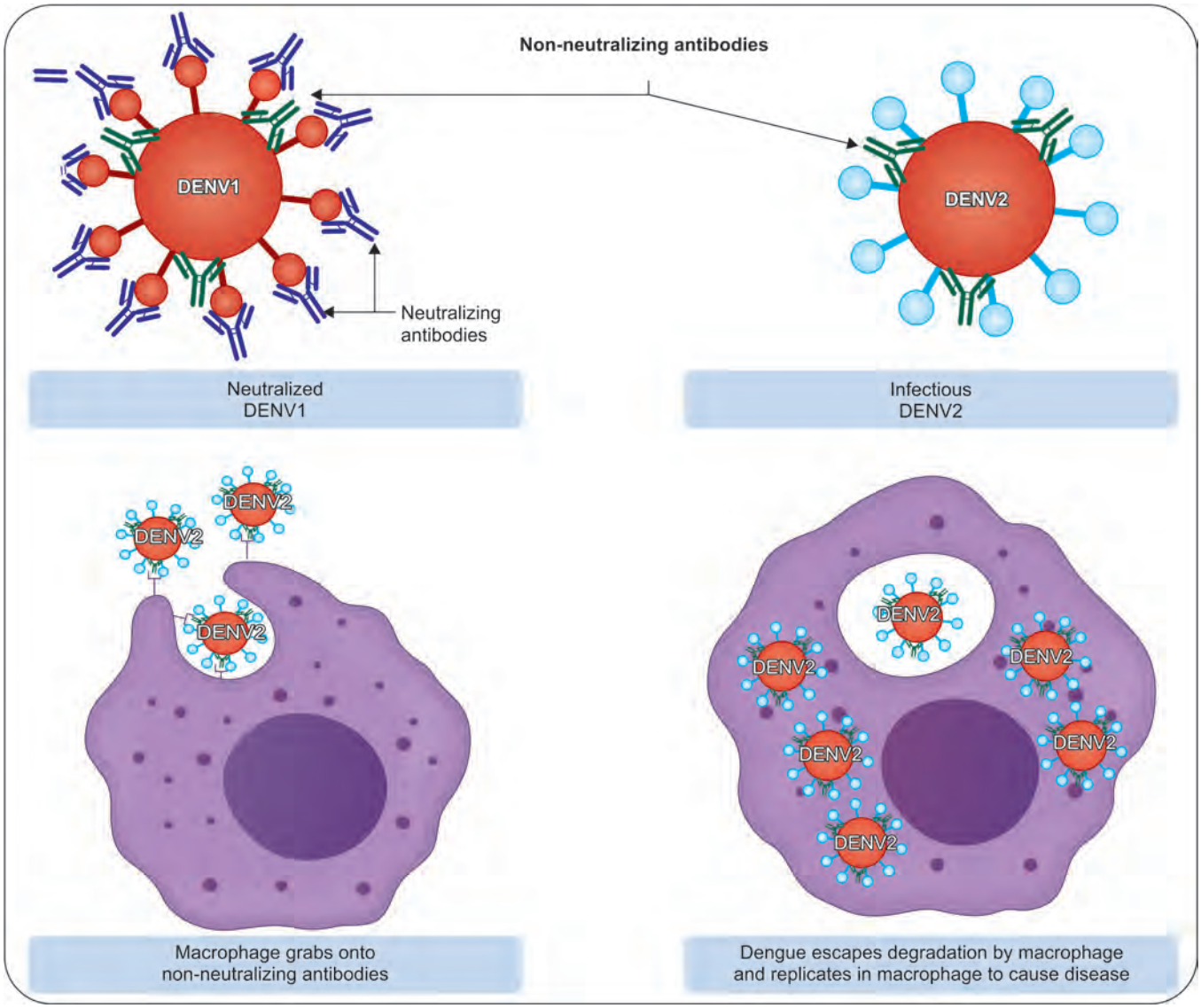

Fig. 1: Neutralizing and non-neutralizing antibodies in dengue infection

Current Recommendations

Children and adults ages 9 through 26 years: HPV vaccination is routinely recommended at age 11 or 12 years; although it can be started as early as age 9 years. HPV vaccination is recommended for all women before attaining 26 years of age who were not adequately vaccinated earlier. Children below 15 years require only two doses to be fully protected. People who start the series at age 15 or older and people with weakened *immune system* need three doses to be fully protected.

Adults ages 27 through 45 years: Despite the facts that HPV vaccine is approved by FDA to be given through age 45 years, HPV vaccination is not recommended for all adults ages 27 through 45 years as effect of vaccination starts to diminish by age 18. Therefore, its benefit for cancer prevention is doubtful as people get older. The ACS (American Cancer society) does not recommend HPV vaccination for persons older than age 26 years.[22] Instead, ACIP[23] recommends that because more people have already been exposed to the virus. HPV vaccination

in this age range provides less benefit; clinicians consider discussing with their patients in this age group about the benefits of the vaccination.

Male HPV vaccination: The US Advisory Committee on Immunization Practices (ACIP)[23,24] licensed HPV4 for boys and young men in 2009. HPV vaccine in males can help prevent genital warts as well as a variety of cancers associated with HPV.

Influenza Vaccination

Influenza (flu), which caused a pandemic in 2009 accounting for 100,000–400,000 deaths, still remains a cause of global concern. According to the World Health Organization (WHO), 1 billion cases surface every year globally, causing about 200,000–600,000 deaths.[25] According to Flu Net, the WHO Global Influenza Surveillance and Response System (GISRS) laboratories; out of total cases 98.6% were influenza A and 1.4% were influenza B cases. Out of these influenza A viruses, 65.2% were influenza A H1N1 and 34.8% were influenza A H3N2. Influenza A H3N2 infection was *more virulent* than influenza A H1N1. In India also the strain influenza A (H1N1) has accounted for most cases—which peaked in the third week of February 2019.[23] Although the report said that vaccination was the most effective tool to create immunity against the disease, but certain doubts remain there about vaccination.

- Which type of vaccination in India should be used? Northern hemisphere/Southern hemisphere.
- High dose versus routine dose in 65 year plus people (High dose vaccination not available in India).
- Serial vaccination and do annual vaccination cause less immunization in subsequent vaccination? Antigenic distancing hypothesis.
- Universal vaccination: Will single vaccination for lifetime (like other vaccines) see some light in time to come?

Seasonal Influenza Vaccine Recommended for the Season of 2019-2020 in India[26]

In India, ICMR and Ministry of Health and Family Welfare, Government of India, have recommended Northern hemisphere quadrivalent/tetravalent vaccine.

Due to the constant changing of antigenicity, the efficacy of influenza vaccination is potentiated when circulating viruses and vaccine viruses correspond to each other. Even when they do correspond, efficacy of vaccine is not beyond 40–60%. But, if the vaccine virus as recommended by WHO is different from the locally circulating virus, it may be partially effective or not effective at all. Hence, vaccines are not foolproof method of protection against influenza. Instead due attention must be given to personal hygiene, frequent washing of hands, social distancing, use of proper masks, etc. should not give a false sense of security.[27]

In various studies it was found that high-dose vaccine (fluzone) was 24.2% more effective (CI 9.7–36.5%) in preventing flu in adults 65 years of age and older relative to a standard-dose vaccine[28] and high-dose influenza vaccine can reduce risk of respiratory-related hospital admissions from nursing home residents aged 65 years and older.[29]

In people who received vaccination in two consecutive seasons, protection against H3N2 was lesser than those who had only been vaccinated in current season suggesting that repeated vaccination against influenza may weaken the immune system[30] However, as per CDC recommendations, annual flu vaccination remains the first and most important step in protecting against flu and its complications. One of the studies[31] postulated that twice annual influenza vaccinations in elderly population of tropical and subtropical areas has improved efficacy. However, the observations were in contradiction to the above said postulation.

Future Vaccine Considerations[32]

An ideal universal vaccine should be:

- Effective for longer duration of time and 75% effective against all strains of Influenza A virus in all age groups.
- A cell based or a recombinant formulation should be favored over an egg-based vaccine.
- The hemagglutination inhibition response for a nanoparticle vaccine formulated with a saponin-based adjuvant was greater than a high dose vaccine.
- Traditional influenza vaccine target IgG portion. However, since different parts of IgA trap many parts of influenza virus simultaneously, IgA may be a more effective target.
- Manufacturing time should be shortened.

Universal Influenza Vaccine

A ball and spike model depicts well of a structure of influenza virus where hemagglutinin protein on the surface represent as spikes. Each spike having a stalk and a cap.

While all current influenza vaccines target at the cap portion of the hemagglutinin proteins which change its antigenicity frequently requiring annual vaccination. Instead the stalk portion of the hemagglutinin protein is stable among different influenza viruses and does not alter antigenicity annually. Therefore, a vaccine targeted at the stalk portion of the hemagglutinin protein can turn out to be a universal vaccine.

Measles Cases in 2019[2,33]

It is worth understanding the mechanism of transmission of measles as it is highly contagious like COVID-19 virus. It has been noted that the viability of the virus lasts for about 2 hours and individuals who have not been vaccinated against measles have a 90% chance of contracting measles. These people now have the potential to spread the disease to 9–18 other people.[2] However, in the global scenario, measles is the leading cause of vaccine-preventable disease and deaths despite the widespread use of vaccines and in fact every year 100,000 people die from measles.[2] World Health Organization reports that there were 1,234 cases of measles in the US and 91 cases in Canada from January 2019 to September 2019. On the other hand, in 2018, 372 cases were reported in the US and 28 in Canada. The recent spike in measles outbreak is due to vaccine deterrence (out of fear of Autism and ignorance and inertia). This along with increase in international travel has facilitated the disease to enter into areas where it was once considered eliminated.[34]

Current Recommendations for Adults

It is advisable for the adults including students at post high school educational institutions, health-care personnel, international travelers who do not have significant evidence of immunity to get a single dose of MMR vaccine. However, certain adults especially students at post high school educational institutions may need two doses separated by at least 28 days. Also, the killed measles vaccine available in 1963–1967 was not very effective. So, they should be vaccinated again.

Tdap/DTaP Vaccination[35,36]

Bordetella pertussis may be the etiologic agent in 12–30% of adults with cough that does not improve within 2 weeks. This is a highly contagious disease with attack rates of 80–100% among unimmunized household contacts and 20% within well immunized household contacts. Despite their efficacy whole-cell pertussis vaccines have been associated with adverse events both common (fever, pain at injection site, erythema and swelling; irritability) and uncommon (febrile seizures, hypotonic hyperresponsive episodes). There have also been alleged associations of whole-cell pertussis vaccine with encephalopathy, sudden infant death syndrome, and autism, which although not substantiated, have succeeded in initiating an active anti-immunization lobby.

Low dose diphtheria toxin along with acellular pertussis vaccine in otherwise previous DPT vaccine has reduced its dreaded side effects. Currently, diphtheria toxoid vaccine is coadministered with tetanus vaccine (with or without acellular pertussis). DTaP (full-level diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine) is currently recommended for children up to the age of 6 years. DTaP replaced the earlier whole-cell pertussis vaccine DTP in 1997. Tdap is formulated for adolescents and adults and consists of acellular pertussis, tetanus toxoid and reduced diphtheria toxoid, and acellular pert Tdap was licensed for use in the US in 2005 and is recommended for children ≥7 years old and for adults. It is recommended that all adults who have never received Tdap before; a single dose of Tdap should be given regardless of the fact that they got Td vaccine before. This should be followed by either a Td or Tdap booster every 10 years.

Efficacy of vaccine can be ascertained by certain historical events. During the 1990s, an epidemic affecting 150,000 people occurred in the former states of the Soviet Union out of which 5000 had died. This was associated with a clonally related strain of ET8 complex. This outbreak was attributed to the failure of the public health infrastructure to vaccinate the people.

Controversy: In the United States, routine vaccination that started in 1940s led to a 100-fold reduction in the incidence of pertussis, and the disease appeared to be on the road to elimination.[2] However, since the mid-1970s, the disease has once again resurfaced,[2] steadily increasing in incidence to 15.1 cases per 100,000 in 2012.

The recent surge of pertussis in developed countries led to a controversy as to its cause. Domenech de Cellès et al. modeled the transmission of pertussis using incidence data from Massachusetts, US. They found that it was not the switch to acellular pertussis vaccine but rather the waning vaccine conferred immunity that contributed to the Massachusetts outbreak This could be explained by the local increased incidences in pertussis cases in the subpopulation who were not vaccinated. Simulations suggested that administration of existing boosters to children may be an effective strategy to halt the transmission of pertussis.

Current recommendation: Every Adult >10 years of age should be given Tdap followed by booster dose of Td or Tdap every 10 years including pregnant women in early pregnancy.

COVID-19 Vaccination

Three types of mechanisms are involved for manufacturing of Covid SARS 2 vaccines (as depicted in **Figure 2**) which are being developed by more than 300 drug companies.

As of now following vaccines **(Table 2)** are at various stage of development:[38]

Controversy and Concern[39-41]

The development of a new vaccine usually takes around 10–15 years.[40] Mumps was the fastest vaccine which was developed in 5 year time. During this pandemic era there is lot of pressure by public and government agencies on the pharma companies to develop vaccine at a faster pace. Therefore, the vaccines are being developed in a very short period and on trial basis on smaller groups. As a result

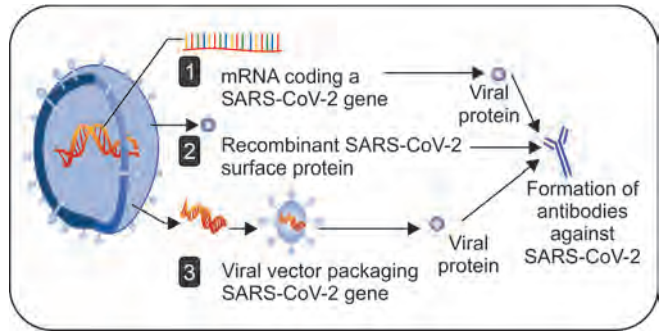

Fig. 2: Vaccine candidates use different mechanisms, such as those shown above, to prompt the body to produce antibodies against SARS-CoV-2
(*Source:* GAO-20-583SP)

TABLE 2 Vaccine types and current stage of development

Vaccine candidates, developers, and sponsors	*Mechanism*	*Sponsor*	*Approved/phase*
mRNA-1273	mRNA-based vaccine	Moderna, Pfizer, BioNTech, Fosun Pharma	• UK: MHRA (December 2, 2020) • Bahrain: NHRA (December 5, 2020) • Saudi Arabia: SFDA (December 10, 2020) • US: FDA (December 11, 2020) • MX: COFEPRIS (December 11, 2020)
Ad5-nCoV	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	**Approved** China
AZD1222	Replication-deficient viral vector vaccine (adenovirus from chimpanzees)	The University of Oxford; AstraZeneca; IQVIA; Serum Institute of India	Phase 3
Covaxin	Inactivated vaccine	Bharat Biotech; National Institute of Virology	Phase 3
JNJ-78436735 (formerly Ad26.COV2.S)	Non-replicating viral vector	Johnson & Johnson	Phase 3
NVX-CoV2373	Nanoparticle vaccine	Novavax	Phase 3
Gam-COVID- Vac (Sputnik V)	Non-replicating viral vector	Gamaleya Research Institute of Epidemiology and Microbiology	Russia: Ministry of Health

when the vaccines are released for public use on mass scale, the side-effects which were unnoticeable during trial phase may become overt.[39] RNA-based vaccines are a major new tool to combat pandemics like COVID-19 outbreaks as they require only viral genetic sequence information to initiate development.

In the past DNA and RNA vaccines have not been successful for human diseases and m-RNA based vaccines will be used for the first time in human being and that too in the pandemic period with trials done for less than a year duration.

The vaccine candidates using human adenovirus as vector such as Cansino Biologics (Wuhan, China) could reduce immune response as there is lot of pre-existing immunity to Adenovirus.[41] Mutations of virus is another important factor that can result in having limited effectiveness of vaccines. There is also concern that vaccines may cause antibody dependent enhancement ADE (as was seen in Dengue Vaccines) or antibody dependent cellular cytotoxicity (ADCC).

Response to vaccines may differ in various age groups and in people with different status of immunity. During phase II trial Sanofi's recombinant DNA derived vaccines did not yield adequate antibody titer in people aged 50 years or more.

The trial so far has been conducted in non-pregnant and younger population. Therefore, side effects and concerns in extremes of age and pregnancy are still to be decided.

Cost of vaccine, hesitancy, manufacturing capabilities, logistics, maintenance of cold chain, and transportation are other issues which may burden our country in terms of money and manpower in delivering vaccines to target population. (At the time of submitting of this article FDA has approved **Tozinameran** (BioNTech, Pfizer) on 11 December 2020, while on the same day Sanofi has postponed phase III trial due to poor antibody titer in people aged 50 years or more.)

Conclusion

This is an established fact that due to proper immunization of masses we have been able to either eradicate certain diseases like smallpox or polio or incidences of many communicable diseases like measles, pertussis, etc. have been brought to minimum. But due to lack of communication between people and HCP there has been apprehension and doubts in the mind of public at large which precludes them of using vaccines. Affordability of certain vaccines and Inertia on the part of HCP is another reason for underutilization of vaccination. The adverse effects of vaccines are so highlighted and dramatized by media (including social media) that it overshadows the efficacy of vaccinations. Need of the hour is to remove this misconception in mind of people with help of HCPs, Govt. agencies, media, etc. to help us overcome this menace as was done in case of polio and smallpox.

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CHAPTER

157 Infections in Critically ILL Patients

Nitin Sinha

Abstract

Critically ill patients are prone to many infections due to multiple interventions being carried out in them by means of indwelling catheters, endotracheal tube, etc. These infections lead to increased morbidity and mortality among critically ill patients. It is, therefore, imperative that these are recognized early and treated appropriately. More important than treating these would be to prevent them from occurring. This chapter deals with various infections in critically ill patients, their pathogenesis, diagnostic, and treatment guidelines and also the preventive guidelines.

Introduction

Critically ill patients are those who suffer from a critical illness that requires them to have intensive monitoring. This intensive monitoring entails them to have complete dependency on caregivers for their daily activities. These patients often are in coma/drowsy, mechanically ventilated, bed-ridden, and have many indwelling catheters. These factors make these patients prone to infections, which can be multi-drug resistant. This chapter deals with different infections that can occur in critically ill patients, their pathogenesis, and their preventive strategies.

Different Types of Infections Seen in Critically Ill Patients

Catheter-associated Infections

Pathogenesis and Risk Factors

Critically ill patients mostly have multiple catheters inserted. It may be urinary catheter, peripheral intravenous cannula, arterial catheter, or central venous catheter. These help in critical monitoring of the patient. In a certain survey in the United States, 87% of blood stream infections were associated with central lines. In the same survey, catheter associated urinary tract infection (CAUTI) was responsible for 95% of urinary tract infections.[1] Mortality attributable to central venous catheter-related infections is 12–25% and mortality attributable to CAUTI is less than 5%.[2]

A biofilm formation is critical in pathogenesis of catheter-associated infections. A biofilm is basically composed of a conditioning film (formed by the body fluid bathing the catheter) and the microbes that attach to it (sessile), which secrete an extracellular polysaccharide matrix on the condition film. This biofilm facilitates growth of microbes of different species and it is from here that some microbes become mobile (planktonic) and lead to infections. The biofilm leads to decreased penetration of antibiotics, local alteration in the microenvironment leading to decreased susceptibility to antimicrobials and antimicrobial resistance. Many microbiological culture results are only of planktonic organisms and these do not apply to sessile organisms embedded in the biofilm. It is because of this that sometimes antibiotics merely suppress the infection.[2]

The intravascular catheters get infected on their outer surface by the microbes present on the skin, especially within 10 days of the insertion. So, short-term intravascular catheters like peripheral intravenous cannula, arterial catheters, and non-cuffed central venous catheters mainly get contaminated on outer surface. The common organisms that migrate to outer surface of catheters from skin are coagulase negative staphylococci and *Staphylococcus aureus*. The hub of intravascular catheters gets contaminated by microbes that chiefly come from caregiver's hands. This especially occurs if the catheter is in situ for greater than 30 days or more. Intraluminal spread to catheter can also occur from a distant source (e.g., urinary tract) or from an infected infusate. Most common organisms implicated in these instances are *Stenotrophomonas*, *Candida*, *Pseudomonas*, enterococci. Immune compromised and elderly patients are more likely to develop contamination. Multilumen intravascular catheters and catheters inserted at femoral site are more likely to get contaminated. Internal jugular central venous catheter is more likely to get contaminated than the subclavian counterpart. Peripheral intravenous lines are more likely to get contaminated if inserted in lower extremities. Catheters inserted by non-sterile/improper techniques are more likely to get contaminated.[2]

The urinary catheter can also get externally contaminated either at the time of insertion or later by fecal matter. Intraluminal contamination can occur by reflux of microbes from the container bag or due to a break in collecting system. Commonly isolated organisms are *Escherichia coli*, *Pseudomonas*, *Enterobacter*, *Candida*, *Klebsiella*, and enterococci.[2] *Staphylococcous* and coagulase negative staphylococci have also been isolated. As with intravascular catheters, immune compromised patients are more likely to develop contamination. The other risk factors for developing bacteriuria in catheterized patients is longer duration of catheterization, diarrhea, female gender, renal insufficiency, improper catheter insertion technique, and improper catheter care.[3]

Diagnosis of Catheter-related Blood Stream Infection (CRBSI)

The Infectious Disease Society of America (IDSA) has published updated detailed guidelines for diagnosing intravascular CRBSI in 2009.[4] The commonly used terminologies for intravascular catheter-related infections are catheter colonization, phlebitis, exit site infection, and blood stream infections. The details regarding all these can be read from the guidelines. From the guidelines it was noteworthy that catheter tips should be cultured only quantitatively and not qualitatively and that catheters to be cultured only after removal.

Diagnosis of CAUTI

The 2009 IDSA Guidelines define CAUTI in catheterized (urethral, suprapubic, and condom) patients and in those in whom catheter (urethral, suprapubic, and condom) has been removed in last 48 hours by the presence of symptoms and signs of urinary tract infection with no other identified source of infection and having 1,000 or more colony-forming units (CFU)/mL of 1 or more bacterial species.[5]

Pulmonary Infections

Definitions, Etiological Agents, and Risk Factors

Pulmonary infections are major causes of mortality in critically ill patients. Among intubated patients, ventilator associated pneumonia (VAP) diagnosis is made if pneumonia develops 48 hours after intubation.[6] Any pneumonia other than VAP developing in hospital is called hospital-acquired pneumonia (HAP).[7] VAP occurrence rates are quite different in different studies. This is due to use of different diagnostic criteria, variations in study population, differential evaluation of radiological images, and different methods of sampling. Fever, leukocytosis, purulent secretions, new infiltrates on chest x-ray/worsening infiltrates on chest X-ray carry high sensitivity in suspecting VAP, but at the cost of low specificity. Clinical Pulmonary Infection Score (CIPS) of greater than 6 strongly suggests VAP.[8] Common risk factors for developing VAP are advanced age (>60 years), male gender, increased mechanical ventilation time (>2 weeks), prolonged hospital stay, altered consciousness, burns, comorbidities (diabetes, CAD, COPD, chronic renal failure, Hashimoto's thyroiditis), prior antibiotic use (leading to MDR pathogen infection), placement of gastric tubes, invasive procedures in ICU (reintubation, tracheostomy, fiberoptic bronchoscopy), smoking, raised intra-abdominal pressure, hypoxia, and gene polymorphisms (single nucleotide polymorphisms of TNFα gene, ATG16L1 gene, and TREM 1 gene). Commonly

organisms causing early VAP (occurring within first 4 days of hospitalization) are *Enterobacteriaceae* and *Staphylococcus aureus* and those causing late VAP are non-fermenting bacteria and *Enterobacteriaceae*. *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *E. coli,* and *Klebsiella* are commonly isolated. Mortality from early VAP is nearly 19% and that of late VAP is 31.4%.[6]

Common organisms causing HAP are *Pseudomonas aeruginosa*, *S. aureus*, *Klebsiella pneumonia*, *E. coli*, *S. marcescens*, *Stenotrophomonas maltophilia,* and *Acinetobacter baumanii*.[9]

Diagnosis of VAP and HAP7

Diagnosis of VAP should be made preferably by noninvasive sampling (endotracheal aspiration, spontaneous expectoration) rather than invasive sampling [protected specimen brush (PSB), bronchoalveolar lavage (BAL), and blind bronchial sampling (mini-BAL)]. Also, semiquantitative culture should be used for diagnosis. Diagnostic threshold for diagnosing VAP is more than 10^3 CFU/mL by PSB or more than 10^4 CFU/mL by BAL.

Dermatological Infections

Skin infections are also common in critically ill patients. In a study by Malheiro et al. in ICU patients, it was observed that immunosuppressive drug use, intravenous drug abuse, Type 2 diabetes mellitus, previous cutaneous or soft tissue infection (STI), HIV, cirrhosis, obesity, renal failure, etc. were risk factors for developing skin and soft tissue infections.[10] They, however, included patients with necrotizing fasciitis, abscesses and cellulitis only. Fournier's gangrene and cervicothoracic fasciitis were two most commonly observed fasciitis. Abscesses were commonest in cervical/thoracic region and cellulitis was observed in abdomen and lower limb. Myriad of organisms from *E. coli* to *Staphylococcus aureus*, Proteus, *Klebsiella*, etc. were isolated from different infection sites.

In a prospective analysis of ICU patients admitted due to surgical causes, 12.1% developed dermatological disorders out of which 28.8% had infectious dermatological lesions, 26% had dermatosis and 45.2% had drug reactions. Longer ICU stay (>10 days) was associated more with dermatological disorders. Comorbidities like diabetes, CAD, hypertension, etc. were commoner in patients who developed dermatological disorders. Wound infection was the commonest infection observed, frictions blisters were most commonly observed dermatoses, and maculopapular drug eruption was the commonest drug reaction observed.[11]

Almost similar findings (though with different proportions) were observed in patients admitted in Medical ICUs. The only difference from surgical ICU patients was that fungal skin infection was the most commonly observed infectious dermatological lesion. Mortality was significantly more in those who had dermatological lesions as compared to those who did not.[12]

Treatment

Treatment of any infection that develops in a critically ill patient depends upon the etiology, site, severity, and antibiotic sensitivity. Some infections like cellulitis, fasciitis may also require surgical intervention. Catheter removal might sometime need surgical assistance. Empirically started antibiotics must be according to the antibiogram of the hospital/institute.

Prevention of Infection in Critically Ill Patients

This is the utmost important part in critical care. Prevention is always better than cure.

Prevention of CRBSI[13]

Centre for Disease Control and Prevention has laid down extensive guidelines for prevention of CRBSI. Some salient points are:

- Staff should be adequately trained and educated regarding insertion, care, and removal of catheters.
- Peripheral catheters to be inserted in upper extremities.
- Use midline catheters/PICC line if duration of intravenous therapy is likely to exceed 6 days.
- Do not remove gauze dressing at insertion site daily. Palpate the site for any tenderness or swelling. Remove peripheral catheter if there are signs of phlebitis.
- Use subclavian site for central venous catheter (CVC) insertion for nontunneled catheters to minimize infection. There is no recommendation for site for tunneled CVC insertion.
- Use CVC with minimum ports.
- Remove CVC as soon as its use is over.

- Perform hand hygiene before and after catheter insertion, dressing, removal, guide wire change or catheter site palpation. This can be achieved by washing hands with soap and water or by applying alcohol based hand rubs (ABHR).
- Use maximum sterile barrier precautions (sterile gown/drape, sterile gloves, mask, and cap) while inserting arterial catheter, PICC, or CVC.
- Insert CVC preferably by using ultrasound.
- Clean skin with antiseptic (70% alcohol, tincture of iodine or alcoholic chlorhexidine gluconate solution) before peripheral venous catheter insertion. Prepare clean skin with more than 0.5% chlorhexidine preparation with alcohol before inserting CVC, PICC, or arterial catheter.
- Use 2% chlorhexidine wash for patients daily skin cleansing.
- Use a chlorhexidine/silver sulfadiazine or minocycline/rifampin-impregnated CVC if the catheter is likely to be in place for more than 5 days and only if the Central Line Associated Blood Stream Infection (CLABSI) rate is not decreasing despite using a comprehensive strategy, which at least should include these three components: educating persons who insert and maintain catheter, using maximum sterile barrier precautions (as detailed in point 9) and more than 0.5% chlorhexidine preparation with alcohol for skin preparation before CVC insertion.
- There is no need to use antibiotic prophylaxis while catheter is in-situ. Also, there is no need to use anticoagulation.
- Use antibiotic lock solution prophylaxis in patients who have long-term catheters and have history of multiple CRBSI despite optimal and maximal adherence to aseptic precautions.

Certain recommendations (apart from those mentioned above) in CDC guidelines were changed/added in 2017. The details can be checked from CDC website.

Prevention of CAUTI[14]

- Insert catheter only for appropriate indication and leave in place for only as long as needed. Even for operative patients, use catheter only if required.
- In males with bladder outlet obstruction/urinary retention, consider using external catheter in place of indwelling catheter. Intermittent self-catheterization can be done in patients with bladder dysfunction or with spinal cord injury.
- Catheterization to be done by well-trained persons and hand hygiene to be practiced prior to insertion or after any manipulation of the catheter. Sterile technique to be used for insertion of catheter which entails using sterile gloves, gowns, and sponges and cleaning of periurethral area with appropriate antiseptic solution. There is no need to use antiseptic lubricants routinely. Catheter needs to be secured adequately after insertion.
- Maintain a closed drainage system. Avoid kinking of catheter and collecting tube and ensure that collecting bag does not rest on the floor. Collecting bag to always be below the level of urinary bladder. Empty the container bag regularly using separate clean container. There is no role of systemic antibiotic prophylaxis while catheter is in-situ. There is again no role of putting antiseptic/antimicrobial solution in collecting bag routinely. There is no recommendation for using urinary antibiotic (methanamine). Routine use of any catheter with antibiotic release cartridge installed in the catheter's drain port is not necessary. There is no need to clean periurethral area with antiseptic solution daily when catheter is in place; cleaning of meatal area while daily bathing/sponging is sufficient.
- Use antibiotic impregnated catheters only, if CAUTI rate is not improving despite using a comprehensive strategy.
- Silicone catheter might be preferable over other catheter materials in long-term catheterized patients who have frequent obstruction as it prevents encrustations. Hydrophilic catheter might be preferable to standard catheter in patients requiring intermittent self-catheterization.

Prevention of VAP[15]

VAP can be prevented by following methods:

- Avoid intubation, if possible. Use noninvasive positive pressure ventilation (NIPPV).
- Minimize sedation. Try to give off to sedation once a day (awakening trial). Give spontaneous breathing trials. Try to club the two trials together.
- Provide early exercise and mobilization.

- Use endotracheal tubes with subglottic secretion draining ports if intubation is likely to last for greater than 48–72 hours.
- Elevate head end of the bed to 30–45 degrees.
- Change ventilator circuits only if visibly soiled.
- There are certain special approaches but they have insufficient data. These are selective oral or digestive decontamination, regular oral care with chlorhexidine, and use of prophylactic probiotics.
- Certain approaches like using ultrathin polyurethane cuff endotracheal cuffs, saline, automated control of endotracheal cuff pressure, saline instillation before tracheal suctioning, and mechanical tooth brushing have low quality evidence to prevent VAP.

Conclusion

Infections in critically ill patients can increase the morbidity and mortality in these patients. Appropriate preventive measures can curtail occurrence of such infections.

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CHAPTER

158 Current Controversies in Sepsis Management

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Abstract

Sepsis syndrome, a dysregulated host response in infection, has multimodality and multifaceted treatment which has been changing over the decades since its recognition. Advances in management of the syndrome brought along with it many controversies and failures in treating it. The advances made in treatment kept changing with emergence of newer definitions, its assessment scores, role of infusion and combination empiric antibiotic therapy. The prognostic value of biomarkers to guide duration of antibiotics, fluid therapy, its role in endothelial glycocalyx protection along with antioxidant therapy and steroids is being evaluated.

Introduction

Sepsis is a life-threatening syndrome of a dysregulated host response to infection. Despite advances in diagnosis and treatment, sepsis still remains a significant cause of morbidity and mortality. Many aspects of the diagnosis and clinical management of sepsis require further study and remain controversial. Relevant literature and controversies regarding the overall evaluation and management of sepsis and septic shock need to be revaluated time and again for management.

Newer Definitions of Sepsis and Its Impact on Diagnosis

The last two decades have seen ever changing definitions of sepsis, thus creating "more controversies" in the minds of bedside clinicians and emergency physicians. The changing clinical scenarios for the treating physicians at bedside further add to the already complicated issues of labeling the patient in sepsis. The effort to simplify the definition or criteria for defining sepsis, in recent times, has lead to increased diagnosis of this life-threatening syndrome of a dysregulated host response to infection. As of 1991, the initial definition stated that systemic inflammatory response syndrome (SIRS) to infection would be called sepsis. While subsequent revision of the definitions in 2001 specified the organ damage. Similarly, the new definitions 2016 defined it as a life-threatening organ dysfunction due to dysregulated host response to any infection. Later the role of Sequential Organ Failure Assessment (SOFA) was brought in where an organ dysfunction is assessed as an acute increase in total SOFA score by two points as a consequence of infection. Further adding to dilemma, the Sepsis-3 investigators introduced a new bedside index, called the quick Sequential Organ Failure Assessment (qSOFA). This was introduced to identify patients evolving into sepsis or could be in early sepsis in suspected infections. The qSOFA has just three easily measured physiological variables, that is, systolic arterial blood pressure ≤100 mm Hg, respiratory rate >21 breaths/min and altered mental status (GCS ≤ 13), with each receiving one point and range being zero to three. It is quite obvious that by these parameters there is a tendency to over diagnose sepsis in many patients having above

variables. As any two of these constitute a "positive" result and an indication that the patient is at risk of sepsis. The difficulty here is that it has a very low threshold (all that is needed is tachypnea and a slightly low blood pressure) to over diagnose sepsis. It needs to be understood that it is not a surrogate definition of sepsis but just an indication of increased risk.

Though this was a step to increase specificity of definition and has eliminated SIRS as was there in previous definitions, but it still has its own deficits. In absence of gold standard definition, the clinicians still adopt various parameters to diagnose sepsis by combining non-specific physiological and laboratory anomalies.

Similarly, the statement of definition as "life-threatening organ dysfunction caused by a dysregulated host response to infection" is more controversial in defining the terms like life-threatening, dysregulated, quantitative assessment of dysregulation.

Though the new Sepsis-3 definitions have reduced complexity, removed terms like severe sepsis, defined the role of qSOFA and has helped the emergency team categorize patients early into sepsis but still has major drawbacks. The controversies around microbiological confirmation, quantitative assessment of dysregulated syndrome, a syndromic approach, and over sensitivity of qSOFA remains to be further evaluated in bedside practices and epidemiological studies.

Sepsis or Septic—Is there a Difference in Assessment

The word "Sepsis" is being confused with "being septic." As understood over the decades, sepsis by definition is bacteriological culture positivity of disease in any previously sterile body tissues or blood. While the word Septic signifies presence of any viral, protozoan, fungal, or any other illness leading to a diseased state. While SIRS also included non-infectious cause's of sepsis syndrome. Simplicity of the term sepsis, defined as an invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms can never be disputed, in spite of the fact that a microbiological confirmation is difficult at times. All the definitions of sepsis do not differentiate or distinguish between viral, parasitic, and other causes of sepsis. Similarly, regional infections, which necessitate the treatment variations, also need to be catered to especially when planning the health-care policies of the region. This will specifically target and reduce the mortality and morbidity in a particular region due to endemic diseases causing critical illnesses.

Abandoning terms like severe sepsis, septic shock, MODS, and septicemia have further widened the difference in concept of ideal or specific management strategies of these illnesses. Emergency physicians need to think more broadly and initiate appropriate management strategy on the basis of differential diagnoses, which is important factor in management and this has obviously been neglected in initial resuscitation strategies. In our endeavor to simplify criteria, there is a deficit in understanding disease pathophysiology and its impact on management strategies. The practical guidelines for the management in accordance with specific etiologies and organ involvement need to be considered and managed accordingly.

Combination Empiric Antibiotic Therapy

Combination of antibiotics is usually initiated on a clinical diagnosis of sepsis and this is usually done with broad spectrum antibiotics, in optimal doses. This is done with a view to have maximal coverage with a perspective to de-escalate once the organism is recognized and antibiogram available for further management. Though there are both advantages and disadvantages of using combination therapy, but no measurable survival benefit has been seen on routinely using a combination therapy except in few instances. The current recommendations for combination therapy as per Surviving Sepsis Campaign are only meant for the neutropenic patients, patients with suspected multidrug resistant organisms especially (Acinetobacter or Pseudomonas) and respiratory failure with sepsis. Though the combination therapy, for many multidrug resistant Gram-negative sepsis infections, is essential, but this cannot be followed as rule in light of studies suggesting that combination therapy was only effective if the drugs were effective in vitro too. Thus negating the suggestion that combination was always logical, as together the combinations overcome the so-called target attainment minimum inhibitory concentration (MIC) threshold, despite in vitro resistance. The definite advantage of combination therapy in form of a broad spectrum of activity, reduction in development of drug resistance, and synergism can never be denied but all this adds to the risk of toxicity, super infections, and additional cost.

Antibiotics Infusion in Sepsis

Different antibiotics differ in their mechanism of action, and in the case of β-lactams, the time above the MIC (T > MIC) (i.e., the duration of time that the antibiotic concentration in the relevant tissue space exceeds the minimal inhibitory concentration required to kill the bacteria) is the critical pharmacokinetic characteristic that determines its efficacy. This makes it pharmacokinetically more effective if it is administered as a continuous infusion to optimize the T > MIC. Dulhunty et al. showed that continuous infusion improved the pharmacokinetics but it did not improve the ICU survival rate or the statistically significant clinical cure.[1] Similarly, the BLISS trial reached nearly, identical conclusions. A meta-analysis of 632 patients concluded that there was a statistically significant benefit of continuous infusion for both the clinical cure and its survival benefits. When this was analyzed by multivariate analysis the independent effect of continuous infusion was lost. Arguably it stands to reason that this intervention improves the clinical cure of infection, but as the survival of critically ill patient is a multifactorial variant thus the outcome may not be as expected in view of its dependency on various other factors.[2]

Biomarkers to Guide Duration of Antibiotics

Duration of an antibiotic therapy has always been based on the evidence of clinical course, cure, and the outcome of the infectious disease being treated. The duration of antibiotic therapy has been, as controversial as its initiation without a documented infection, and that too in critically ill patients. Though there is no conflict on the general principle that, it should be given for the shortest duration, but the exact duration of therapies have always been controversial except in few clinical conditions. The same holds for the patients being treated in critical care units.

The role of biomarkers in the last decade have changed the guidelines and treating principles, but the controversies in their potential use a sole criteria to guide a therapy also exist. The role of procalcitonin has been much studied, with over more than eight thousand papers defining its role in treatment of sepsis. The question which haunts any treating physician after the normal Procalcitonin report is whether the patient is infected and should an antibiotic be withheld. In case of abnormal reports even after adequate antibiotic therapy is whether the physician can de-escalate it. And obviously the answer stands to a good reason of clinical assessment.

As per recommendations of the Surviving Sepsis Campaign all biomarkers, including procalcitonin can be used by clinicians to assist him in withdrawal of antibiotics in septic patients especially those who have not been proven to have an infection on subsequent investigations after the initial therapy under septic bundle protocol therapy.

Procalcitonin

Among other biomarkers Procalcitonin has been advocated the most. Procalcitonin is up regulated by the cytokines that are secreted in bacterial infections in sepsis. Thus ideally it should not be used as guide in such patients, especially as a guide to decision-making regarding initiation of antibiotics. However, its use as in guiding de-escalation of antibiotic therapy after initial rise has more significance. All the studies, that is, PRORATA, ProGUARD, and SAPS trial's found a non-significant reduction in days of antibiotic use in their intervention arms, while the impact on mortality showed no differences. However, in view of false positive levels in non-infectious inflammatory diseases and false negative in severe infections clinical decision and judgment should always be used to override the importance of serum levels.[3]

Fluid Therapy and Its Role in Endothelial Glycocalyx Protection

As controversies in fluid resuscitation in sepsis and septic shock exist even after three decades of active management, it is still eluding the question whether, under or over resuscitation is beneficial or not for sepsis management.

Endothelial glycocalyx, an endothelial cell surface layer composed of membrane anchored proteoglycans and heparan sulfate, essentially acts as a endothelial barrier and opposes leukocyte-endothelial adhesion.[4] During sepsis, activation of heparanase in vessel wall leads to degradation of glycocalyx heparan sulfate thus furthering the endothelial dysfunction and injury caused due to sepsis. A hormone, released due to volume loading causing atrial stretching, that is, atrial natriuretic peptide furthers the degradation of endothelial glycocalyx, thus aggravating the septic vasoplegia. Though this phenomenon has not been explored much in humans,

but animal models have proved beyond doubt the amount of injury caused and the aggravation of the vasoplegia. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. As expected, injurious effects of fluid therapy following resuscitation would worsen the outcome primarily by causing microcirculatory dysfunction. The potential beneficial hemodynamic effects of fluid resuscitation, thus being negated. Several recent randomized trials have demonstrated such worsening of sepsis after initial bolus intravenous fluids.[5] The exact mechanisms by which such harm is caused need to be further evaluated and documented. Few studies also documented an association between volume of fluid used in resuscitation and intubation in high risk patients of heart failure, ESRD and Cirrhosis having sepsis. But similarly no differences in such events were detected in these patients who had received as per recommended guideline of 30 mL/kg of fluid for initial therapy.

Steroids in Sepsis

The immunosuppressive effects of steroids have harmful effect on severe sepsis but its role as anti-inflammatory and vasoactive substance cannot be denied. The controversies on the dose and duration are the most important issues in the management of sepsis. Though the harmful effects of high dose therapy have been well documented, but its therapeutic effects in low dose in sepsis are also less clear. The critical illness-related corticosteroid insufficiency has been well known. The ongoing efforts to prove the insufficiency as a diagnostic modality and the therapeutic options to correct have neither been proved or validated.[6] The two studies, CORTICUS in 2008 and HYPRESS in 2016, evaluated the low-dose hydrocortisone *versus* placebo for their role in sepsis. Both the studies could not show any survival benefit over 28 days. Corticus trial did show faster resolution of shock but there was a non-statically significant increase in infections within the corticosteroid arm. Various other trials also lacked the uniformity in proving efficacy of steroids with respect to improvement in the severity of shock; along with ideal time of initiation of this therapy.[7] Similarly, the duration and dose of therapy could not be ideally evaluated. The Surviving Sepsis Campaign guidelines in 2016 recommended the use of this therapy in septic shock refractory to fluid resuscitation. The meta-analysis of various studies showed reduction in 28-day mortality but such an effect could not be proven in all cause mortality in 90 days. Similarly, steroids therapy was associated with more-rapid resolution of shock and shorter duration of ICU stay. Therefore, in respect to above, an adjunct dose with 200 mg per day intravenous therapy was used in a study.[8]

Antioxidant Therapy with Vitamin C and Thiamine

Protective effects of vitamin C against oxidative-stress-mediated cell damage and organ dysfunction in sepsis and septic shock are well known.[9] Similarly, its deficiency has been observed in critically ill patients. During sepsis there is production of reactive oxygen species leading to endothelial injury and dysfunction, which is seen along with mitochondrial injury and both of these together lead to organ failure.

Antioxidant activity of vitamin C helps in scavenging free radicals prevents production of the reactive oxygen species, acts as a neuroprotector, and helps as cofactor for synthesis of vasopressors, thus reducing the oxidant injury to vessel walls in sepsis. As humans cannot synthesize vitamin C, there develops a state of hypovitaminosis due to increased vitamin C consumption and reduced recycling, which needs to be corrected. This deficient state can only be restored efficiently with parenteral high-dose administration.

Decrease in multi-organ failure and improvement in SOFA scores was documented in critically ill patients when treated with high dose of the antioxidants like vitamin C and E. Marik et al. in study concluded in 2017 that there was a significant decrease in mortality when vitamin C, hydrocortisone, and thiamine were used.[10] Two prospective trials are currently underway that may shed more light on the efficacy of vitamin C as a treatment for sepsis.

Similarly, thiamine levels are reduced in 20–70% of the septic patients, and this is associated with worse outcome. Thiamine deficiency decreases the activity of enzyme involved in aerobic glycolysis, Krebs cycle, and pentose phosphate pathway. These in turn lead to reduced ATP production. ATP helps in maintenance of cellular pH and preservation of neurotransmitters both of which are important for cellular metabolism in critical illnesses. Thiamine also helps in protecting the kidneys from oxalate nephropathy due to high-dose vitamin C. Thus, thiamine

played an important role in improvement of renal function without any impact on mortality.[11]

Hydrocortisone and vitamin C, both together improved the endothelial barrier and microcirculation, and therefore together they increase the production of catecholamines and thus augment its vasopressor effects. Vitamin C also restores glucocorticoid expression of the vitamin SVCT2 transporter thus in turn improving glucocorticoid receptor function.[12] And similarly both when combined showed higher in vitro barrier-protective effect after lipopolysaccharide exposure.[13]

Choice of Vasoactive Agents

Several vasoactive agents can be used to support perfusion in septic shock. Catecholamines and vasopressin both function by stimulation of cardiac contractility and/or peripheral vasoconstriction, depending upon individual mechanism of actions. The Surviving Sepsis Campaign suggests norepinephrine, a potent agonist of both alpha and beta receptors, as the initial vasopressor of choice in septic shock. Norepinephrine is an endogenous catecholamine that stimulates alpha and beta receptors, while dopamine an endogenous catecholamine stimulates dopaminergic alpha, and beta receptors. Initiation of vasopressor therapy after initial fluid resuscitation is done to achieve an adequate mean arterial pressure (MAP). Norepinephrine has been used as a first-line vasopressor agent for a long now.[14] As per the new recommendations, the vasopressors should not be delayed until fluid resuscitation is completed, but should be started rather early to achieve a target MAP of 65 mm Hg or more. During the recent decades, terlipressin, vasopressin V1A agonist, and even Ca^{2+} sensitizer have been increasingly used to treat septic shock. A meta-analysis of forty-three trials with 5,767 patients assessing seventeen treatment modalities showed vasopressor therapy with norepinephrine plus dobutamine to be most effective followed by norepinephrine plus epinephrine or terlipressin.[15] The studies have proved beyond doubt that norepinephrine should be used as a first-line treatment, but when followed by addition of dobutamine it would reduce the 28-day mortality. The serious potential adverse effect of precipitating ventricular and supraventricular arrhythmias needs to be actively monitored during its use especially with individuals having low-cardiac output due to impaired contractility.

Conclusion

Sepsis a multifaceted disease needs to be managed with simpler and universal guidelines, which are appropriate and can be delivered at all categories of health-care system. Initial approach needs to be aggressive and time bound even if diagnosis is underway as per clinical bedside guidelines and the clinical scenario. Initial resuscitation with fluids and in responsive patients the fluid therapy needs to be modified. Role of vasopressor is well documented and it should not be denied early in treatment with its weaning as per documented response. Initial antimicrobial therapy with a goal to target pathogens found in the suspected disease followed by change in antibiotics as per antibiogram and susceptibility should be done. Antimicrobial therapy guided by the relevant biomarkers reduction should be administered for a total duration of 7–10 days. Though, this can be of shorter or longer duration as per the clinical scenarios. Antioxidants and steroids have been documented to improve the outcomes and should be administered till further studies evaluate their role.

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CHAPTER

159 Viral Hemorrhagic Fever: Indian Perspective

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Abstract

Viral hemorrhagic fevers (VHFs) are a group of severe multisystem syndromes that are caused by several distinct families of viruses. Five distinct families of RNA viruses *Arenaviridae*, *Filoviridae*, *Bunyaviridae*, *Flaviviridae*, and *Paramyxoviridae* are well known for various VHFs in different geographic regions. The recent ongoing pandemic of SARS-CoV-2 Coronaviridae virus primarily presents with high-grade fever, cough, and breathlessness due to primary involvement of lungs. But COVID-19 has been found to have multisystem inflammation with Kawasaki Disease like presentation in children, human-to-human transmission, and thromboembolic phenomenon; therefore, it can be considered as emerging VHFs. The CDC-USA defines VHF as acute onset fever (>40°C) with any one of the following clinical finding: severe headache, muscle pain, erythematous maculopapular rash on the trunk with fine desquamation 3–4 days after rash onset, vomiting, diarrhea, pharyngitis (arenavirus only), abdominal pain, bleeding not related to injury, retrosternal chest pain (arenavirus only), and proteinuria (arenavirus only). VHF viruses spread in a variety of ways, but share some common pathogenic features. They have the potential for aerosol dissemination via respiratory droplets and are dependent on an animal or insect host for survival. These viruses are usually restricted to some geographic place of domicile of the host species. After the accidental transmission from the host, human-to-human transmission is possible in some viruses. The mortality rate is highly variable, 0.5% for dengue to 90% for Ebola virus disease. The VHF outbreaks cannot be easily predicted, as they are sporadic and irregular. The blood, urine, vomitus, pus, stool, semen, and saliva from the VHF patient are usually infectious. Barrier nursing practices (such as wearing personal protective equipment) help in reducing the risk of transmission to health-care workers. There is no specific treatment for majority of VHFs, except supportive care.

Introduction

The term "viral hemorrhagic fevers" (VHFs) depicts a group of diseases that are caused by several distinct families of viruses. In general, it is used to describe a severe multisystem syndrome.[1] The VHFs is mainly caused by six distinct families of RNA viruses *Arenaviridae* (lassa), *Filoviridae* (ebola), *Bunyaviridae* (Crimean-Congo hemorrhagic fever, CCHF), *Flaviviridae* (dengue), *Paramyxoviridae* (nipah), and Coronaviridae (COVID-19). The SARS-CoV-2 virus (family-coronaviridae) with the recent pandemic has shown to cause multisystem disease with respiratory illness as the primary organ involvement. The properties of multisystem involvement with Kawasaki like disease presentation, aerosol transmission, human to human spread, and various thromboembolic phenomenon reported from autopsy series, makes COVID-19 a new candidate for VHF. The SARS-CoV-2 virus has already spread to more than 216 countries and territories and was declared pandemic by WHO on March 11, 2020, it has already caused >550 million infections and 13 million deaths worldwide.

Though VHF viruses spread in a variety of ways, they share some common pathogenic features. They have the

potential for aerosol dissemination via respiratory route (except dengue), but they are dependent on an animal or insect host for survival. However, these viruses are geographically restricted to the place of domicile of the host species. After the accidental transmission from the host, human-human transmission is possible in some viruses. VHF may impair the blood clotting ability and can also damage the walls of small blood vessels.[2] The mortality rate of viral hemorrhagic fever ranges between 0.5–90%, depending on the pathologic agent.[3] The VHF outbreaks cannot be easily predicted, as they are sporadic and irregular.

Clinical Criteria for VHF

The Center of Disease Control (CDC), USA, has made the VHF definition (2010).[4] A person with acute onset disease with ALL of the following clinical finding:

- A fever >40°C, and
- One or more of the following clinical finding: Severe headache, Muscle pain, Erythematous maculopapular rash on the trunk with fine desquamation 3–4 days after rash onset, Vomiting, Diarrhea, Pharyngitis (arenavirus only), Abdominal pain, Bleeding not related to injury, Retrosternal chest pain (arenavirus only), Proteinuria (arenavirus only).

The predominant signs and symptoms noted in common VHFs are listed in **Table 1**.[5]

TABLE 1 Predominant signs and symptoms noted in common VHFs

Disease	*Signs and symptoms*
Ebola virus disease	Fever, headache, muscle pain, fatigue, weakness, diarrhea, vomiting, abdominal pain, conjunctival injection, chest pain, hemorrhage
Marburg virus disease	Fever, chills, headache, muscle pain, maculopapular rash, nausea, vomiting, chest pain, sore throat, abdominal pain, diarrhea, jaundice, hemorrhage
Lassa fever	Fever, nausea, vomiting, diarrhea, retrosternal chest pain, sore throat, muscle pain, enlarged cervical lymph nodes, abdominal pain, bleeding, maculopapular rash, conjunctivitis, headache
Crimean-Congo hemorrhagic fever	Fever, headache, back pain, join pain, abdominal pain, vomiting, conjunctival injection, facial flushing, petechial rash, jaundice, bleeding, photophobia, sore throat

Ebola Virus Disease

Ebola virus disease (EVD) is a rare, but deadly disease commonly affecting humans and non-human primates. The EVD viruses are mainly located in sub-Saharan Africa and their periodic emergence has caused several outbreaks in African countries. The EVD gets transmitted to humans through direct contact with an infected animal (bat or non-human primate) or a sick or dead person infected with the virus. Ebola virus was first described in 1976 near the Ebola River, which currently belongs to the Democratic Republic of Congo (formerly Zaire).

In 1995, an outbreak of Ebola hemorrhagic fever affected more than 300 people in and around the city of Kikwit, Democratic Republic of the Congo. The outbreak caused the death of approximately 80% of the patients and more than one-fourth of all the patients were health-care workers.[6] The 2014–2016 outbreak of EBV caused a mortality rate of up to 80–90%, and the death of many health-care workers were due to human-to-human infection.[7] On March 23, 2014, the World Health Organization (WHO) reported the EBV disease within the forested rural region of southeastern Guinea. It was the beginning of the West Africa Ebola epidemic, the largest in history. On August 8, 2014, WHO declared the Public Health Emergency of International Concern (PHEIC), which is designated only for events with a risk of potential international spread or that require a coordinated international response.[7] Over the duration of the epidemic, the disease had spread to seven more countries: Italy, Mali, Nigeria, Senegal, Spain, UK, and the US.

EBV: Ecology and Transmission

Humans get initially infected with EBV through contact with an infected animal, such as a fruit bat or non-human primate. This is called a spillover event. After the spillover event, the virus can spread from person to person through the following routes:

- Direct contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth)
- Blood or body fluids (urine, saliva, sweat, feces, vomit, breast milk, and semen) of a person who is sick with or has died from EVD
- Objects (such as needles and syringes) contaminated with body fluids from a person sick with EVD or the body of a person who died from EVD

- Infected fruit bats or non-human primates (such as apes and monkeys)
- Semen from a man who recovered from EVD (through oral, vaginal, or anal sex)
- Handling and consumption of bushmeat (wild animals hunted for food)

There is no treatment for EBV and only supportive management can be adopted. Ebola survivors mostly complaint of myalgia and muscle pain even after treatment.

Dengue Fever

Dengue fever, the most important mosquito-borne viral disease with global epidemic potential, occurs mainly in tropical and subtropical areas of the world. The virus is transmitted to humans through the bites of infected female mosquitoes of the species *Aedes aegypti*.[8] It is a mild to fatal disease with no cure and only palliative care. The following factors have contributed to the emergence of dengue as the classic disease of 21st century: urbanization, increase in travel/trade, highly efficient and adaptive mosquito vector, thriving of larvae and adults in urban areas, inability to avoid day biting of *Aedes* vectors, and difficulty in effectively implementing environmental vector control.

A 30-fold increase in the dengue cases has been recorded globally during the past 50 years, and it is associated with substantial social and economic burden.[9] An average dengue episode results in a loss of 14.8 days for ambulatory patients, at an average cost of USD 514. However, the mortality rate is less than 0.5%, and it is asymptomatic in nearly 80% of the subjects.

The first evidence of occurrence in India was reported in 1956 from Vellore district in Tamil Nadu. In 1996, one of the most severe outbreaks of dengue fever occurred in Delhi, with 10,252 reported cases and 423 deaths. In 2006, the country witnessed an outbreak of dengue fever with 12,317 cases and 184 deaths. During 2014, a total of 40,571 cases were reported, which increased to 1,29,166 in 2016 and 1,88,401 in 2017.

Clinical Presentation

The clinical presentation of dengue progresses through the following three phases:

- Febrile phase (4–7 days after exposure): Headache, eye pain, nausea/vomiting, myalgias, arthralgias, and macular rash
- Critical phase (may develop following resolution of febrile phase, lasts 24–48 hours): Shock, hemorrhage, organ failure, and acute respiratory distress syndrome (ARDS)
- Recovery phase: Clinical stabilization, may develop confluent rash

Diagnosis and Management

Initial diagnosis may be established by clinical suspicion. Serum RT-PCR or viral antigen testing within first week of illness, followed by enzyme-linked immunosorbent assay (ELISA), may assist in concluding the diagnosis.

The national vector borne disease control program (NVBDCP) 2014 guideline revised the case definition and made a new classification with moderate dengue **(Flowchart 1)** and guidelines also modified clinical management of severe dengue with bolus fluid regimen. The bolus infusion of 10–20 mL/kg crystalloid infusion and frequent monitoring drastically reduced mortality in dengue patients with profound shock **(Flowchart 2)**.[10]

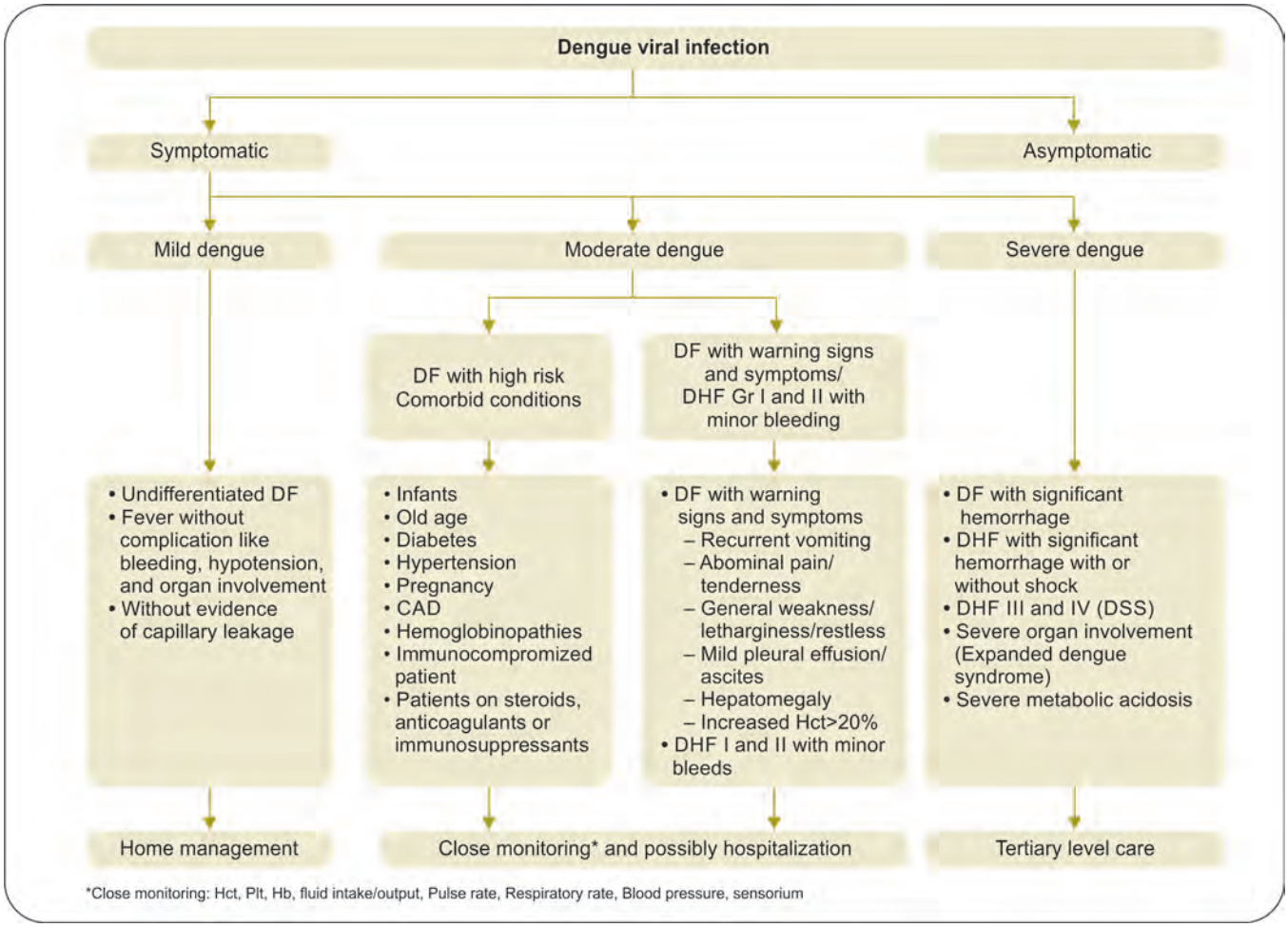
Chikungunya Fever

Chikungunya virus is a self-remitting febrile viral illness transmitted through the bite of infected mosquito *Aedes aegypti*.[11] The clinical presentation includes acute infection, high-grade fever, polyarthralgia (typically bilateral/symmetric, distal > proximal joints), and macular rash. The severe complications are meningoencephalitis, respiratory failure, renal failure, hepatitis, hemorrhagic, and heart failure/cardiomyopathy. The disease can be diagnosed by RT-PCR or serology. Testing for dengue and Zika can also be considered. Management includes supportive care and fluid therapy. Aspirin and other non-steroidal anti-inflammatory drugs should be avoided to reduce the risk of hemorrhage, until patient is afebrile for 48 hours, and there are no additional warning signs for dengue.

Zika Virus Infection

Zika virus is spread mostly through the bite of an infected *Aedes* species mosquito (*Aedes aegypti* and *Aedes albopictus*). Common symptoms of Zika infection include fever, pruritic rash, and arthralgia.[12] The severe complications of the disease are Guillain-Barré syndrome and neurologic complications including encephalitis and transverse myelitis. The recent ongoing outbreak

Flowchart 1: The NVBDCP dengue case definition[10]



in Madhya Pradesh and Rajasthan (Oct-Nov, 2018) has claimed two lives. Diagnosis and management strategies are similar to that of dengue and chikungunya.

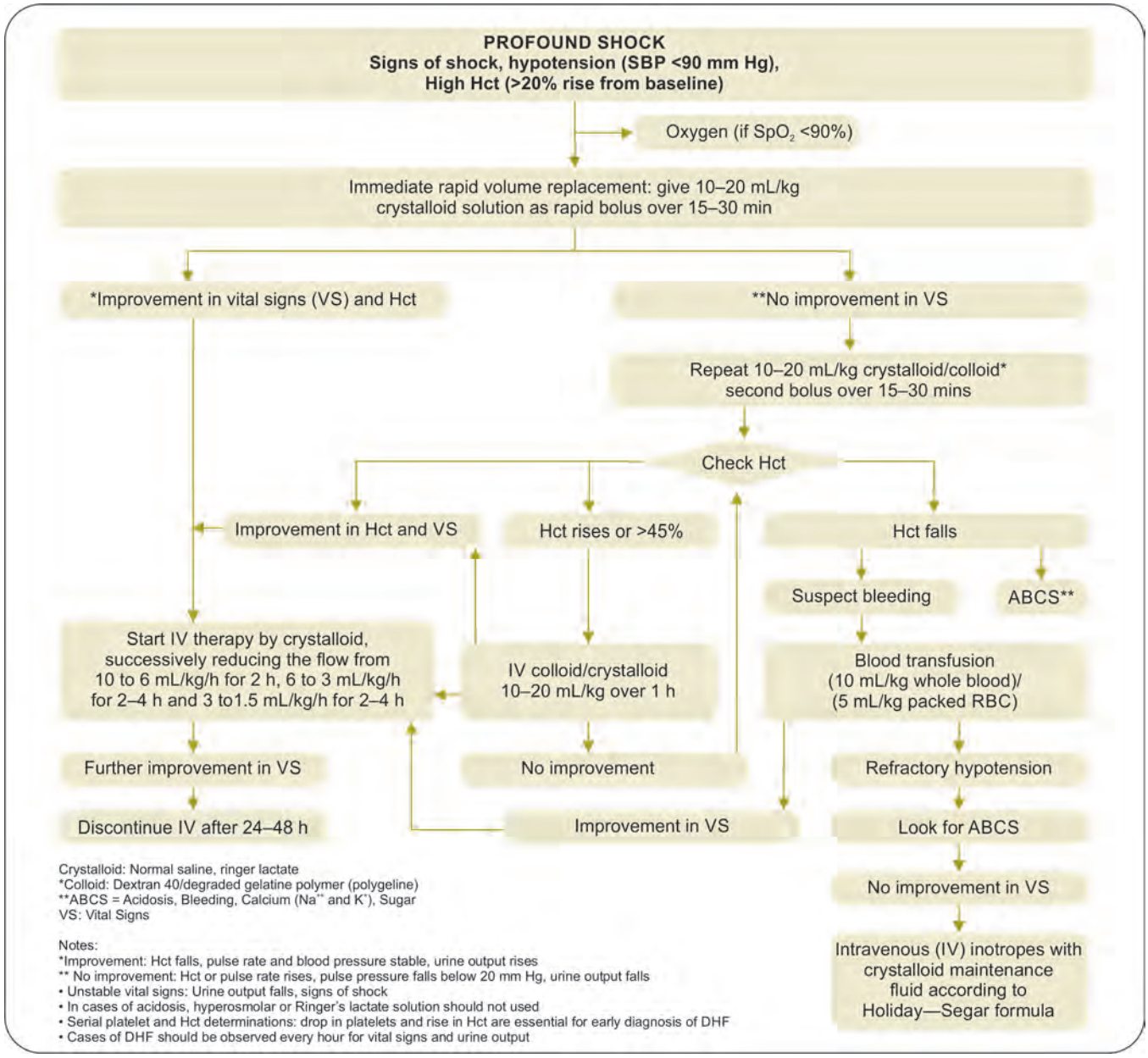
Crimean-Congo Hemorrhagic Fever

Crimean-Congo hemorrhagic fever (CCHF) is caused by a tick-borne virus (Nairovirus) belonging to the family *Bunyaviridae*. The disease is usually seen in Crimea, Africa, Europe, and Asia; and human-to-human transmission occurs through direct contact with infectious blood/body fluids. In India, the first confirmed case of CCHF was reported during a nosocomial outbreak in Ahmadabad, Gujarat, in January 2011. The outbreak claimed the death of 3 health-care workers due to multiple organ failure, specifically failure of the liver and kidney. During the period of 2012–2015, several outbreaks of CCHF infections were reported in the states of Gujarat and Rajasthan.[13]

Kyasanur Forest Disease

Kyasanur forest disease virus (KFDV) was first identified in 1957 when it was isolated from a sick monkey from the Kyasanur forest in Karnataka (formerly Mysore) state, India. Since then, around 400–500 human cases per year have been reported. KFDV is a member of the virus family *Flaviviridae*. Hard ticks (*Haemaphysalis spinigera*) are the reservoir and rodents, shrews, and monkeys are common hosts for KFDV. The disease is endemic to South Asia and the human transmission may occur after a tick bite or contact with an infected animal. No person-to-person transmission has been reported.

Flowchart 2: Volume replacement algorithm for patient with dengue with profound shock[10]



The disease begins with chills, fever, and headache. Severe muscle pain with vomiting, gastrointestinal symptoms, and bleeding problems may occur 3–4 days after initial onset of symptoms. Patients may experience abnormally low BP, low platelets and red blood cells, and leucopenia. However, after 1–2 weeks of symptoms, some patients recover without complications.

Nipah Infection

Nipah virus (NiV) infection is an emerging zoonotic disease of public health importance in the WHO Southeast Asia region. The possible routes of transmission include consumption of fruit contaminated by the saliva of infected bats, from direct contact with infected bats or their feces/urine. NiV was first recognized in 1998–1999

during an outbreak among pig farmers in Malaysia and Singapore, and it was first recognized in India and Bangladesh in 2001. In July, 2018, a total of 19 NiV cases, including 17 deaths, were reported from two districts in Kerala state (Kozhikode and Malappuram).[14]

COVID-19

The recent outbreak of COVID-19 in Wuhan city, Hubei province, China caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) mainly leads to the respiratory illness. The virus is transmitted mainly by respiratory droplets[15] and causes mild symptoms (asymptomatic/fever/cough/myalgia/sore-throat/anosmia) to severe symptoms (ARDS, shock, respiratory failure, multi-organ dysfunction) and deaths. The COVID-19 can cause some cutaneous manifestations which can be grouped into five major clinical patterns:

- Acral areas of erythema and edema with vesicles or pustules (pseudo-chilblain),
- Vesicular eruptions,
- Urticarial lesions,
- Maculopapular lesions,
- Livedoid or Necrotic lesions.

This is significant as it tells about the severity with pseudo-chilblains in mild disease to livedo-necrosis in severe disease.[16] The current epidemiological update by WHO for COVID-19 (30th October, 2020) showed 4,48,88,869 confirmed cases and 11,78,475 confirmed deaths. The diagnostic laboratory studies are rtPCR, rapid antigen testing, Antibody Testing (IgG,IgM), viral culture, computed tomography, chest X-ray. Laboaratory tests of serum LDH, CRP, Serum Ferritin, D-Dimer, and CBC may be helpful in severe diseases with cytokine storm. The various antiviral therapies are only approved as emergency use authorization with no survival benefit. Steroid and oxygen therapy have been found to be effective in reducing mortality in hypoxic patients with moderate to severe COVID-19 (SpO_2 <95%). The general measures for infection control: handwashing, wearing masks, social distancing, and isolation of infected individuals have been found to be effective in controlling the infection in hospital and society.

Differentiating COVID-19 from other tropical disease (dengue/chikungunya) is a challenge for clinician. Similarly, coinfection of COVID-19 with other VHF dengue fever etc. is another big problem in endemic regions of vector borne diseases **(Table 2)**.[18]

Management of VHF

VHFs are a group of distinct RNA viral diseases and it needs individualized care. The EVD has the highest mortality rate, while COVID-19 disease has affected maximum number of countries and population. The blood, urine, vomitus, pus, stool, semen, and saliva from the VHF patient are infectious. Barrier nursing practices (such as wearing protective clothing) help in reducing the risk of transmission to health-care workers.

No specific treatment, except supportive care, is available in most of VHFs. Correction of coagulopathies is needed. Antiplatelet drugs and IM injections are contraindicated due to the risk of hemorrhage. Investigational treatment approaches include ribavirin for 10 days for *arenaviridae* and *bunyaviridae*, and convalescent plasma within 8 days of onset for alkhurma hemorrhagic fever. Upon percutaneous/mucocutaneous exposure to infected blood or body fluids, wash thoroughly with soap and water, and irrigate mucous membranes with water or saline. Medical surveillance for all potentially exposed persons is needed for up to 21 days in ebola infection. The surveillance measures include: reporting hemorrhagic symptoms, recording fever 2×/day, reporting temperatures ≥101°F (38.3°C), and initiating presumptive therapy.

Viral hemorrhagic infection can be prevented using N-95 mask or powered air purifying respirator (PAPR). Keeping the patient in negative pressure room and using personal protective equipment (PPE) while handling the patient are essential. The health-care workers should be trained on the use of PPE.

Assessment for VHF Risk

The following CALM (Consider, Act, Laboratory, Monitor) algorithm is used to assess the risk of VHF infection in travelers:

- *Consider:* Travelers return from a region endemic for and/or currently experiencing VHF outbreaks are considered infected.
- *Act:* Isolate the patient. Limit the health-care workers who enter the room. Appropriate PPE should be

TABLE 2 Differentiating clinical features between COVID-19 and other similar viral diseases[17]

	COVID-19	*Dengue*	*Chikungunya*	*Seasonal influenza*
Incubation period and onset	Ranges 2–14 days (onset of symptom average 5–7 days). Acute onset of low-to-moderate grade continuous fever	Ranges 3–14 days (onset of symptom average 4–7 days). Acute onset of high-grade continuous fever	Ranges 1–12 days (onset of symptom average 3–7 days). Acute onset of moderate-to-high grade continuous fever	Ranges 1–4 days (onset of symptom average 2 days). Acute onset of moderate-to-high grade continuous fever
Clinical presentation symptoms	Cough, dyspnea, fever, myalgia, headache, sore throat, diarrhea, abdominal pain, anosmia, ageusia, fatigue, confusion	Fever, headache, Nausea, vomiting, retro-orbital pain, myalgia, arthralgia, rash, bleeding	Fever rash malaise arthralgia myalgia red eyes	Fever, cough, sore throat, and nasal discharge, headache, myalgia and malaise
Signs	Tachypnea, decreased oxygen saturation, multi-organ involvement	Signs of hypotension and shock, hemorrhagic manifestations (petechiae), positive tourniquet test	Swelling and tenderness of joints	Pharyngeal wall hyperemia, cervical lymphadenopathy
Warning signs	Respiratory distress SpO_2 <94%	Persistent vomiting, abdominal tenderness, fluid accumulation, mucosal bleed	High grade fever, progressive increase of myalgia and arthralgia	Respiratory distress SpO_2 <94%
Complications	ARDS arrhythmias acute cardiac injury shock pulmonary embolism shock acute stroke	Hypotensive shock, bleeding, organ involvement, metabolic derangement	Respiratory failure, cardiovascular decompensation, myocarditis, acute hepatitis, renal failure, hemorrhage, meningoencephalitis acute flaccid paralysis GBS	ARDS myositis rhabdomyolis acute MI myocarditis pericarditis encephalitis myelitis GBS

worn by all personnel entering the patient's room. Immediately notify your state/local health department.

- *Laboratory:* Inform the laboratory. Decision to test for VHF should be made in consultation with relevant health department/CDC viral special pathogens branch.
- *Monitor contacts:* Facilities should maintain a log of all the persons entering the patient's room, including full name and contact information.

Conclusion

VHF is a diverse group of illnesses caused by RNA viruses belonging to various viral families. Though, the diseases differ by geographic occurrence and vectors/reservoirs, they share some common clinical features. The diseases are considered as having international health risk due to their potential for aerosol dissemination and human-to-human transmission. Management is only through supportive treatment. Infection control in health-care workers and relatives is of utmost importance. Surveillance of returning travelers by CALM algorithm is important to prevent any outbreak in other geographic area.

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CHAPTER

160 Antimicrobial Stewardship in Clinical Practice—Role of Biomarkers

Anupam Dey

Abstract

Antimicrobial stewardship focusses on interventions to improve and measure the appropriate use of antimicrobial agents. To fight antimicrobial resistance, timely diagnosis of infections, justifiable use of drugs, and avoidance of antimicrobial overprescribing and overuse are of paramount importance. Novel biomarkers aid in this process and are thereby gaining prominence. Biomarkers may be included into clinical guidelines to make their roles clear. This chapter discusses various biomarkers specific to bacterial, viral, and fungal infections which can be used for point of care testing. Biomarker based clinical algorithms prepared using regional data will help in clinical decision-making, thereby aiding rational prescription of antimicrobials.

Introduction

Antimicrobial stewardship is defined as "coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration."[1]

In the background of increased incidence of antimicrobial resistance throughout the world, antimicrobial stewardship programs are focusing on timely diagnosis of infections and the justifiable use of drugs. Frequently, ignorance of the etiology of infection leads to antimicrobial overprescribing and overuse. This diagnostic dilemma may also result in late initiation of antimicrobial therapy and poor outcomes. Recently new biomarkers have been used to help making a clinical diagnosis. Novel biomarkers are an important addition in the repertoire of antimicrobial stewardship program, to aid in timely diagnosis and appropriate antimicrobial use.

In one estimate from the USA it was observed that close to 50% of antibiotic prescriptions in the outpatient scenario were avoidable,[2] thus leading to unnecessary expenditure, antibiotic resistance, adverse drug reactions, and secondary infections with Clostridium difficile. Rapid biomarker testing is need of the hour. However, till now the rules for integrating biomarkers in antibiotic prescription decisions are not well known. Defined reference values for bacterial infections are often absent, thus affecting the sensitivity and specificity of biomarkers.[3] Use of biomarkers may be included into clinical guidelines to make their roles clear. This will be particularly helpful in the primary care setting where patient turnover is quite high and antibiotic prescription is widespread.[4,5]

Biomarkers

The following biomarkers will be discussed further and their use particularly for suspected pneumonia or sepsis will be defined:

- Bacterial—C-reactive protein (CRP), procalcitonin (PCT)
- Fungal—1,3-beta-D-glucan (BDG), *Candida albicans* germ tube antibody (CAGTA), and Galactomannan (GM)

- Viral markers—Myxovirus resistance protein A (MxA)
- Others—Adrenomedullin (ADM), Triggering receptor on myeloid cells 1 (TREM 1), Urinary clusterin, etc.

Bacterial Infection Biomarkers

C-reactive Protein

An acute phase reactant that indicates inflammation due to multiple causes. Use of CRP in differentiating between bacterial and viral etiology has been studied widely. It has been proven that CRP is very sensitive in identifying infections of bacterial etiology and thus helps in taking decision on instituting antibiotics.[6]

In a study of patients in Vietnam suffering from acute respiratory tract infections it was found that using CRP threshold of 20 mg/L in adults, there was reduction of antibiotic prescription from 78% to 64%. Similarly, in primary care setting, rapid CRP testing with a threshold of 40 mg/L resulted in a significant reduction in antibiotic prescription.[7,8]

Procalcitonin

PCT is an amino acid prohormone of calcitonin. On exposure of body to bacterial toxins, serum PCT becomes detectable in blood. Interferon-gamma released in viral infection downregulates its release. Other inflammatory states usually do not affect the serum concentrations of PCT. False positive increase of levels have been seen in burns, post-surgery, trauma, and renal dysfunction. False negative results may occur in too early testing or in loculated infections.[9]

Role in Respiratory Tract Infections

PCT has been used as a tool to help in diagnosis of bacterial pneumonia when there is clinical dilemma or negative culture results. Serial PCT concentrations have helped in deciding escalation/de-escalation/discontinuation of antimicrobial therapy. Various guidelines (Surviving Sepsis guidelines and IDSA) recommend repeating PCT levels serially to decide duration of antibiotic therapy in critically ill patients.[10] Standard reference value of PCT in adults is usually 0.15 ng/mL or less. PCT rises within 2–6 hours and peaks at 12–24 hours.[2,11]

Role in Sepsis

Meta-analyses have established PCT as superior to CRP for the diagnosis of sepsis. Levels of 1–2 µg/L are considered for diagnosis of sepsis.[12] Serial PCT measurements should be taken in sepsis and levels of less than or equal to 0.5 µg/L should signal the need for discontinuation of antibiotics.

From available literature, use of PCT for antibiotic stewardship in respiratory infections (specially LRTI) has been found to reduce initial prescription of antibiotics by 40–50% in emergency patients and by 70–80% in ambulatory patients. It has also reduced antibiotic prescription in pneumonia (CAP) by 40–50%.[13-15]

Fungal Infection Biomarkers

Detection of invasive candidiasis is challenging. High cost of new antifungals adds to the problem. Traditional culture methods are unable to detect close to 50% of cases. Thus, fungal infection biomarkers may improve patient outcomes.[16]

1,3-beta-D-glucan

BDG is a component of the cell wall of most fungi including Candida species. Elevated levels in blood can act as a biomarker to diagnose candidemia or invasive fungal infection and thus rationalize antifungal administration. False-positive results can be found with intravenous immunoglobulin, intravenous albumin, certain hemodialysis filters, and with some antibiotics. Serial BDG assays have a greater negative predictive value thereby guiding discontinuation of empirical antifungal therapy.

Candida Albicans Germ Tube Antibody

Candida albicans germ tube antibody can be released during invasive candidal infection. Its sensitivity and specificity to detect invasive candidiasis has been reported as more than 75% and more than 90%, respectively.[17] Although study results are variable, CAGTA with or without BDG can aid in diagnosis of invasive candidiasis. However, the utility of CAGTA on course of illness is debatable.[18]

Galactomannan

Blood assay for GM has improved detection of invasive aspergillus infection at an early stage, particularly among the immunocompromised. Sensitivity and specificity of this marker are more than 70% with cut-off value of 0.5.[19] The IDSA guidelines recommend use of GM for prompt diagnosis of invasive aspergillus infection especially in

patients with hematological malignancy or post-stem cell transplant state.[20]

Viral Infection Biomarkers

Viral (Myxovirus Resistance Protein A)

Myxovirus resistance protein A is induced by interferons and is specifically elevated in patients with viral infections. It has the potential to allow rapid differentiation between viral and bacterial respiratory infections. In combination with CRP or PCT, elevated levels of MxA can help identify patients with likely viral infection, thus helping antibiotic stewardship activities.[21]

Other Biomarkers

Adrenomedullin

ADM is a peptide hormone. Its half life is very less; hence pro ADM (cut-off values 3.5–5.5 nmol/L) is often measured clinically. ADM has been used clinically as a mortality predictor and prognostic marker in inflammation and particularly in Community acquired Pneumonia.[22] Increased ADM concentrations will indicate increased severity and mortality in SIRS and septic shock. Pro-ADM may be better in this regard.

Triggering Receptor Expressed on Myeloid Cells 1

TREM 1 is an immunoglobulin expressed on the surface of macrophages, neutrophils, and monocytes. Phagocytes release soluble TREM 1 (sTREM 1) on stimulation, which acts as a marker of infection specifically for pneumonia and sepsis.[23] Measurement thresholds are 725 pg/mL to diagnose sepsis (sensitivity up to 70% and specificity up to 60%),[23] and 5 pg/mL in the diagnosis of pneumonia (sensitivity of 98% and specificity of 90%).[24]

Urinary Clusterin

Its use has been studied as a biomarker of nephropathia epidemica (a type of hemorrhagic fever with renal syndrome) caused by Puumala virus infection.[25]

Methicillin-resistant *Staphylococcus Aureus* (MRSA) Nasal Screens

It can be used in de-escalation of MRSA therapy, mainly in patients with suspected or confirmed pneumonia. The ATS/IDSA guidelines endorse the routine use of MRSA nasal PCR screening for the de-escalation of MRSA coverage. This has been shown to allow a median decrease of 2.1 days of vancomycin therapy.[26]

Other Potential Bacterial Biomarkers in Development

These are Amyloid A, Liposaccharide binding protein, Interleukin-10, and nCD64.[27]

Conclusion

Point-of-care biomarker testing allows rational antimicrobial use. Stewardship programs should analyze regional data of local population for using biomarkers in clinical decision-making. More regional studies are required for preparing biomarker based clinical algorithms.

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CHAPTER

161 Misutilizing Medicine for Biological Warfare

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Abstract

Biological Warfare is the intentional use of biological agents to cause morbidity and mortality in humans. The Bioweapons, those used in wars and by terrorist groups are attractive because of their ability to produce wide range of diseases, low production costs, no easy accessibility by routine security systems, and their easy transport from one place to another. In addition, after development of novel technologies that are primarily designed for use in early diagnosis and treatment and decreases the burden of diseases and its consequences on humans health, but this development of medicinal novel technology has often been used in wrong direction to produce more Bioweapons which ultimately threaten the well-being of the whole mankind.

Introduction

From ancient ages to modern era, history reveals there were multiple number of biological wars among persons, among states, and among nations to empower over others. There was an intention behind use of biological agents like microorganisms, and toxins, generally of microbial, plant, or animal origin to produce not only disease and/or death in humans and damaging live stocks and crops but also to create fear, panic, and paralyze uncertainty.

To protect this there were developments of biodefense in the form of biological weapons convention from time to time, but still there is continuous research on development of bio-weapons by the nations. Now for protection against biological warfare each nation continued research along counter measures, including vaccines and antisera.

Definitions

Bioterrorism: It is an action by a non-state actor to achieve a political, ideological, or religious goal. (Desire to terrorize as much or more than causing casualties.)[1,5]

Biocrime: Biological agent used by a person/group against a person/small group often for revenge or extortion.[1]

Biological warfare: A state actor uses a biological agent as part of its armamentarium in waging war.[1,5]

Biological agents: Biological agents (bio-weapons) are living organisms or replicating entities (viruses) that reproduce or replicate within their host to cause harm.[2,3]

CDC category[4] of biological agents:

- *Category A:* These are high priority agents that easily disseminated or transmitted from person to person with high mortality rates. With a potential for major public health impact, might cause public panic and social disruption.
- *Category B:* Second highest priority. These are moderately easy to disseminate. They have moderate morbidity rates and low mortality rates. These agents require specifically enhanced diagnostic capacity.
- *Category C:* Emerging pathogens that could be engineered for mass dissemination in the future because of availability, ease of production, and

TABLE 1 CDC categories of biological agent

Category A	*Category B*	*Category C*
Anthrax (*Bacillus anthracis*)	Psittacosis (*Ch. psittaci*)	(Emerging infections)
Botulism (*Cl. botulinum* toxin)	Epsilon toxin of *Cl. perfringens*	Hantavirus
Plague (*Yersinia pestis*)	*Melioidosis* (*B. pseudomallei*)	SARS coronavirus
Smallpox (*Variola major*)	Glanders (*Burkholderia mallei*)	Pandemic influenza
Tularemia (*Francisella tularensis*)	Food safety threats (e.g., *Salmonella* spp., *E. coli* O157; H7, *Shigella*)	Nipah
Viral hemorrhagic fevers: Lassa, New World (Machupo, Junin, Guanarito, Sabia), Crimean Congo, Rift Valley, Ebola, Marburg	Viral encephalitis [alphaviruses (e.g., Venezuelan, eastern, and western equine encephalitis)]	
	Brucellosis (*Brucella* spp.)	
	Q fever (*Coxiella burnetii*)	
	Ricin toxin from Ricinus communis (castor beans)	
	Staphylococcal enterotoxin B	
	Water safety threats (e.g., *V. cholerae, Cr. parvum*)	

dissemination and potential for high morbidity and mortality rates and major health impact.
The category and agents are shown in **Table 1**.

Anthrax (*Bacillus anthracis*)[6]

- The most misused agent in biological warfare
- Rout of transmission: By cutaneous and inhalation
- Signs and symptoms:
  - Prodermal—fever, headache, tiredness
  - Cutaneous (95%)—pustules, eschar **(Figs. 1A to C)**
  - Pulmonary (5%)—cough, chest pain, dyspnea

Diagnosis:
- Skin biopsy for cutaneous lesions
- Blood culture
- ELISA, PCR
- Chest X-ray- widened mediastinum (Hilar and mediastinal lymphadenopathy) with or without infiltrate and pleural effusion **(Figs. 2A and B)**

Treatment:
- Ciprofloxacin, Penicillin, Doxycycline
- Treated for 60 days

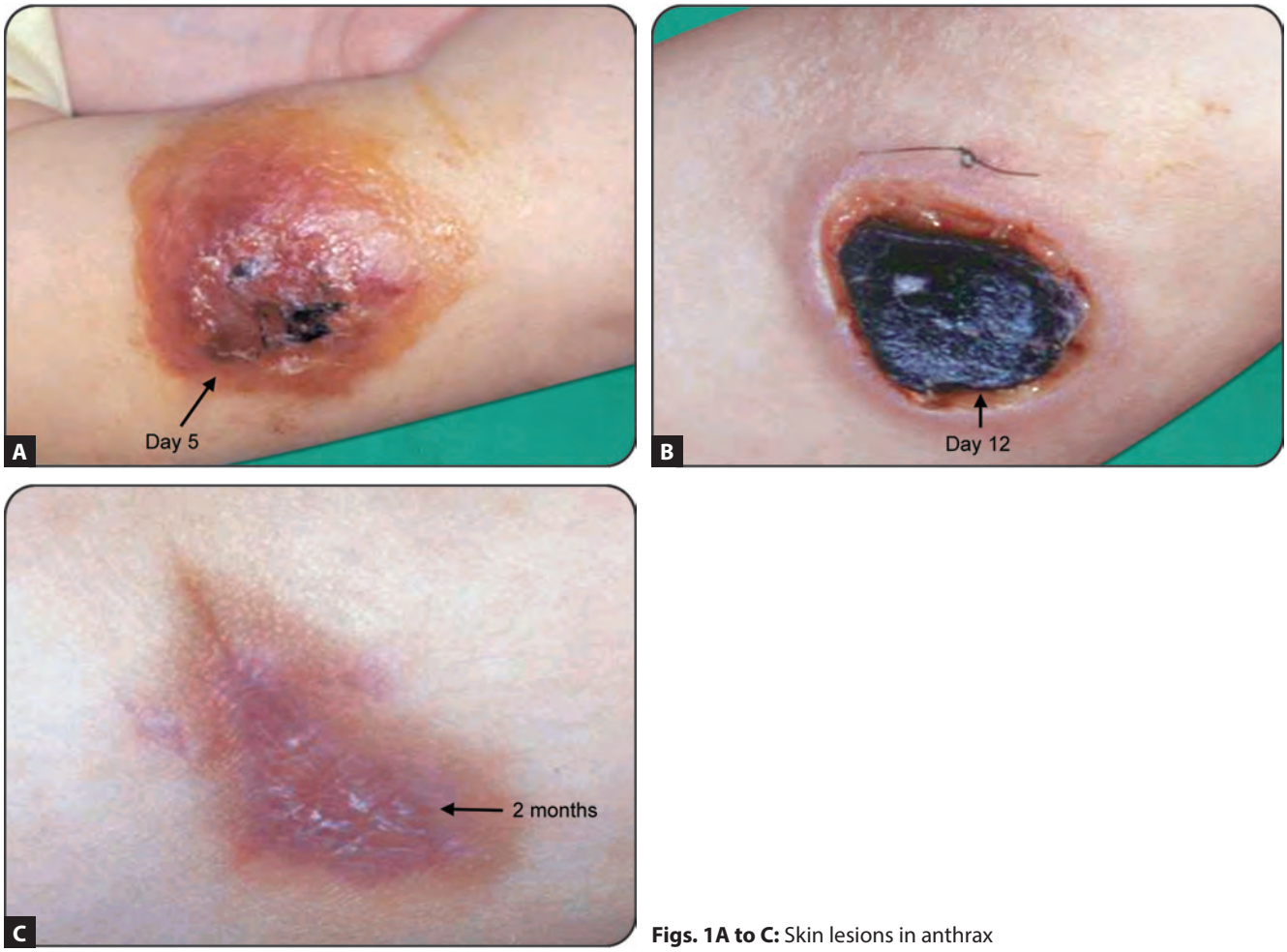
Prevention:
- Vaccination—6 doses over 18 months, booster annually
- Chemoprophylaxis—Cipro/Doxy 4 weeks before exposure
- Infectious form: Spores-Hardy, resistant to environmental conditions
- Relatively easy to weaponize

Example:
- September 2001, Anthrax used as bio-weapon through US Postal system
- 22 cases (18 confirmed)—11 inhalational + 11 cutaneous.
- 5 deaths (all among inhalational)
- Ames strain used (beta lactamase + cephalosporinase), but luckily susceptible to antibiotics
- Maximum amount of spore in a letter—2 g (100 billion to 1 trillion spores) (LD 50 = 10,000)

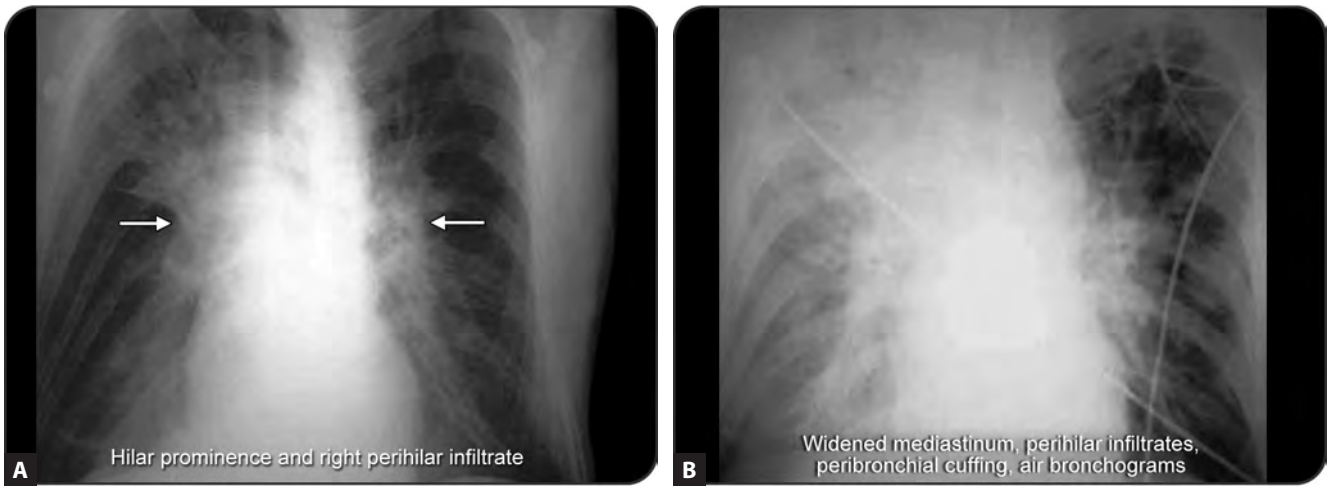
Plague (*Yersinia pestis*)[7]

Highly contagious. Pneumonic plague is most severe.

Signs and symptoms:
- *Pneumonic plague:* Due to inhalational exposure. Cough with blood tinged sputum.
- *Bubonic plague:* Due to infection through skin causes ulcers **(Fig. 3)**, Fever, Chills, Nausea, Vomiting, Buboes **(Fig. 3)** (1–8 days).
- *Septicemic plague:* Usually from bubonic plague fever, chills, nausea, vomiting, bleeding in skin, ischemia in limbs.



Figs. 1A to C: Skin lesions in anthrax



Figs. 2A and B: X-ray findings in anthrax

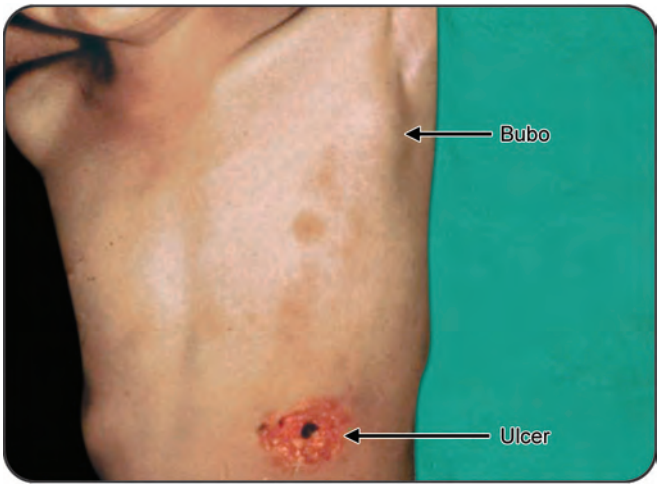


Fig. 3: Skin lesions in plague

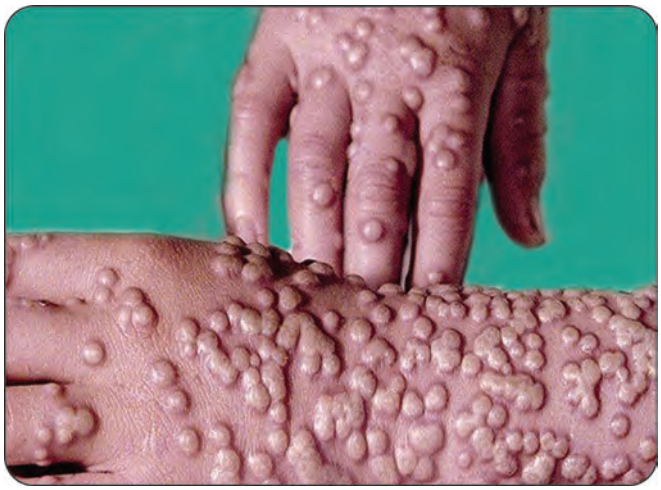


Fig. 4: Eruptions in small pox

Diagnosis:
- Clinical features: Microscopic examination of bubo fluid/sputum
- Cultures and PCR/DFA

Treatment:
- Gentamicin, Streptomycin, Doxycycline

Prevention:
- Formalin fixed vaccine, Flea control measures

Spread:
- Through bite of infected fleas
- Through droplet spread from pneumonic plague patients
- Through direct contact with non-intact skin

Weapon potential:
- Labile in environment (1 hour)
- Highly contagious, person to person spread
- Can be weaponized as aerosols (10 km)

Smallpox (*Variola*)

By 1980, close to whole world population was immune and not important as bio-weapon then. Now susceptible population (50%).

High infectivity, can spread at a factor of 10–20
Between 10–30% mortality in untreated

Signs and symptoms:
- Incubation period: Between 7–17 days (12–14)
- Fever, malaise, headache, backache, emesis, maculopapular to vesicular to pustular skin lesions. Centrifugal, same stage of development, hemorrhagic and malignant forms (5–10%) **(Fig. 4)**

Diagnosis:
- Culture, PCR, Electron Microscopy

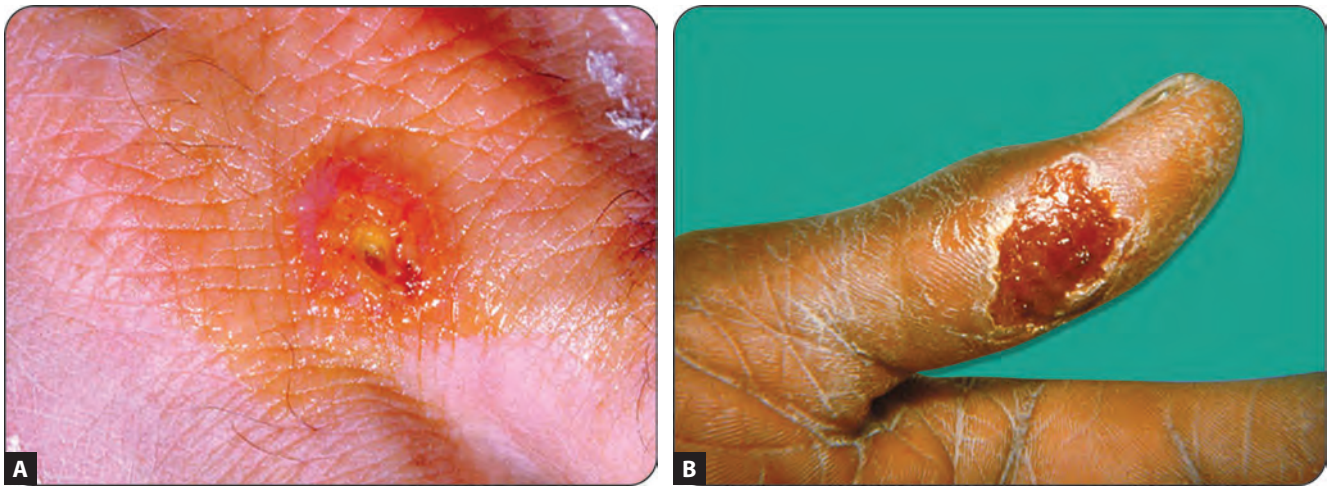
Treatment:
- Supportive treatment—Cidofovir, Anti-vaccinia immunoglobulin

Prevention:
- Vaccinia immunization
- Weaponization—Infected fomites (historical use), Aerosol sprays

Tularemia (*Francisella tularensis*)[9]

- Extremely infectious (10–50 by inhalation)
- Infection through non intact skin, mucous membrane, GI tract, Respiratory tract
- Vactors: Rabbits, ticks, water rats, deer.

Signs and symptoms:
- Incubation periods 1–14 days
- Ulceroglandular (75%) **(Figs. 5 and 6)** and Typhoidal (25%)
- Fever, chills, malaise, myalgia, headache, chest discomfort, dyspnea, skin rash, pharyngitis, conjunctivitis Hilar adenopathy on chest X-ray



Figs. 5A and B: Skin lesions in tularemia

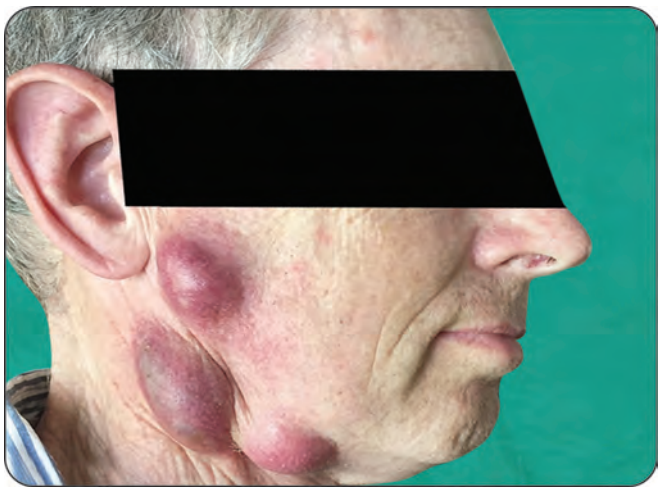


Fig. 6: Glandular lesion in tularemia

Diagnosis:
- Gram stain, culture (blood, ulcer discharge, sputum), immunohistochemistry, PCR

Treatment:
- Streptomycin, Gentamicin, Doxycycline, Ciprofloxacin

Prevention:
- Chemoprophylaxis: Doxycycline, 100 mg PO bid × 14 days or Ciprofloxacin, 500 mg PO bid × 14 days
- Weaponization—Aerosol sprays

Hemorrhagic Fever Viruses

- *Arenaviridae:* Lassa, New World (Machupo, Junin, Guanarito, and Sabia)
- *Bunyaviridae:* Crimean Congo, Rift Valley
- *Filoviridae:* Ebola, Marburg

Transmission:
- Person-to-person transmission through direct contact with body fluids (Lassa, Ebola, Marburg)
- Aerosol sprays infectious (animal studies)
- Up to 90% mortality

Signs and symptoms:
- Fever, myalgia, prostration, and DIC with thrombocytopenia and capillary hemorrhage
- Maculopapular or erythematous rashes
- Leukopenia, temperature-pulse dissociation, renal failure, and seizures

Diagnosis should be suspected in anyone with temperature >38.3°C for <3 weeks who also exhibits at least two of the following: hemorrhagic or purpuric rash, epistaxis, hematemesis, hemoptysis, or hematochezia in the absence of any other identifiable cause.

Diagnosis:
- RT-PCR, Antigen isolation

Treatment:
- Supportive therapy: Ribavirin, IFα, Hyperimmune Ig

Prevention:
- No known chemoprophylaxis, no vaccines
- Strict isolation and PPE (N95 mask or PAPR)

Botulinum Toxin (*Clostridium botulinum*)[8]

- One of the most potent toxins. Produced by *Clostridium botulinum*

- Toxin is labile in atmosphere (1% per min), Organism is easily destroyed (chlorine, heat)
- Botulism can occur: infection in a wound or the intestine, the ingestion of contaminated food, or the inhalation of aerosolized toxin

Signs and symptoms:
- Incubation period: 12–72 hours
- Dry mouth, blurred vision, ptosis, weakness, dysarthria, dysphagia, dizziness, respiratory failure, progressive paralysis, dilated pupils

Diagnosis:
- Mouse bioassay and toxin immunoassay

Treatment:
- Supportive—Intubation, mechanical ventilation, TPN
- Equine antitoxin (only against A & B)

Prevention:
- Botulinum toxoid is available for high-risk workers, lab workers, military personnel.

Examples of use: Botulinum toxin was the primary focus of the pre-1991 Iraqi bio-weapons program. (19000 l conc. toxin.), Aum Shrinrikyo cult unsuccessfully attempted on a least three occasions to disperse botulism toxin into the civilian population of Tokyo.

1990—Outfitted a car to disperse botulinum toxin through an exhaust system and drove the car around Parliament.

1993—Attempted to disrupt the wedding of Prince Naruhito by spreading botulinum in Tokyo via car.

1995—Planted three briefcases designed to release botulinum in a Tokyo subway.

Cholera (Vibrio Cholera)

- Causes acute, potentially severe gastroenteritis
- Spread through contaminated drinking water

Signs and symptoms:
- Begins in 12–72 hours
- Watery rice water diarrhea, abdominal pain, cramps, dehydration, electrolyte imbalance, seizures and cardiovascular collapse in children

Diagnosis:
- Stool microscopy—dark field

Treatment:
- Fluid and electrolyte replacement
- Antibiotics—Doxycycline, Ciprofloxacin, Erythromycin

Prevention:
- Live vaccine—50% efficacy, 2 doses + booster
- Inactivated vaccine—rapid protection, 2 doses, 85% efficacy, 2–3 years

Spread:
- By contamination of drinking water supply. Easily destroyed by heat, boiling, chemical disinfectants.

Corona Viruses

They are mostly contagious in nature mainly causing three dangerous diseases: SARS, MERS, COVID-19.

Severe Acute Respiratory Syndrome (SARS)

Caused by SARS-CoV corona virus.

In November 2002, it started from Guangdong province of Southern China, eventually reaching Hong Kong. From there it rapidly spread, causing infections in more than 24 countries.

Spreads—by aerosols

Signs and symptoms:
- Begins over 7 days
- Dry cough, chills, diarrhea, breathlessness, body ache, pneumonia
- Mortality rate of 9.6%

Diagnosis:
- RTPCR, cell culture

Treatment:
- Supportive—Corticosteroids, oxygenation, ribavirin, lopinavir and ritonavir, ET tube intubation
- Prevention—Hand washing, PPE wearing, using face mask (N95, 3-layered surgical)

Middle East Respiratory Syndrome (MERS)[10]

Caused by MERS-CoV corona virus

First recognized by scientist in Saudi Arabia after severe respiratory illness. Since then it has spread to other countries

Spread by—Aerosols

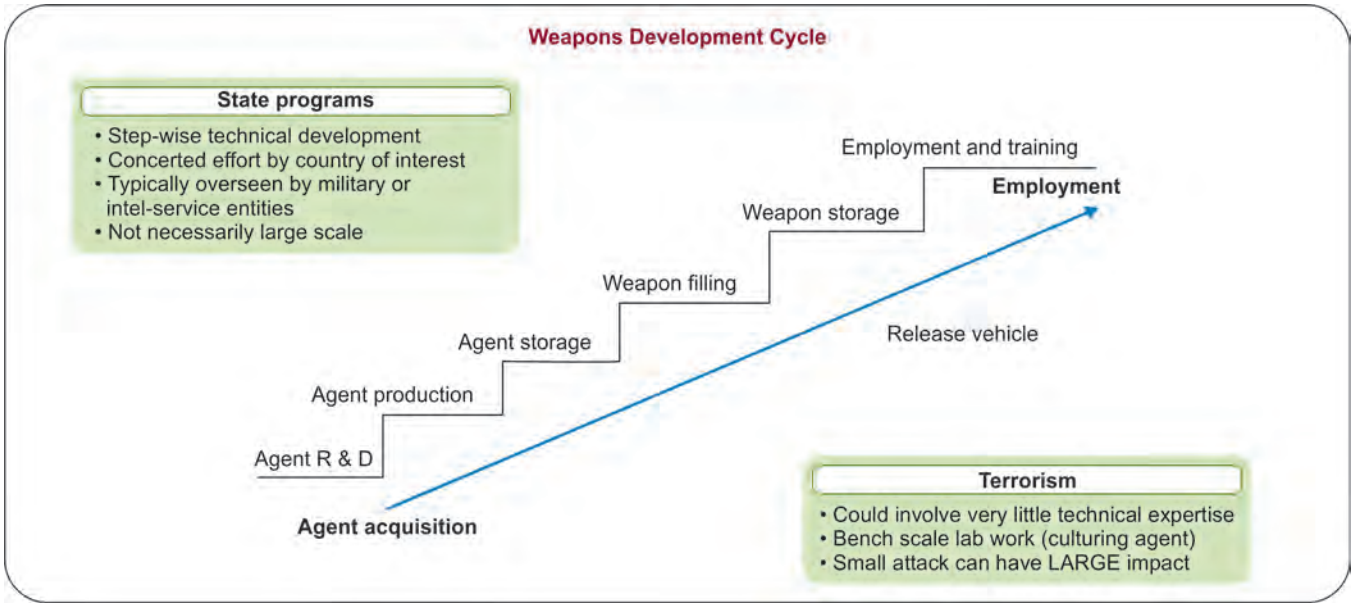


Fig. 7: Weapons development cycle

Signs and symptoms:
- Fever, cough, breathlessness
- Mortality rate—35.2%

Diagnosis:
- RTPCR

Treatment:
- Supportive—ET tube intubation, NSAIDs, oxygenation

Prevention:
- Hand washing, PPE wearing, using face mask (N95, 3-layered surgical)
- No vaccine available

COVID-19[10]

In December 2019, CDC started monitoring the outbreak of a new corona virus named SARS-CoV-2, which started from Wuhan city of China and then spread to nearly every country leading the WHO to declare a pandemic.

Spreads by—Aerosols

Signs and symptoms:
- Fever, cough, breathlessness, loose motion, loss of taste and smell, body ache, chest pain
- Mortality rate—Varies among countries
- 6% in the US
- 3% in India

Diagnosis:
- Rapid antigen test, RTPCR

Treatment:
- Supportive—Azithromycin, doxycycline, ivermectin, HCQs, favipiravir, remdesivir, corticosteroids, LMWH, ET tube intubation

Prevention:
- Hand washing, PPE wearing, using face mask (N95, 3-layered surgical)
- Weaponization—It is the process of converting the biological agent into a usable weapon.
- Delivery device—Bombs, Missiles, Spray systems – Aerial, Aerosol based.
- Non-traditional—Food, water supplies, animals, insects.

Treaties and Conventions

Geneva protocol,[5,13] *1925:* Geneva Protocol for the prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases and of Bacteriological Methods of Warfare was adopted by international community on 17th June, 1925. It banned the use but didn't proscribe the research, production, or possession. It was appeal by international Red Cross and Poland. It was customary international law. A no first use agreement only.

Biological weapons convention[5,13] *1972:* Eighteen-Nation Disarmament Committee in 1969. Convention on the prohibition of the development, production, and stockpiling of bacteriological and toxin weapons and on their destruction was signed on 10th April 1972. Entered into force in 1975. First treaty to ban an entire class of weapons doesn't address non-state actors, e.g., terrorists. No protocol to monitor compliance **(Fig. 7)**.

Prevention Against Biological Warfare

It is necessary to be aware of common epidemiological clue for detecting early of a biological attack.

- At particular time there is a single cause of certain disease of unknown cause in a large area which may not have epidemiological explanation.
- Genetically engineered agent.
- High morbidity and mortality rates with the same or similar symptoms.
- In a particular geographical or seasonal distribution.
- Transmission through aerosols, food, water.
- Rare illness affecting large population or certain age group; with unusual trends of mortality and morbidity.
- Clustering of cases for treatment.

Primary Prevention

By creating a strong global norm that rejects development of such biological weapons.

Secondary Prevention

Early detection and prompt treatment of disease. There is important role of medical community by participating in disease surveillance and reporting, and thus providing the first indication of biological weapons use. In addition, continued research to improved diagnostic capabilities, therapeutic agents, and effective response plans[14,15] will further strengthen secondary prevention measures.

Tertiary Prevention

Prevention of disability from disease.

Biological warfare with India:[11,12]

- Nodal agencies—DRDO (MoD), NDMA, MoHA, MoHFW
- Indian Biodefence Program—started in 1973

Conclusion

Time and again Medicine has been misutilized for biological warfare to satisfy human ego and the desire to harm the mass by the knowledge and the commodities of healing. We misutilize our discoveries to injure and kill innocent people in the name of war instead of fighting against the microbe to prevent the diseases and save the suffering mass. The recent pandemic of COVID-19 has originated at Wuhan state of China from a virology lab with similar attempts and the whole world has suffered for a year and we don't know what is there in future. At least now the pandemic should open the vision of our world leaders to resolve to stop such heinous suicidal act for the benefit of everyone.

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CHAPTER

162 Antimicrobial Resistance: Is It Worrisome?

Ritu Karoli

Abstract

Antimicrobial resistance (AMR) is said to occur when microbes are protected from effects of antimicrobial agents by evolving genetic or acquired mechanisms. Rising AMR is a global threat to public health across the globe. There are various causes of AMR in community, health-care system, and agriculture industry. The need of the hour is to identify and remove these causes, prevent the misuse of antimicrobial agents by antibiotic stewardship, and apply the knowledge of novel research and technology to address this growing menace.

"There is probably no chemotherapeutic drug to which in suitable circumstances the bacteria cannot react by in some way acquiring 'fastness' [resistance]."

–Alexander Fleming, 1946

Introduction

The discovery of antibiotics was an important landmark in the history of medicine that revolutionized treatment and saved countless lives. Antibiotics are one of the most commonly prescribed drugs in clinical practice. Unfortunately, resistant strains of microbes have religiously followed the path of these "magic bullets" antimicrobial resistance (AMR) is the ability of microorganisms such as bacteria, fungi, or protozoans to grow despite exposure to antimicrobial substances designed to inhibit their growth. Reduction in or loss of an agent's antibacterial effect is referred to as resistance, and the properties of or alterations in the bacterium that result in reduced antimicrobial activity are termed resistance mechanisms. AMR is one of the biggest public health problems of recent decades that poses significant challenge to prevention and treatment of various infections. It is a complex issue that affects different sectors of society and is multifactorial in origin. Coordinated action is required to minimize the emergence and spread of AMR.

Antimicrobials have made the management of infectious diseases easier thereby decreasing morbidity and mortality. If current trends continue, it is projected that, by 2050, AMR could result in over 10 million deaths per year and over 100 trillion USD in lost output globally.[1] World Health Organization (WHO) is coordinating a global campaign to raise awareness of antibiotic resistance and encourage best practices among the public, policymakers, health and agriculture professionals, to avoid further emergence and spread of antibiotic resistance.[2]

What is Superbug?

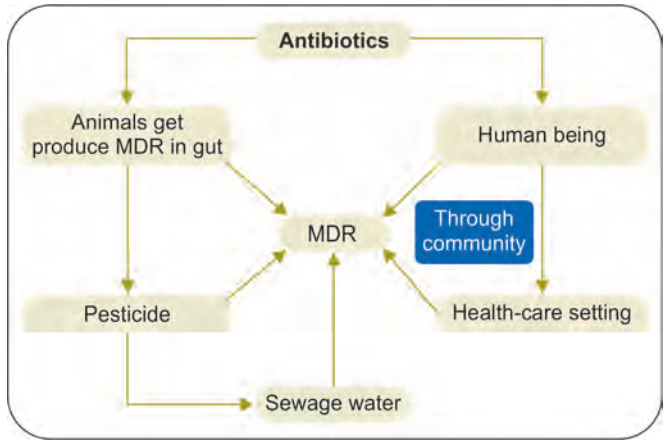
There has been emergence of microbes which are resistant to multiple antimicrobials are called as superbugs. They cause difficult to treat life threatening infections and require higher doses of antimicrobials along with alternative or adjuvant medications. They increase rate of hospitalization, duration of stay at hospital, and lead to economic burden on society and health-care system. Many of them are multidrug resistant infections such as *Mycobacterium tuberculosis, Acinetobacter, Enterobacter*

spp., Enterococcus, Escherichia coli, Pseudomonas, and *Staphylococcus aureus*. These infections are caused by a range of opportunistic pathogens (organisms that only cause disease in immunocompromised individuals). Device-associated infections, ventilator-associated pneumonia (VAP), and urinary tract infections (UTI) account for approximately 60% of all hospital-associated infections.

Causes of AMR

- Community—
  - Overuse of antibiotics—Over the counter availability of antibiotics in absence of valid prescription by a qualified medical professional
  - Inappropriate use/misuse of antibiotics
  - Inappropriate choices because of diagnostic inaccuracy
  - Inadequate dosing/timing and noncompliance
  - Self-medication
- Hospital-acquired infections—
  - Intensive and unjustified/irrational use of antimicrobial drugs
  - Emergence and spread of multidrug resistant nosocomial infections
  - Immunocompromised patients
  - Prolonged stay in hospitals/intensive care units, treatment of immunocompromized patients
  - Failure to implement effective infection control measures
  - Absence of antimicrobial stewardship programs
- Environmental causes of AMR (as shown in **Flowchart 1**)
  - Overwhelming use of antibiotics in animal husbandry and agriculture. This results in the evolution of multidrug-resistant organisms that act as reservoirs. These organisms or their genes can spread to humans either through direct contact or through the environment.
  - Organic pesticides used in agriculture may persist in the soil.
  - Sewage-water contamination with soil and environment.
  - The excessive use of antiseptics and biocides leads to resistance against these compounds and cross-resistance to antibiotics.
  - Many antibacterial drugs are derived from natural products of environmental microbial species.

Flowchart 1: Environmental factors of MDR (multidrug resistant strains)



Exposure to antibacterial agents results in the selection of resistant strains within an otherwise susceptible bacterial population.

Mechanisms of resistance—Microbes have outstanding quality to survive among variety of environmental adversities. Plasmids are extrachromosomal DNA, mostly present in bacteria. They replicate autonomously. The size varies from a few base pairs to thousands base pairs. Many antibiotic resistance genes are present in plasmids. It is common that resistant bacteria have combinations of resistance mechanisms[3] either within one category or among categories, and many plasmids contain more than one resistance gene. Thus, plasmid acquisition itself can in many cases confer resistance to multiple antibacterial agents.

Mechanisms of resistance have been shown in **Figure 1**.

- Reduced penetration and permeability and increased efflux pumps—Some bacterial species are intrinsically resistant to certain group of antibiotics because of reduced penetration and permeability of cell membrane and increased efflux pumps. TetA efflux pumps specifically pump tetracycline out of the cell. Mutations in Porin (protein channels present incell membrane) lead to porin los or change in size and conductance or decrease in expression results in less concentration of antibiotic in the cell and can lead to AMR.
- Enzyme inactivation and chemical modification—Enzymes produced by certain bacteria inactivate the target site, such as β lactamase enzyme, which prevent β lactam to bind to target site. Another mechanism mediated by bacteria in which they acquire an

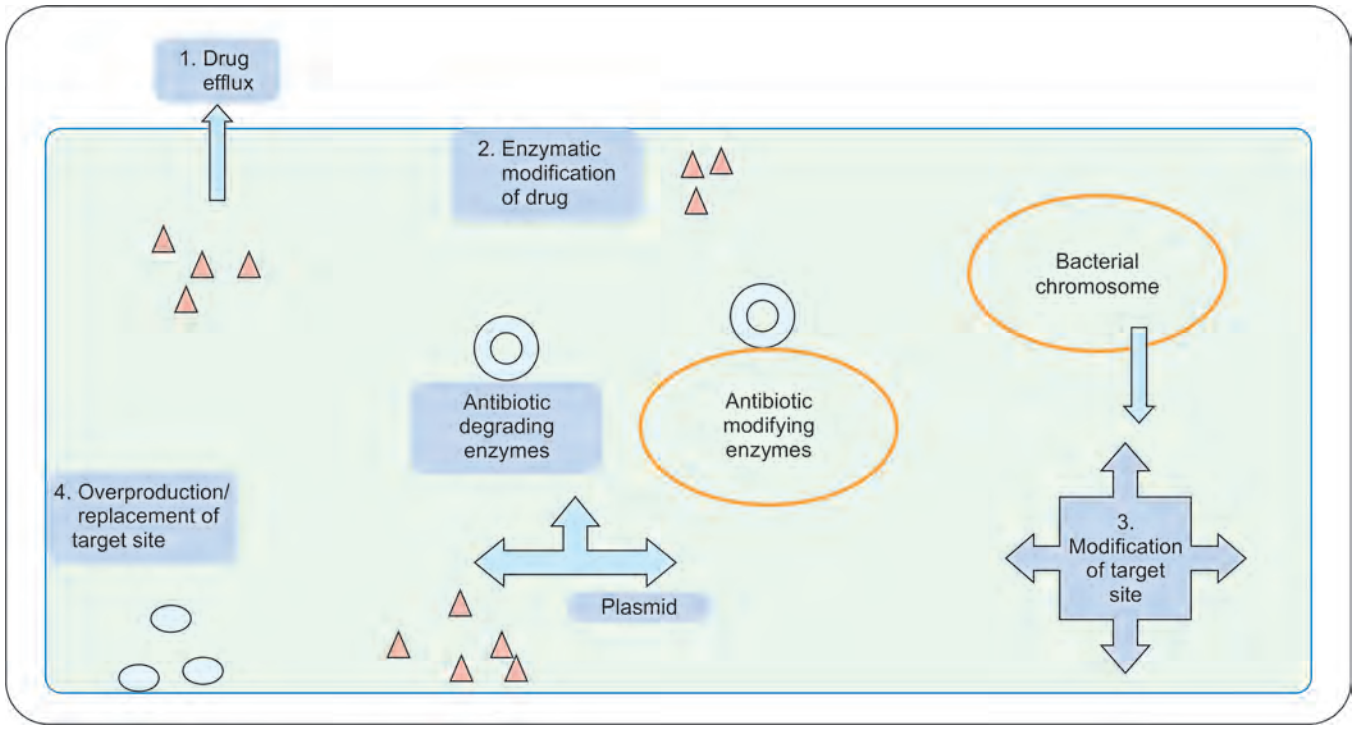


Fig. 1: Mechanism of antibiotic resistance

enzyme that chemically modify the target of the antibiotics. Ribosomal methylation of erythromycin makes it ineffective and N Acetyltransferase modifies aminoglycosides.

- Modification of antibiotic target site—Mutations in the bacterial genes, which encode for the protein that is target of an antibiotic. Resistance to penicillin in streptococcus species is due to acquisition of mutation in penicillin binding proteins.
- Overproduction/replacement of target site—Sometimes there is overproduction of target sites by replication of bacteria, which is found in combination with mutation that lowers the ability of antibiotics to bind to bacteria, e.g., trimethoprim resistance in *E. coli*. Some of mutations cause replacement of target site of bacteria for a particular antibiotic and result in resistance. *S. aureus* is resistant to most of the β lactam antibiotics.

Implications of AMR

Management of critically ill, cancer chemotherapy, organ transplantation, orthopedic surgery, intensive care for preterm newborns are being affected.

- Economic burden on patient and health-care system.
- Infections caused by multidrug-resistant bacterial strains lead to increased societal costs in terms of mortality and loss of productivity.

Antimicrobial Stewardship[4]

"Using the right antibiotic at the right time at the right dose for right duration."

Goal of antimicrobial stewardship to optimize clinical outcome while minimizing toxicity and emergence of resistance. Antimicrobial stewardship programs are the need of the hour to limit indiscriminant use of antimicrobials. These programs require leadership commitment, accountability, and drug expertise. They include systemic evaluation of ongoing treatment, tracking and monitoring of antibiotic prescription and resistance pattern and education to clinicians about AMR and optimum prescription.

Antimicrobial stewardship programs are typically multidisciplinary and often include infectious disease physicians, pharmacists, pharmacologist, clinical microbiologists, administrators, and epidemiologists. It is

for practice of promoting the selection of the appropriate drug, dosage, route, and duration of antimicrobial therapy.

Solutions to Combat Antibiotic Resistance

AMR is a major concern globally. Infections due to drug-resistant pathogens are becoming difficult and a challenge to treat. Following strategies can be adopted:

- Mitigation of emergence of MDR strains and prevent spread
- Strengthen National one health surveillance program
- Rapid and innovative diagnostic facilities to be made available
- Antibiotic stewardship programs should be mandatory in health-care systems
- Accelerate applied and basic research to develop new antibiotics and new treatment options
- Capacity building across the globe by improving international collaborations to prevent AMR
- Novel therapeutic options can be explored such as antimicrobial peptides, biologics, nanoparticles, polymer-controlled delivery

Conclusion

AMR is increasing due to overuse and misuse of antibiotics in human beings and animals. There should be societal commitment to fight against AMR. Health-care professionals should demonstrate dedication and accountability to optimize antibiotic prescriptions and patient safety.

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CHAPTER

163 Chikungunya Arthropathy

Liyakat Ali Gauri, Somya Goyal, Asim Khan, Nadeem Liyakat, Qadir Fatima

Abstract

Chikungunya is a vector born disease transmitted to humans by the bite of infected female Aedes aegypti or Aedes albopictus. It causes a multisystem disorder with predominant involvement of musculoskeletal system. Chikungunya arthropathy can develop into chronic phase which may lead to disability and debilitating joint pain. Current treatment options include NSAIDs, Opioids, Anticonvulsants/Antidepressants, Colchicine, DMARDs, Methotrexate. Biologicals, Ultrasound, and Transcutaneous Electrical Current Stimulation have shown promising results. Newer researches are undergoing to provide evidence-based therapeutic options.

Introduction

The word chikungunya, in Makonda language, means "that which bends up" or "to become contorted." It refers to the prostrated appearance of affected patients.[1]

Chikungunya virus **(Fig. 1)** is an alpha virus belonging to *Togaviridae* family. ChikV was first isolated in 1953, in Newala District, Tanzania. The vector-borne disease is transmitted to humans by the bite of infected female Aedes aegypti (tropics) or Aedes albopictus (temperate).[2]

Fig. 1: Aedes albopictus or Asian tiger mosquito

Clinical Features

ChikV is a multisystem disorder with a predominant involvement of musculoskeletal system. Incubation period is 5–7 days:[1]

- Neurological manifestations are meningoencephalitis, myelitis, peripheral neuropathy, Guillain-Barré syndrome (GBS).
- Ophthalmology-keratitis, episcleritis, optic neuritis, uveitis, and renal detachment.
- Cardiac—uncommon, but serious arrhythmias, vasculopathy, myocarditis, pericarditis, or dilated cardiomyopathy[1]
- Sepsis and septic shock
- Renal failure
- Toxic hepatitis
- Pneumonitis
- Bullous dermatosis, alopecia[3]

Mother-to-child Transmission

A study of pregnant women concluded in Reunion Island, 2005–2006 epidemic showed that vertical transmission rate was 50% when ChikV infection occurred during intrapartum period (2 days either side of deliver). Cesarean section did not prevent this transmission.[4]

Chikungunya Arthropathy

Clinical manifestations can be divided into:

- Acute phase (<3 months)
- Chronic phase (>3 months)

Acute phase is further divided into viremic (5–10 days) and subacute post-viraemic phase (6–21 days).

Viremic phase is characterized by sudden onset high grade fever, severe polyarthralgia, myalgia, conjunctivitis, exanthema.[5]

Subacute phase is in which fever settles but articular symptoms persists.

There is symmetrical, peripheral polyarthralgia involving small, medium, and large joints, which tends to be more intense in morning and worsens with physical activity.[6]

Chronic Phase

Prevalence of ChikV arthritis progressing to chronicity is 4.1–78.6%. This phase is similar to rheumatoid arthritis (RA), spondyloarthritis.[7] Various joints are involved in chikungunya. There have been many studies studying involvement of joints **(Fig. 2)**.

Chikungunya has been reported with changes similar to rheumatoid arthritis. Similar case was reported by jose kennedy Amaral **(Fig. 3)**.[16] Study from Colombia reported 25% patients remained symptomatic for joint pain after 20 months follow-up.

Similar findings were reported in a meta analysis, chronic inflammatory rheumatism (CIR) was present in 25% cases and chronic arthritis in 14%.[8]

In study involving 121 patients from Martinique Island in Caribbean, 21% patients progressed to seronegative RA in 1 year, 37% had flare of underlying degenerative arthritis, 35% had relapse of previous inactive spondyloarthritis and 7% had fibromyalgia.[9]

An observational study from Kerala found 57% patients had chronic polyarthralgia, 19.5% chronic tenosynovitis after 15 months of ChikV.[1]

Risk Factors for Developing Chronicity

- Comorbidities: RA, diabetes mellitus
- Age more than 45 years
- High viral load (>10^9/mL) during acute phase
- In a study involving 140 patients with ChikV, smoking, and female gender were identified as main risk factors for severe joint pain in acute disease as well as chronicity as similar to RA
- Genetic predisposition
- Viral persistence
- Auto immune diseases[6,10]

Immunopathogenesis of Chikungunya Arthropathy

The mechanism of chikungunya arthropathy is unclearly understood.

In acute phase, there is an intense viremia, which is associated with activation of Type I IFN & IL-6. Proinflammatory cytokines and chemokines are activated.

This strong immune response clears the virus by CD+4 T cells, NK cells and macrophages and within 7–10 days of acute infection virus levels become undetectable.

For this reason, ChikV PCR for diagnosis after 7 days is not useful.[2]

Il-17 is also implicated in chronic joint disease, which upregulates IL-1,6, TNF alpha, RANK-L. RANK-L osteoprotegerin ratio is disturbed, which further increases bone erosions. Whether ChikV persists in synovial tissue in chronic phase is unclear.[1]

Sixteen patients from Reunion Island epidemic were studied for persistent viral infection by synovial fluid RTPCR in 10 patients and tissue biopsy in 6 patients. All samples were negative suggesting viral replication is not the cause of chronic articular disease.[11]

In a study conducted by Dr Chang on 38 patients during 2014–2015 Colombian epidemic, no evidence of viral persistence was found by synovial fluid RTPCR, mass spectrometry, and viral culture.[8]

Diagnosis

- *Clinical:* ChikV should be suspected in endemic areas or in travelers from affected areas or in patients presenting with high grade fever and joint pain

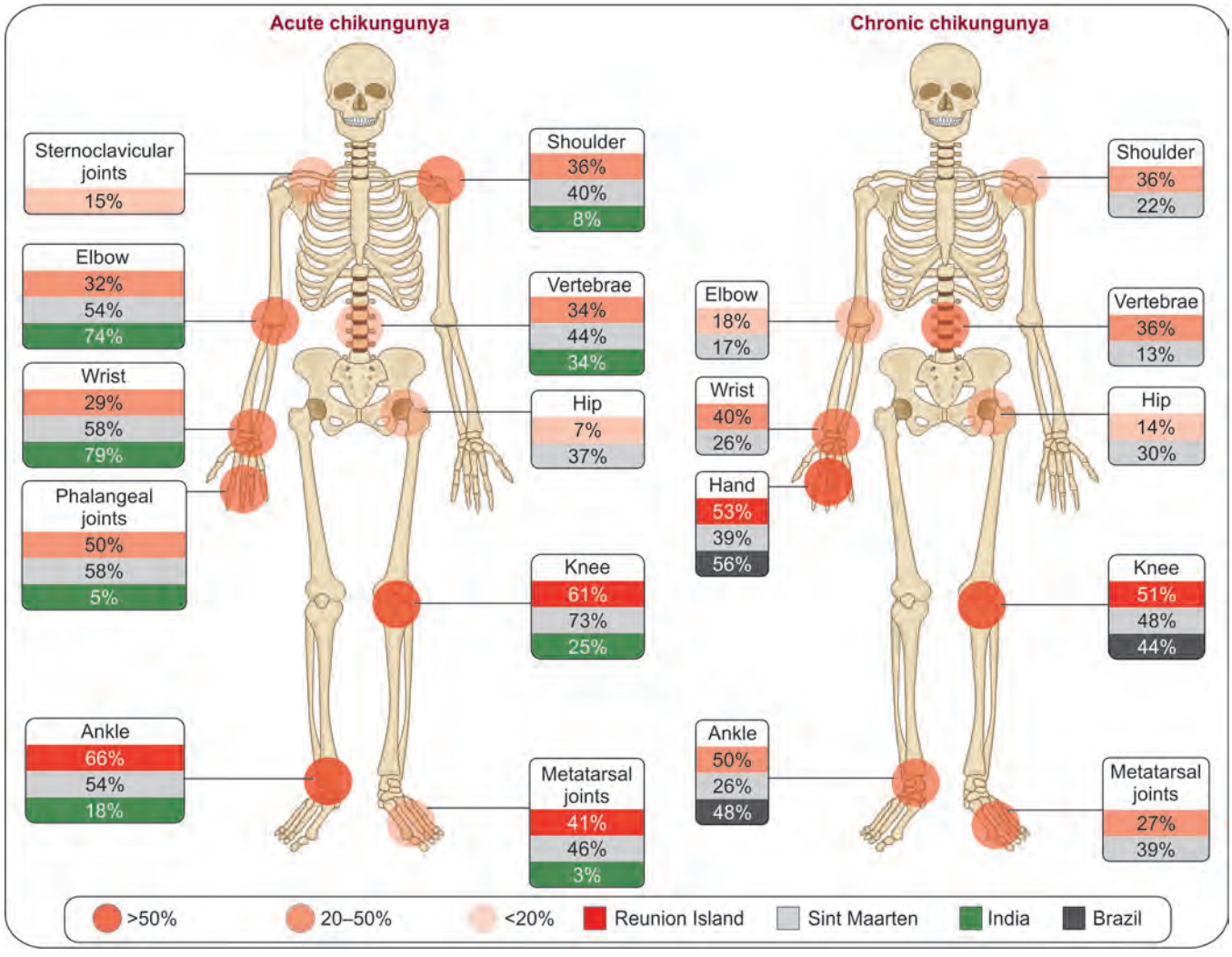


Fig. 2: Joints involved in chikungunya as observed in various studies[3]

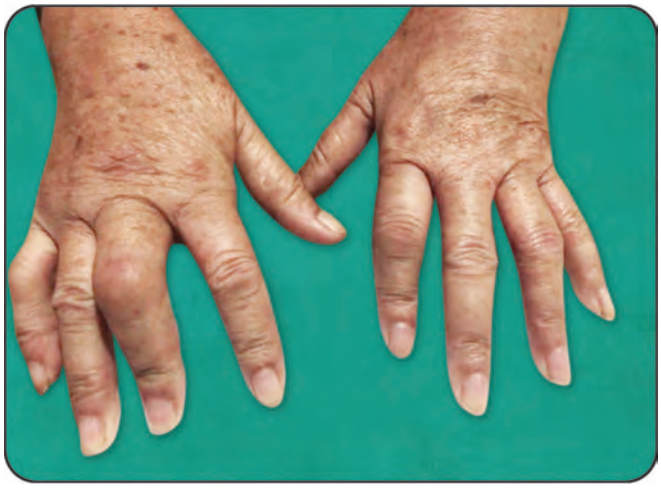
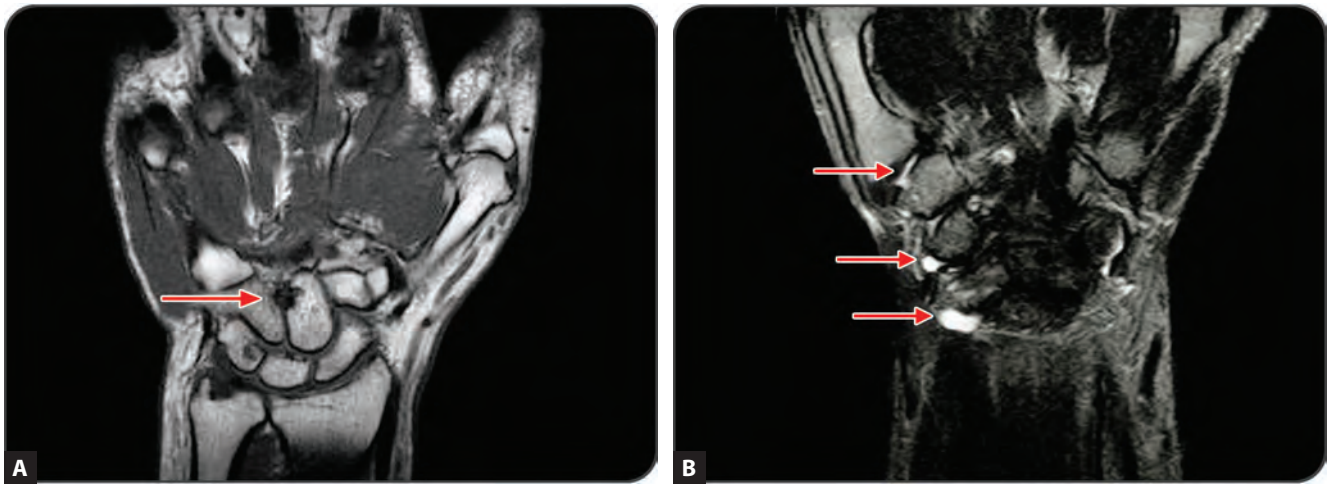


Fig. 3: A 50-year-old woman with CCA and synovitis of right 3rd PIP and left 2nd PIP joints. She had acute Chik F 3 years prior and subsequently developed CCA



Figs. 4A and B: Coronal magnetic resonance (MR) T1 image (A) reveals extensive intermediate-signal-causing carpal styloid erosions (arrow), similar to those of rheumatoid arthritis. Axial MRT2 image (B) reveals small fluid collections in the wrist (arrows)

- *Complete blood count:* Anemia, leukopenia, lymphopenia, mild thrombocytopenia
- *Biochemistry:* Increase in liver enzymes and serum creatinine levels
- *RT-PCR:* Sensitive from 0 to 7 days after which it is unreliable
- *IgM ChikV:* Detectable in 5–10 days after onset of infection, maximally positive after 3 weeks. May remain positive up to 2–3 months
- *IgG:* Positive after first week of infection and remain positive for years

As a general rule, serological markers (IgM & IgG) should not be checked in first week of infection:

- RA factor, anti CCP antibodies, HLA B27, ANA in chronic arthritis
- MRI—greater sensitivity. Can show synovial thickening, bone marrow edema, effusions, tenosynovitis **(Fig. 4)**.[24]

Treatment

NSAIDs

PCM remains the initial choice for fever and arthralgia. NSAIDs should be avoided until dengue has been ruled out as dengue can be complicated by hemorrhage.

Corticosteroids

Low dose prednisone starting at 5–10 mg OD followed by gradual tapering over weeks can be used for intractable symptoms in subacute phase and chronic phase. Maximum dose of steroids recommended is 0.5 mg/kg.

Use is not advised in acute phase.

In an uncontrolled case series during 2005–2006 Indian Ocean pandemic, short-term corticosteroids showed improvement in arthritis and tenosynovitis and decreased disability in patients with CCA.[1]

Long-term use is discouraged due to side effects.

Opioids

Weak opioids like codeine and tramadol can be used as adjunctive.

Anticonvulsants/Antidepressants

Pregabalin, amitriptyline, and gabapentin can be used for peripheral neuropathy and intractable pain.

Colchicine

Study by Rendel showed that colchicine used at 0.6 mg/kg/day in a patient with persistent ankle and wrist arthralgia showed significant improvement.[12]

After 2–3 days, there was resolution of swelling and improvement in joint pain. After 2 months, symptoms were resolved.

Patient continued treatment for 6 months with no adverse effects. Study suggested colchicine as a treatment option.[12]

DMARDs

Study on 50 chikungunya patients by Gauri LA et al. shows that chikungunya patients who had persistent arthralgia on 5-year follow-up mimicked rheumatological disorder Like rheumatoid arthritis in 70.58% cases. Therefore, disease-modifying anti-rheumatic drugs (DMARDs) can be effective.[13]

Methotrexate (MTX)

In a study from Reunion islands by Javelle et al. on a patient with post-chikungunya CIR with 21 months follow-up, 15 mg weekly MTX lead to clinical improvement in 75% (54/72) patients and 8%(6/72) achieved partial recovery while 9% (7/72) had radiographic worsening of joints. Remaining had to stop MTX due to side effects.[14]

In another small study, MTX given to patients with poor response to HCQ and SSZ combination therapy led to improvement in 93% cases after 3 months. Only 7% were symptomatic at the end of 2 years.

Bouqillard & Combe treated 19 patients with acute chikungunya with MTX, 13 patients (68.4%) had good clinical response.[15]

Combination DMARD Therapy

Amaral et al. treated 48 CCA patients with 7.5 mg weekly MTX with dose escalations for refractory symptoms at 4 weeks. Final MTX dose was 9.2+3.2 mg/week.

MTX was combined with oral prednisone at 9 weeks with 6.1+2.2 mg for 9 patients (18%). Two patients received 400 mg daily HCQ with MTX and one received SSz 1,000 mg. Pain VAS score decreased to 3.0 & 2.6 at the end of 4 & 8 weeks respectively from a baseline value of 7.7+2.0.[16]

An open label study by Ravindran & Alias randomized patients on HCQ who had persistent arthritis (>1 year) patients were divided into two groups:

Group A: Received fixed dose combination (MTX 15 mg weekly + SSz 1,000 mg OD + HCQ 400 mg daily.

Group B: Continued to take HCQ 400 mg OD.

Both groups also took prednisolone for 6 weeks. At 25 weeks, combination therapy showed significant improvement in both disease activity & disability. VAS score was significantly less in combination therapy group.[17]

Pandya treated 149 patients with MTX 15–20 mg weekly with HCQ. At 16 weeks, ACR20 was seen in 48.9%, ACR50 in 18.8%, ACR70 in 4% patients. One patient achieved clinical remission (DAS28-ESR <2.6) and 4/149 showed good clinical response (DAS28-ESR <3.2).[18]

Biologicals

No human trial to evaluate the efficacy.

Bouqillard & Combe treated patients of acute Chik developing CIR, with TNF alpha inhibitors. These patients were refractory to initial MTX therapy. All Patients had good clinical response.[15]

Ultrasound and Transcutaneous Electrical Current Stimulation

Ribeiro et al. reported the efficacy of ten sessions of continuous ultrasound with 1 MHZ OD applied from Monday to Friday followed by infrared laser at dose of 4J & 3S per hour. TENS burst with a pulse width of 250US and frequency of 2 HZ.

This association showed post-intervention improvement in quality of life, which was assessed by SF36 (medical outcome study 36) and VAS.[19]

Ultrasound transmits heat by convection causing vasodilation and increased blood flow, hence increasing metabolic rate of the cell.

TENS stimulates large afferent sensory fibers that block first degree nociceptive fibers by releasing endorphins.

Laser therapy causes photochemical reactions within cells, increasing mitochondrial function and ATP productions, cell proliferation, and accentuating the healing process.

When to Give? What to Give?

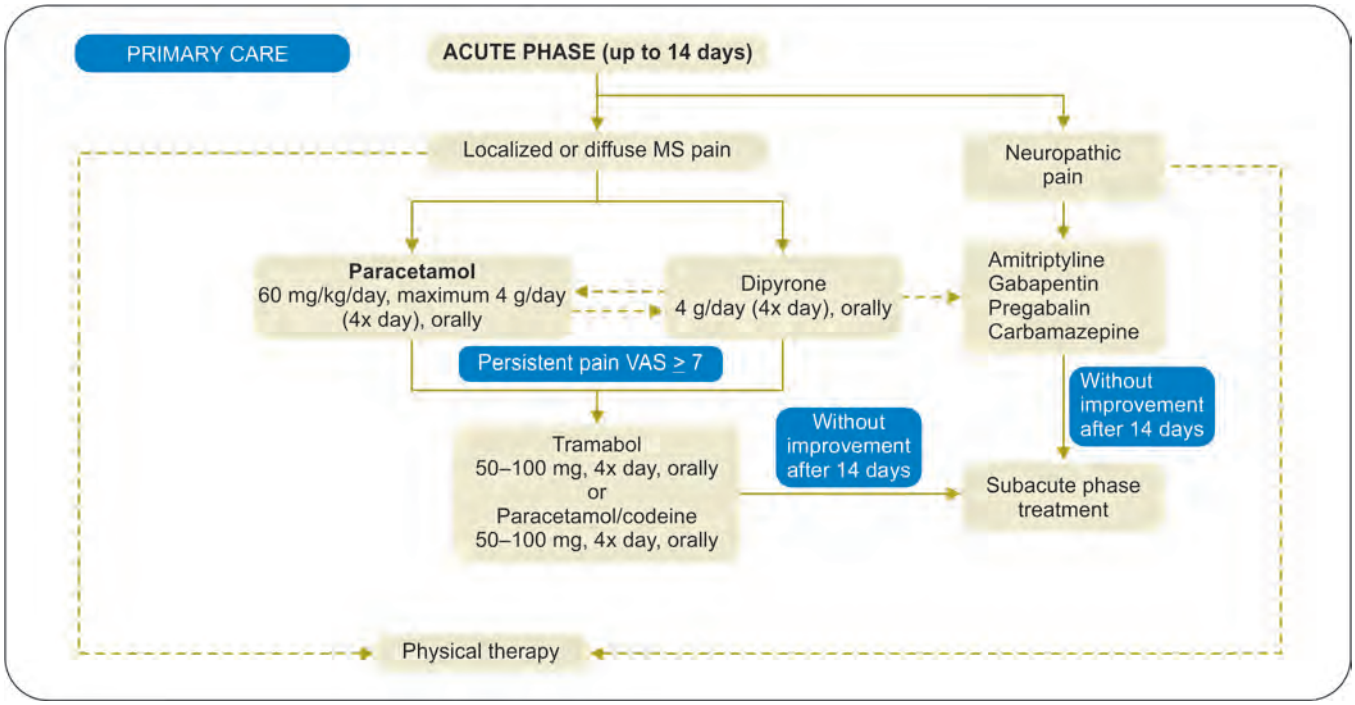
Based on French, Brazilian, and WHO guidelines as well as the studies conducted in India, we can follow these points:[20,21]

Acute Phase

Acute viremic phase **(*see* Flowchart 1)**:

- Supportive care, hydration
- WHO recommend home treatment for non-complicated acute cases
- Common analgesics, weak opioids should be used
- NSAIDs to be avoided until dengue has been ruled out

Flowchart 1: Treatment algorithm for patients presenting in acute phase of chikungunya arthropathy[2]



- Guidelines do not recommend use of steroids during acute viremic phase
- Use of heat generating rehabilitative procedures should be avoided in acute phase

Subacute phase ***(see* Flowchart 2)**:

- NSAIDs, opioids, or adjunctive treatment for pain management
- Anticonvulsant/antidepressants like pregabalin and amitriptyline in cases refractory to opioids, NSAIDs.
- Use of prednisolone at 5–20 mg/day with gradual tapering
- WHO guidelines support use of HCQ 200 mg OD or CQ 300 mg Od for 4 weeks for resistant symptoms

Chronic phase ***(see* Flowchart 3)**:

- Analgesics
- Weak opioids
- NSAIDs
- Oral corticosteroids may be used at 5–20 mg/day with gradual tapering
- HCQ with or without MTX or sulfasalazine (SSZ)
- Corticosteroid dependent disease—use of MTX at 10–25 mg/weekly is recommended
- SSZ 2–3 g/day with or without MTX. SSZ should especially be used in failure or contraindications to MTX
- Biological therapy (particularly TNF alpha) may be used after rheumatological evaluation or in patients refractory to treatment of corticosteroids or DMARDs
- A dictum is—"if it looks like RA, treat like RA" should be followed

Rehabilitation intervention in all phases of ChikV is recommended as a complementary non-pharmacological measurement.

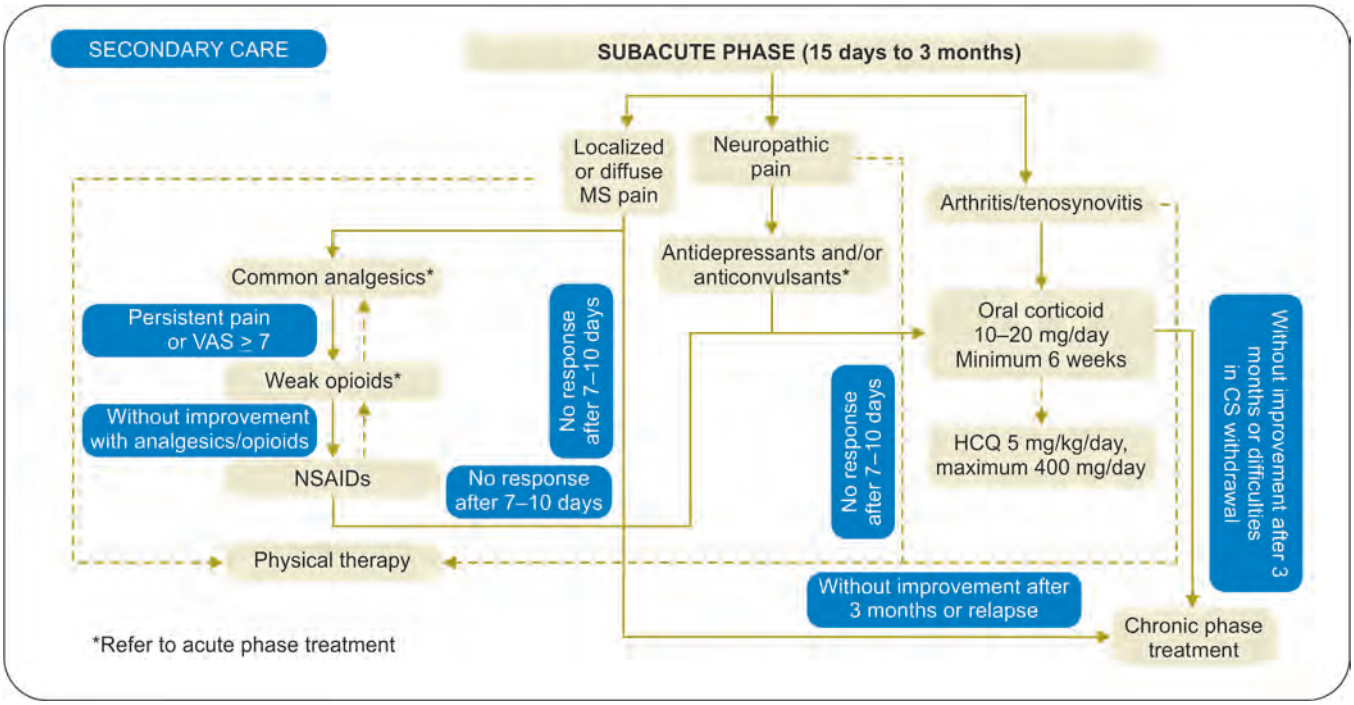
Newer Therapeutic Approach

Ribavirin

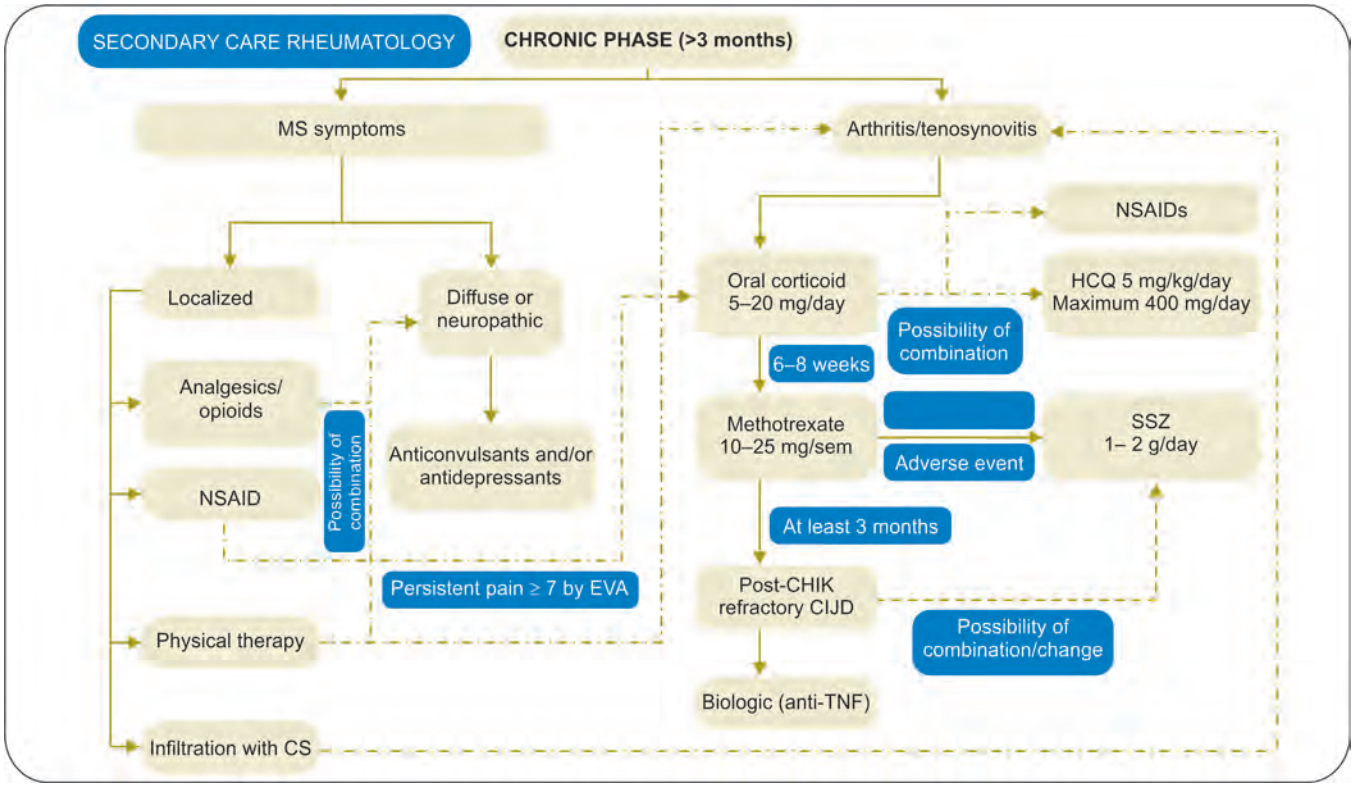
In studies by Ravindran et al., Ribavirin was used in a group of patient with chronic ChikV, analgesics discontinued, and Ribavirin started at 200 mg BD for 7 days. All patients reported improvement in pain.[6]

Favipravir, Ribavirin with a combination of IFN alpha, *umifenovir* (antiviral) and *Suremein* (anti-protozoal) have shown some benefit.[2]

Flowchart 2: Treatment algorithm for patients presenting in subacute phase of chikungunya arthropathy[2]



Flowchart 3: Treatment algorithm for patients presenting in chronic phase of chikungunya arthropathy[2]



Abatacept

T-cell costimulation blocker. In mouse models has shown a significant decrease in periarticular swelling and proinflammatory cytokines.[2]

Pentosan Polysulfate

NOVEL glycosaminoglycan like molecule developed for the treatment of alpha virus infection. Treatment of ChikV infected mice reduced cartilage thinning and immunological infiltration of joints.

Intra-articilar levels of proinflammatory cytokines were decreased and anti-inflammatory IL-10 increased through unclear mechanism.[1]

Fingolimod

Sphingosine-1-phosphate receptor agonist used in multiple sclerosis. In ChikV infected mice, Fingolimod treatment decreased migration of CD4 T-cells into joints without affecting viral replication. However, its utility in CCA is unknown.[1]

Curcumin

Turmeric derived compound used as food additive. Treatment exhibited antiviral properties through inhibition of virus binding to cells in vitro studies.[22]

Pimozide and 5-Tetra Decyloxy-2 Fusoic Acid

Found to exhibit synergistic antiviral activity in studies causing genomic wide loss of function screen.[22]

Neutralizing Monoclonal Antibodies-SVIR001

Neutralizing IgG MAB to E2 envelope glycoprotein inhibit entry, fusion, and egress of virus. Robust viral clearance and decreased cytokines and chemokines level have been observed.

Renders protection against multiple alpha virus including ChikV.[22]

E2 Glycoprotein Mutation

Studies showed the presence of highly conserved amino acid on E2 glycoprotein, which promoted ChikV persistence in mouse joints.

Mutation of this conserved region allowed viral clearance in mice.[22]

Prophylaxis with MDEF201

It is an adenovirus vectored IFN alpha.

Studies have shown decreased cytokines and decreased footpad swelling in mice treated with intranasal MDEF 201.

Prophylaxis with MDEF201 may have clinical potential in endemic areas of ChikV. Especially during outbreaks, it would be useful as a single prophylactic agent that could protect over several weeks to those at high risk.[23]

Vaccine

- Recombinant measles and chikungunya vaccine (MV-Chik)
- Virus like particle (VLP) vaccine

Vaccines induce neutralizing antibodies against E1 and E2, which may block viral entry into cells.

2018, CEPI (coalition for Epidemic Preparedness Innovation) reported that four vaccines are in phase I trial and two in phase II trial (VLP, MV-Chik).

Phase III field trials are complicated by inability to predict the geographical location and size of next outbreak.

Newer Mosquito Control Measures

- *Biotechnology:* Introducing insect toxin into fungus that infects mosquitoes
- *Wolbachia:* It is a gram negative bacteria affecting mosquitoes. Large field trial of Wolbachia is underway in Yogyakarta, Indonesia, with hope that transmission of DENV, ChikV can be decreased.

Conclusion

ChikV is an arboviral multisystem disease primarily affecting joints. Chikungunya arthropathy can develop into chronic phase, which may persist for months to years creating distress, disability and debilitating joint pain. Available research on treatment options is limited based on which use of DMARDs, corticosteroids, NSAIDs is advised. Newer researches are undergoing to provide evidence-based therapeutic options. Vaccine development is under phase II trial. Newer therapies have shown benefit in animal models and are being studies in human subjects. To prevent the economic burden that the disease causes, there is an urgent need to formulate universal guidelines and to test newer drugs as well as vaccines.

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CHAPTER

164 Atypical Manifestations of Dengue

Ashok Kumar, Shubha Laxmi Margekar, Purnima Margekar, Urvashi Khan

Abstract

Globally dengue is the most common arboviral disease being transmitted. Since past five decades disease is rapidly spreading in the world with a 30 fold increase in incidence. The common manifestations of dengue fever includes, fever, retro-orbital headache, generalized body ache, petechial rashes, and bleeding manifestations. Over the period of decades there has been occurrence of other manifestations which are different from typical dengue fever. These manifestations have been called as atypical manifestations and it has been observed that almost all the organ system of body has been affected by dengue fever. Focus of this article is to elaborate the atypical manifestations of dengue fever which also includes the expanded dengue syndrome. Knowledge of these manifestations is necessary to recognize the disease process, limit the complication, and prevent the morbidity and mortality associated.

Introduction

Worldwide dengue is the most common arthropod borne disease, which is being transmitted by the bite of mosquitoes. Since past five decades disease is rapidly spreading in the world, and incidence of dengue infections has been rise by approximately 30 times. There is estimated 100–400 million people gets infections each year. The first confirmed epidemic of dengue hemorrhagic fever (DHF) was recorded in the Philippines in 1953–1954 and in India it occurred in Calcutta in 1963. Although it is a preventable disease but it also has high mortality and morbidity. Due to lack of awareness among the health-care personnels, atypical presentation is often missed and goes unreported. Dengue virus belongs to the virus of genus flaviviruses of Flaviviridae family. There are various serotype of dengue virus are there namely DEN 1-4. The vector responsible for the spread of dengue virus is mosquito *Aedes aegypti* (*A. aegypti*).[1] Infected Aedes mosquitoes, especially *A. aegypti*, transmit various serotypes to humans through their bites.

The dengue virus infection produces the myriad of clinical symptoms clinical ranging from mild asymptomatic to febrile illness of unknown origin (can be of viral origin), DHF, or dengue fever (DF), or dengue shock syndrome (DSS) **(Table 1)**.[2]

Infection in people who are never been infected is known as primary or first infection, usually causes classical dengue fever. Subsequent or secondary infection by different dengue virus serotype causes more severe illness like dengue DHF/DSS. Major pathophysiologic changes occurring in DHF/DSS are:

- Plasma leakage
- Rising hematocrit
- Thrombocytopenia, and
- Bleeding manifestations.

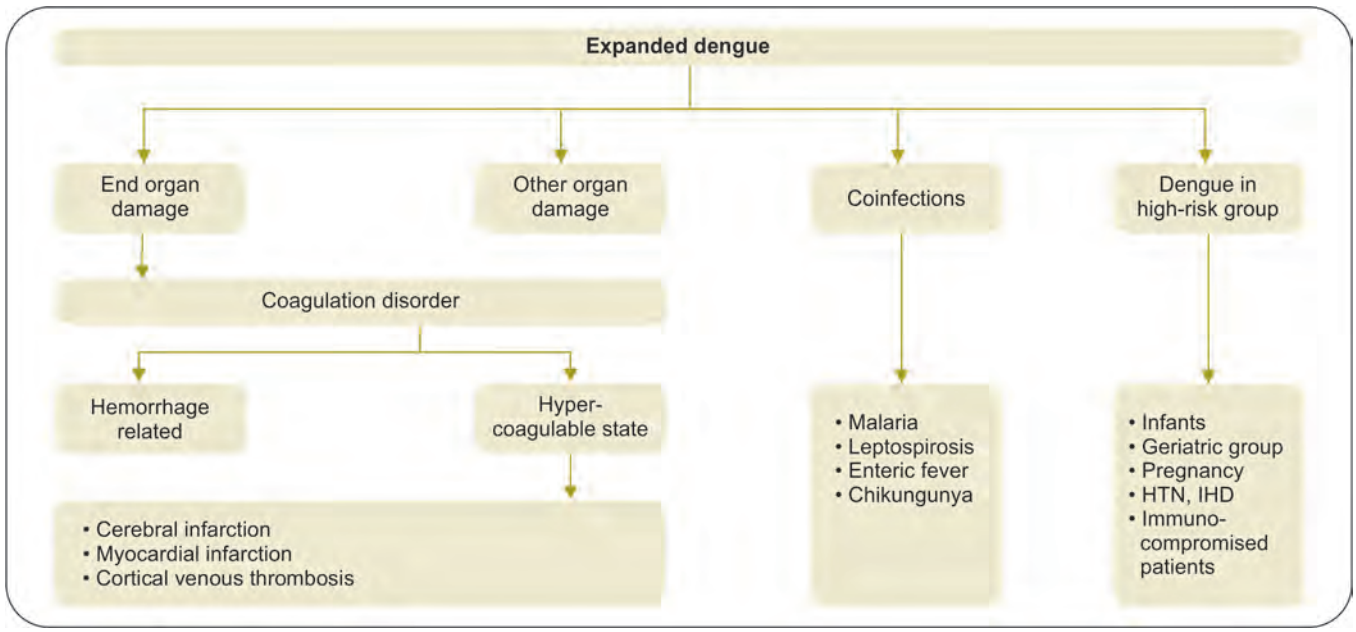
It's an acute febrile illness with rash, arthralgia, leukopenia, headache, retro-orbital pain, hemorrhagic manifestations.[2] As per WHO clinical diagnosis of DHF is made by the following criteria:[1]

- Continuous spikes of high grade fever for 2–7 days

TABLE 1 Manifestation of dengue virus infection

Asymptomatic	*Symptomatic*					
	Undifferentiated fever (Viral syndrome)	*Dengue fever (Classical)*		*Dengue hemorrhagic fever (Classical)*		*Expanded dengue syndrome/ Isolated organopathy (Unusual presentation)*
		Without hemorrhage	With unusual hemorrhage	Without shock	With shock dengue shock syndrome (DSS)	

Flowchart 1: Expanded dengue



- Positive tourniquet test or presence of bleeding tendency
- Platelet count <100,000/μL
- Evidence of hemo-concentration, i.e., 20% rise in hematocrit as per average for age, sex, and population, presence of ascites and pleural effusion

One of the life threatening complications is DSS, which is characterized by DHF (meeting all four criteria) along with circulatory failure. Circulatory failure is manifested by rapid and weak pulse, cold clammy skin and restlessness and narrow pulse pressure (<20 mm HG) or hypotension for age.[2]

Atypical Manifestations

The classic presentation of dengue has been expanded with involvement of various organ systems. Due to diagnostic dilemma some atypical manifestation are often missed and being underreported. Henceforth, a new term Expanded Syndrome has been coined by WHO, in the revised classification in 2012 as shown in **Flowchart 1**.[2,3] Atypical manifestations are correlated with neurological, renal, hepatic, cardiovascular, and other organs involvement **(Table 2)**. It has been reported increasingly in DHF and also in dengue patients with no evidence of leakage of plasma. Most DHF patients who have unusual manifestations are the result of prolonged shock with organ failure or patients with comorbidities or coinfections.

Neurological Manifestations

The association between DHF and neurological disturbances were first described in 1976.[4,5] Different

TABLE 2 Atypical manifestations of dengue

Neurological	*Gastrointestinal/Hepatic*	*Renal*	*Cardiac*	*Respiratory*
• Febrile seizures • Encephalitis • Encephalopathy • Transverse myelitis	• Hepatic failure (Fulminant) • Acalculous cholecystitis • Acute pancreatitis • Acute parotitis	• Acute renal failure • HUS	• Myocarditis • Pericarditis • Conduction abnormalties	• Acute respiratory distress syndrome • Pulmonary hemorrhage
Lymphoreticular/bone marrow		***Musculoskeletal***	***Eye***	***Others***
• HLH • ITP • Spontaneous splenic rupture • Infarction of lymph node		Rhabdomyolysis	Optic neuritis	Psychosis

manifestations including neurological signs may occur due to neurotropicity, which is due to direct invasion of tissue, release of cytokines damaging the blood brain barrier, brain edema, capillary leakage can be leading to bleeding manifestations involving intracranial hemorrhage, and due to extended period of shock there could be hypoperfusion of brain, acute renal injury, liver dysfunction, and electrolyte imbalances like decrease in the sodium levels, i.e., hyponatremia and decrease in the blood glucose levels, i.e., hypoglycemia.[6,7] In the study by Pancharoen and Thisyakorn (2001) they explained that altered sensorium is the most usual neurological finding subsequently seizures were noted among 75% of patients with DSS.[5] Various other patients had manifestations of PN (polyneuropathy), Encephalitis, memory loss, and myelitis.[8] Meningitis was found in (1.2%).[9] In a study conducted by Pothapregada et al. (2016),[10] neurological manifestations were observed in 28 children (11%). In the same study total six deaths (2.4%) were there and out of them four presented with impaired consciousness (66. 6%) during admission with their GCS < 8. Multiorgan failure, refractory shock, and encephalopathy were accounted for the poor outcomes. Mohanty et al.[11] described in his study that fever and altered sensorium were related to typical presentation of the virus, CSF analysis suggestive of viral encephalitis, five deaths due to multiorgan dysfunction, cerebral infarct in neuroimaging seen in one patient. Potassium redistribution in the cells also played an important part in neurological manifestation caused by dengue, which leads to a rare entity described as Hypokalemic periodic paralysis. In the study by Mohanty et al.[11] they found that patients responded well with potassium infusion who had features suggestive of hypokalemic paralysis and whose NCV, i.e., nerve conduction velocity and EMG, i.e., electromyography were completely normal.[11,12] Further unusual manifestation observed in the same study was that of spinal cord involvement including ATM, i.e., acute transverse myelitis, which was managed with steroid, i.e., methylprednisolone and IVIG. Muscle involvement also seen in the form of Myalgia cruris, which may be due to direct muscle invasion by virus causing damage to muscle or may be due to released cytokines.[13] Another rare manifestation is dysarthria clumsy hand syndrome.

Gastrointestinal Manifestations

Gastrointestinal presentations of virus are such as febrile diarrhea, fulminant liver failure, inflammation of pancreas, i.e., acute pancreatitis, cholecystitis mostly acalculous, severe inflammation of parotid gland, i.e., acute parotitis. Severe pain abdomen is one uncommon manifestation seen in dengue. With such presentation, acute peritonitis, acute pancreatitis, or acalculous cholecystitis should be ruled out. Diverse involvement of virus in liver scales from advancing from meagre symptoms of increasing liver enzymes to a full-blown liver failure or fulminant hepatic failure. Elevation of liver enzymes (AST/ALT) is seen commonly in dengue infection. Elevation of liver enzymes like AST/ALT is commonly seen in patient with dengue fever and 9th day of the illness is the most crucial day where the liver enzymes tend to increase from the day of onset of symptoms and it gradually progresses toward normal within 3 weeks.[6,7] Another illustration of acalculous cholecystitis introduces abdominal pain specifically localized to the upper quadrant in the right side, uninterrupted fever and positive elicitation of Murphy's sign. Exact mechanisms are not known, it might be due to invasion by the virus in the gall bladder wall

giving rise to edema of gall bladder and microangiopathic injury, which itself is self-limiting.[10] Cholecystectomy not recommended due to thrombocytopenia as postoperative bleeding. Except in case of peritonitis, gangrene and perforation where surgical intervention is required.[6]

Cardiovascular Manifestations

Cardiac demonstrations of the virus are uncommon though cardiac rhythm abnormalities like AV blocks, Atrial fibrillations, dysfunction in sinus node and ectopic beats in ventricles have been noticed during DHF incidents. The physiopathology of cardiac leads to inflammation causing cytokine storm of both structural and functional integrity by the virus.[11] If clinically and ECG findings are suggestive of myocarditis, CPK-MB is considered the most precious investigation to correlate, whereas tachycardia and volume depletion are suggestive of poor outcome.

Renal Manifestations

Dengue virus also affects renal system leading to acute kidney injury and it exhibits as acute tubular necrosis (ATN), which is a rare manifestation and mostly attributed due to shock. ARF in these individual is of pre-renal origin. There could be various methods but the approved ones are that of invasion by the virus directly into the renal system, i.e., kidneys or immune mediated. Management with appropriate fluid in hyperkalemia unresponsive to conventional treatment, decrease urine output, and uremia hemodialysis is to be used for management.

Respiratory Manifestations

Unexceptional manifestation in the respiratory system caused by the dengue virus is that of ALI, i.e., acute injury to lung and acute distress to the respiratory system, i.e., ARDS. These manifestations in turn lead to edema of alveolus and also there is increased permeability in the alveolar capillary membrane. Better outcomes can be achieved by early identification and treatment. If pulmonary hemorrhage occurs, it becomes the fatal complication.

Musculoskeletal Manifestations

Dengue myositis: It is manifested as break bone fever, severe muscle, bone, and joint pain. There is elevated SGOT, SGPT, and creatine phosphokinase. Direct invasion of muscles by viruses has not been proven and may appear to be myotoxic cytokines, particularly TNF.

Coinfections

It modifies the presentation of dengue clinically and results in delayed diagnosis and treatment of dengue shock.

Malaria

Malaria is the most common infection, which can be found with dengue infection. Because of the similar seasonal variations in the incidence of both infections and similar clinical presentation and even similarity in laboratory parameters sometimes the diagnosis of dengue can be very challenging and coinfection with malaria can be missed which can lead to fatal outcome. Among the four species of plasmodium, as per Indian studies *P. faliciparum* is commonly associated. Its presenting features are headache, myalgias, backache, hypotension, hepatosplenomegaly. Suspicion and treatment of complicated malaria is necessary for prevention of fatal outcome.

Zika Virus Disease

It is confirmed after exclusion of dengue infection with serological tests. As compared to dengue virus infection, symptoms in Zika virus infection are mild fever, mild body ache, ill-defined rashes but no hemorrhage.

Chikungunya

Aedes aegypti is common vector for both Chikungunya as well as dengue. Arthralgia common in both, but in dengue it is self-limiting and latter can progress to disabling arthritis, which may persist for months. Also thrombocytopenia can be found in both infections.

Conclusion

The most effective way to prevent dengue virus transmission is to combat the disease-carrying mosquitoes. Effective vector control strategies appear to be promising for dengue prevention and control. Risks associated with the disease can be assessed with the timely diagnosis and initiation of medical care. Recognizing expanded dengue syndrome in early stage is crucial for optimizing treatment strategies. A high index of suspicion of features of expanded dengue syndrome (EDS) is very important for targeting treatment option. Alteration in sensorium is most devastating atypical manifestation in case of severe dengue infection, which, if not recognized in time, may lead to fatal outcome.

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CHAPTER

165 Cholera and Plague—Is the Threat Over?

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Abstract

Cholera and plague both are communicable diseases which are preventable by targeted multisectoral approach including improvement of sanitation, education regarding good hygiene practices, improvement of housing, and quality of life. As per the WHO, cholera cases have decreased globally and there is a significant downward trend in incidence. WHO has planned a global road map to reduce the cholera-related deaths by 90% till 2030. Plague can also be controlled by breaking the chain of transmission, proper application of insecticides, early identification, notification, isolation, and treatment by appropriate antibiotics.

Introduction

Cholera is often predictable and preventable public health problem, which poses a global threat. It is an indicator of lack of access to clean water and sanitation facilities. Good hygiene practices can eliminate cholera.[1] Pandemics of plague occurred from time to time in the past, but nowadays it can be treated and prevented easily by use of effective antibiotics and standard measures for prevention.[2]

Cholera

Cholera is caused by toxin producing strain of Vibrio cholerae, which is curved shaped Gram-negative, highly motile with single polar flagellum bacterium. It causes acute diarrhea and is known as "Father of public health." There are more than 200 serogroup of V. cholera. Of these, only two toxigenic serogroups O1 and O139 cause outbreaks. El Tor and classical are the two biotypes of serogroup O1. In comparison to classical strains, El Tor biotype causes more of asymptomatic cases and exists in environment for longer time. Classical strain was responsible for previous six pandemic and El Tor was responsible for seventh one starting in 1961. In 1992, O139 was identified as a cause of extensive cholera epidemic in various part of South Asia including India and Bangladesh. Humans become infected incidentally but, once infected, can acts as a vehicle for spread. There is no animal reservoir. Ingestion of contaminated water and food by human feces are the common means of acquisition of V. cholera. Risk factor include poor hygiene, poor water supply, lack of sanitation (peri-urban slums, refugee camps), etc.[3]

Epidemiology

WHO standard case definition: *Suspected cholera case*—when a patient aged ≥5 years develops severe dehydration or dies because of acute diarrhea in an area where the disease is not known to be present or when patient aged ≥5 develops acute watery diarrhea with or without vomiting in cholera epidemic area. *Confirmed cholera case*—any suspected case in which Vibrio cholerae O1 or O139 is confirmed by culture or polymerase chain reaction (PCR) test. *Cholera endemic area*—an area

where cholera confirmed cases have been detected in last 3 years due to local transmission. *Cholera outbreak* is defined by the occurrence of at least one confirmed case of cholera and evidence of local transmission or unexpected increase (in magnitude or timing) of suspected cases over two consecutive weeks, of which some are laboratory confirmed cases in an area with sustained (year-round) transmission.[4]

In 19th century, cholera spread across the world from Ganges delta in India and killed millions of people in seven subsequent pandemics. More than 40% of cholera cases reported annually to the WHO are from Africa, more than 35% from Asia, and more than 20% from the Americas.[3] Researchers have estimated that every year, there are 1.3–4.0 million cases of cholera, and 21,000–143,000 deaths occurs worldwide due to the infection.[5] In year 2017, 34 countries reported 5,644 deaths and 122,7391 cases which came down to 2,990 deaths and 499,447 cases in the year 2018. As per WHO, number of cholera cases decreased globally (60% in 2018) and significant downward trend is continued; however, outbreaks are still ongoing in various countries.

Symptoms

Incubation period is 2 hours to 5 days. Most of the cases (around 75%) are asymptomatic and shed bacteria for 1–2 weeks in their feces. Those who are symptomatic, the majority have mild to moderate symptoms and few patients' presents with sudden onset explosive, painless, non-bilious "Rice water stools". It is not associated with blood and typically fishy, inoffensive odor. Stool of cholera patient contains higher concentration of sodium, potassium, and bicarbonate. It is usually associated with vomiting and severe dehydration even can be life threatening (*cholera gravis*).[3] It can lead to hypotensive shock, renal failure and that can be fatal in 50–70% cases, if dehydration is not addressed properly. Other clinical symptoms are parallel to volume contraction **(Table 1)**. Severity of illness depend on various factors including number of V. cholera bacteria ingested, neither exposed previously nor vaccinated, lack of passive immunity in new born (no breast feeding), pregnancy, immunocompromised conditions, malnourishment, reduced gastric acid production, and blood group O.

TABLE 1 Clinical features and treatment of cholera according to severity

Degree of dehydration	*Loss of TBW*	*Clinical findings*	*Treatment*		
			Fluid (Treatment of choice)	Adjunctive antibiotics (In moderate to severe cases)	Zinc Supplementation
Mild	<5%	Thirst	• ORS required in first 4 hours is equal to weight in kg multiplied by 75 in mL. • As for as daily requirement is concern, it should be given as much as patient can have desire to drink until signs of dehydration subsides	-	Recommended in children for 10 days • <6 month–10 mg/day • 6 months to 5 years–20 mg/day
Moderate	5–10%	Thirst, weakness, postural hypotension, tachycardia, decreased skin turgor, dry mouth/tongue, no tear		Drug of Choice • Azithromycin 1 gm single dose in adult (20 mg/kg in children) OR • Erythromycin-250 QID for 3 days • Second choice • Doxycycline in non-pregnant adult—300 mg single dose OR • Tetracycline (non-pregnant adult)—500 mg QID for 3 days • Third choice • Ciprofloxacin 500 BD in adult and 15 mg/kg BD in children for 3 days	
Severe	>10%	Unconsciousness, lethargy or floppiness, inability to drink, sunken eyes, weak or absent pulse, decreased urine output, hypotension or shock	IV Fluids • Ringer lactate (Preferred) or Normal saline • 100 mL/kg in first 3 hours (in first 6 hours for children <12 months old) to a total of 200 mL/kg in 24 hours • Further requirement of fluids depends on patient condition		

Cholera sicca, another form of cholera, presents with fluid accumulation in intestinal lumen, circulatory collapse and even death in absence of diarrhea. Fever is usually absent and muscle cramps are common due to electrolyte imbalance.[3]

Diagnosis

Diagnosis requires high index of clinical suspicion with severe acute watery diarrhea. Detection of V. cholerae from stool by dark field microscopy or isolation from stool culture on selective TSBS agar (thiosulfate citrate bile sucrose) or TTGA (taurocholate tellurite gelatin agar) remains the standard test. PCR method is also becoming available for diagnosis. Several rapid diagnostic tests (RDTs) such as immune chromatographic lateral flow devices (dipsticks), which detect the presence of the O1 or O139 antigen in rice water stool samples (sensitivity—95% and specificity—65–85%). RTDs can be performed by semi-skilled workers and it provides point of care diagnostic facility.[3]

Treatment

In severe cases, rapid rehydration (oral rehydration solution or intravenous fluid) is the primary treatment for cholera. About 90–95% of all cholera cases can be treated by oral fluid alone. Mild to moderate dehydration cases are treated by reduced osmolarity oral rehydration solution (WHO/UNICEF ORS). Composition of reduced osmolarity ORS is given in **Table 2**. Oral rehydration solution is prepared by dissolving one standard sachet in a 1 liter of clean water. In absence of ORS, mixture consisting of table salt (one level teaspoon) and sugar (6 level teaspoon) dissolved in 1 liter drinking water may be safely used until the proper solution is available. Severe cases need urgent hospitalization and intravenous fluid resuscitation (typically 10–20 mL/kg/hour). Ringer lactate is fluid of choice as it also corrects the acidosis along with electrolytes.[3] While transfusing the fluid regular monitoring for signs of dehydration including urine output, vitals, and chest examination are warranted. Though the rehydration therapy is the main stay of treatment but it neither reduces the duration of the disease nor excretion of bacteria in feces. Antibiotic are added in moderate to severe cases to decrease duration of illness, reduce volume needed for rehydration and hastens the clearance of the organism from the stool **(Table 1)**. Oral supplementation of Zinc in children of 6 months to 5 years, reduces the severity as well as prevent the recurrence of diarrhea.[3]

TABLE 2 Composition of reduced osmolarity ORS*

Constituent	*Concentration (mmol/L)*
Sodium	75
Potassium	20
Chloride	65
Citrate	10
Glucose, anhydrous	75
Total osmolarity	245

*Per sachet (to be added to 1 L of drinking water) contains: NaCl—2.6 gm; tri-sodium citrate dehydrate—2.9 gm; KCl—1.5 gm; Glucose (anhydrous)—13.5 gm

Prevention

Cholera can be prevented by access to potable drinking water, adequate sanitation, educating people regarding good hygiene practices (frequent hand washing with soap, proper disposal of excreta and avoiding consumption of food in unhygienic environment). Cholera vaccinations is a complimentary prevention and control measure **(Table 3)**.[3-8]

In 2018, WHO passed a global road map to reduce the cases of cholera by 90% till 2030 by focusing on three following strategies:[9]

- Early detection of cholera cases and contains outbreaks rapidly
- Prevention of cholera recurrence by targeting multisectoral approach
- An effective mechanism of coordination for technical support, resource mobilization, and partnership at different levels

Plague

Plague is caused by *Yersinia pestis*, Gram-negative coccobacilli, bipolar in appearance (closed safety pin), non-capsulated, facultative anaerobic, non-motile, organism of family Enterobacteriaceae. Human acquires infection via bites of infected rodents, fleas, or infected domestic cats, direct contact with infected human, animal tissue or body fluids, inhalation of infected respiratory droplets from a patient with pneumonic plague or respiratory secretions from infected animals. Consumption

TABLE 3 Oral cholera vaccine[3-8]

Oral killed cholera vaccines		*Oral live attenuated cholera vaccine*
Killed whole-cell monovalent vaccine with recombinant cholera toxin B subunit (WC-rBS)	Three bivalent whole-cell only vaccines (Biv WC), Based on sero-groups O1 and O139 of V. cholerae	**CVD 103-HgR (Vaxchora)**
• **Dukoral (First licensed in Sweden)**	**Schanchol** (licensed in India in 2009), **mORVAX** (licensed in Viet Nam in 1997 for use in endemic region in 2009 for domestic use), **Euvichol** (licensed in the Republic of Korea), Shanchol and Euvichol produced for International markets, available in single dose vials	Approved by USFDA in 2016 for travelers to cholera endemic area
• Vaccine contains a mixture of the recombinant B subunit (rBS) of cholera toxin (1 mg per dose) plus formalin/heat killed whole cell of V. cholera O1 (classical and El Tor, Inaba and Ogawa) • Because of toxin, vaccine provides some protection to Enterotoxigenic *E. coli* (ETEC) • To protect the toxin from gastric acid, it must be given with bicarbonate buffer	WC vaccines do not contain the bacterial toxin B subunit and therefore do not protect against ETEC	Engineered attenuated V. cholerae O1 classical Inaba strain CVD 103-HgR
• Vaccine is available in 3 mL, single dose vials together with the bicarbonates buffer (effervescent granules in sachets) • Vaccine and buffer should be dissolved in 150 mL of water in children >6 years and adult, in 75 mL for children <5 years • Intake of food and water should be avoided 1 hour before and after the vaccination	Euvichol and Shanchol: 1.5 mL glass vial with rubber stopper and aluminum lid	• There are two sachets, one contains lyophilized vaccine and another as buffer powder • Reconstitution is done by mixing the both sachet in 100 mL water and it should be consumed within 15 minutes of reconstitution in a single dose
Primary immunization • Not licensed for use in <2 years of age • Children 2–5 years of age, 3 oral doses given 7 days—6 weeks apart • Two doses are recommended in adults and children >6 years. Interval between the dose should be at least 7 days but not >6 weeks • If second dose is not administered within 6 weeks after the first dose, whole schedule should be repeated	Two doses are given at an interval of 14 days in persons with age ≥1 year	Approved for the use in 18–64 years of age
Booster dose • **Children 2–5 years—**booster dose every 6 month of primary immunization. If booster dose is not administered in time, whole schedule should be repeated • **Children age >6 years and adults—**booster dose every 2 years. If booster dose is not administered in time, whole schedule should be repeated	No recommendation regarding booster dose exists	No recommendation regarding timing and use of booster is currently available, probably because it provides long-term immunity after a single oral dose
Protection • Provides 60–85% protection for the first few months • 60% protection over 5 years among recipient of all age • 40% protection among children ≤5 years of age		Between 80–90% efficacious against severe cholera at 10 and 90 days after vaccination respectively
• If cold chain (2–8°C) is maintained. Self-life is 3 years. It stable only for 1 month at 37°C	Self-life is 2 years at maintenance of cold chain (2–8°C) and remains stable for 14 days at 42°C	Cold chain temperature (–25 to –15°C)
• Can be safely given in among populations with high rate of HIV infection and in pregnancy		Safety in pregnancy is not established

of contaminated food and laboratory exposure are also the source of infection. During bioterrorist attack, primary pneumonic plague caused by aerosolized *Y. pestis* bacteria in non-endemic areas is a public health problem.[10]

Epidemiology

- Three major plague pandemics have been recorded in human history: the "Plague of Justinian" in the 6th century, again in the 14th century (known as the "Black Death," which killed up to one-third of the European population or an estimated 17–28 million people, and at the end of 19th century following the spread of infection from China.
- Plague is prevalent in all part of the world except, Oceania.
- Peru, Madagascar, and the Democratic Republic of Congo are the most endemic countries.
- Plague does occur in Asia, but is restricted to breeders and hunters since the reservoir consists mainly of gerbils in the steppe and marmots in the mountains.
- During epidemic season, cases of bubonic plague are reported every year in Madagascar.

Symptoms

Symptoms of plague usually develop after an incubation period of 1–7 days. Initial symptoms are nonspecific including high grade fever, headache, sore throat, body ache and generalized weakness. Specific symptoms depend upon types of plague.[11]

Bubonic Plague: Most common form (80–95% cases) of plague. Apart from nonspecific symptoms, there is rapidly progressive, painful lymphadenitis (known as "bubo"). The common sites for lymphadenitis are regional lymph nodes, and near the site of flea bite. Suppuration over buboes can occur and it is differentiated from other conditions by absence of cellulitis and ascending lymphangitis. Case fatality rate in untreated bubonic plague is higher (50–90%) in comparison to treated cases (10–20%), mostly because of disseminated infection. In advanced stage it causes secondary pneumonic plague and meningitis due to spread to the lungs and brain, respectively. Bubonic plague patients can presents with abdominal discomfort.

Pneumonic Plague: Depending on the type of exposure it is of two types; Primary pneumonic plague—caused by the direct inhalation of bacteria into the lungs. It manifests earlier, having incubation period of few hours to few days. It starts with non-specific symptoms, then progresses to dyspnea, chest pain, cough, sputum production, hemoptysis, tachypnea, and signs of hypoxemia and toxemia. Secondary pneumonic plague—It is more common form and is caused by hematogenous spread of bacteria to the lungs from a bubo or other source. Ten to fifteen percent of bubonic plague patients develop secondary pneumonic plague, if treatment of bubonic plague is delayed. Diffuse alveolar infiltrates of chest X-ray, and interstitial pneumonitis on computed tomography are typical of pneumonic plague. Untreated pneumonic plague is almost always fatal, and mortality is very high.

Septicemic Plague: It occurs in 10–20% of cases in advance stages of the disease. Patient is febrile having gastrointestinal symptoms and present as Gram-negative septicemia (hypotension, shock, disseminated intravascular coagulation, and multiorgan failure). Risk factors for septicemic plague include, age more than 40 years, diabetes mellitus and hemochromatosis. Their diagnosis is difficult because it occur without any preceding bubo.

Other Types

Meningitis: It can occur as primary manifestation as result of occult bacteremia or associated with bubonic, pneumonic, septicemia plague. It resembles to bacterial meningitis by symptoms and CSF examination (low glucose, increased protein with neutrophilic pleocytosis).

Pharyngitis and Tonsillitis: Manifest with nonspecific symptoms along with anterior cervical lymphadenitis. Patient with no symptoms can act as carrier for bubonic plague cases. In approximately 14% cases, involvement of GIT and urinary tract is also seen. Some patients may present with multiple organ failure and die without diagnosis, if symptoms are non-specific without bubo and there is no outbreak of plague in that geographical area.[10,11]

Laboratory Investigations

In plague endemic areas, neutrophilic leukocytosis (10,000–100,000/μL) with left shift, normal or low-normal platelets and symptoms (fever, unexplained regional lymphadenitis, and hypotension) with known contact with dead rodents is diagnostic clue. Blood culture is positive

in 27–96% cases. *Y. pestis* can be cultured from pus from bubo in bubonic plague, from sputum or broncoalveolar lavage sample in pneumonic plague, from blood in septicemic plague and from CSF in meningitis. Peripheral blood smears, microscopic aspirate of bubo may show rod shaped organism with Wright-Giemsa stain and typical bipolar staining as "closed safety pin" on Wayson's stain. Serologic testing of single titer of >1:16 of F-1 antigen of *Y. pestis* by passive hemagglutination test is diagnostic. Rapid diagnostic test can detect F-1 antigen of *Y. pestis* (0.5 ng/mL) within 15 minutes in serum and sputum in field testing.[8,9] WHO case definition is given in **Table 4**.[10]

Plague Outbreaks Managements[12]

- *Find out the suspected case:* During epidemic situation diagnosis of suspected case is based on clinical ground (acute febrile illness with painful lymphadenopathy) and in other situation rat falls (dead rats) provide a useful warning of a possible outbreak. Suspected case should be confirmed bacteriologically.
- *Notification* of each and every human or rodent plague case.
- *Isolation:* Isolation of suspected pneumonic plague patients is recommended until either the pneumonia is excluded or patient is treated for 48 hours with effective drugs, because they can spread the disease by aerosol generation.
- Maximum infectivity is in final stage of disease when patients are coughing sputum with plenty of blood or pus. Though simple cotton mask or surgical masks usually provides barrier protection against droplets but WHO recommends personal protective equipment's for potential aerosol generating procedures and should include an N-95 face mask, a gown, gloves, and a face shield or goggle.[8]
- *Appropriate antibiotic treatment of cases:* It should be initiated within 24 hours, ideally after specimen for culture are obtained. It is continued for 10–14 days or a course can be continued until 2 days after fever subsided **(Table 5)**.[10,11,13]
- *Surveillance:* Identification and monitoring of individuals having history of close contact.
- *Disinfection:* Disinfection by hand washing with soap and water, use of alcohol based hand rubs or house made disinfectant (10% diluted bleach).
- *Ensure safe burial practices:* Proper disposal of dead body of a suspected pneumonic plague patient should be ensured.

TABLE 4 WHO case definition of plague[10]

Suspected case	Compatible clinical presentation *and* consistent epidemiologic features, such as exposure to infected animals or humans and/or evidence of flea bites and/or residence in or travel to a known endemic focus within the previous 10 days
Presumptive case	Meeting the definition of a suspected case *plus* *Putative new or reemerging focus:* ≥2 of the following tests positive • Microscopy: Gram-negative coccobacilli in material from bubo, blood, or sputum; bipolar appearance of Wayson or Wright-Giemsa staining • F1 antigen detected in bubo aspirate, blood, or sputum • A single anti-F1 serology without evidence of previous *Yersinia pestis* infection or immunization • PCR detection of *Y. pestis* in bubo aspirate, blood, or sputum *Known endemic focus:* ≥1 of the following tests positive • Microscopic evidence of Gram-negative or bipolar (Wayson, Wright-Giemsa) coccobacilli from bubo, blood, or sputum • A single anti-F1 serology without evidence of previous plague infection or immunization • F1 antigen detected in bubo aspirate, blood, or sputum
Confirmed case	Meeting the definition of a suspected case *plus* • Identification of an isolate from a clinical sample as *Y. pestis* (colonial morphology and two of the following four tests positive: phage lysis of cultures at 20–25°C and 37°C; F1 antigen detection; PCR; *Y. pestis* biochemical profile) or • A fourfold rise in anti-F1 titer in paired serum samples or • In endemic areas when no other confirmatory test can be performed, a positive rapid diagnostic test with immunochromatography to detect F1 antigen

TABLE 5 Treatment of plague cases

Drugs	*Dose*
Streptomycin (Preferred-FDA approved)	30 mg/kg/day (up to total dose 2 gm) in two divided doses intramuscular
Gentamicin	2 mg/kg loading dose followed by 1.7 mg/kg every 8 hourly intravenously (in children 2.5 mg/kg IV every 8 hours)
Doxycycline	200 mg loading dose on first day followed by 100 mg every 12 hourly orally or intravenously in adult and child ≥45 kg, child <45 kg—2.2 mg/kg (maximum, 100 mg/dose) IV every 12 hours
Tetracycline	Oral 2 gm loading dose followed by 2 gm/day in four divided doses (not indicated in children <7 years of age)
Levofloxacin	Adult and child ≥50 kg—500 mg OD oral or intravenously, child <50 kg and ≥6 months of age—16 mg/kg (maximum 250 mg/dose) oral or intravenously every 12 hours
Ciprofloxacin	400 mg IV every 12 hours or 500 mg orally every 12 hours in adult In children—15 mg/kg IV every 12 hours or 20 mg/kg orally every 12 hours
Chloramphenicol	In adult and child >2 years—100 mg/kg (maximum, 4 gm) in four divided doses (oral or intravenous), very useful in plague meningitis because of its ability to penetrate the blood brain barrier

- *Protect health workers:* Training of health workers about infection prevention and control measures. Workers having history of close contact with pneumonic plague patients should take 7 days chemoprophylaxis. Disinfection, distancing, and PPE should be used appropriately.

Prevention

Prophylaxis: Post-exposure prophylaxis is recommended to individuals with unprotected close contact (face to face or 1–2 meter) with suspected or confirmed pneumonic plague and family members of a bubonic plague patient. Oral doxycycline 100 mg twice daily for 7 days or oral levofloxacin 500 mg once daily for 10 days are used for this purpose. In pregnancy double strength tablet of co-trimoxazole twice daily and in children trimethoprim 4 mg/kg twice daily has been used safely.[11]

Vaccination: A whole cell killed vaccine given at least a week before anticipated outbreak as its immunity starts after 5–7 days of first dose vaccine. Two subcutaneous doses of 0.5 mL and 1 mL, at an interval of 7–14 days are given. Booster dose is recommended 6-monthly for persons at continuing risk of infection as its immunity persists for 6 months. Vaccination is also recommended for travelers to endemic areas and those having increased risk of disease.

Control of Fleas: To break the chain of transmission (rodent->flea->man) proper application of insecticides (dust containing DDT 2%, BHC 2%, Malathion 5%, and Carbaryls 2%) are used. Rat borrows should be insufflated with the insecticidal dust. This must precede or coincide with anti-rodent measures.

Control of Rodents: Control of rodents is an important plague preventive measure. It improves with improvement of general sanitation, improvement of housing and quality of life.[14]

Conclusion

Though the number of cholera cases has been decreased in India, but the social, epidemiological, and ecological conditions in remote areas continue to favor the occurrence. World Health Organization has planned to reduce the cholera-related deaths by 90% till 2030. They focused on three important strategies; early detection of cholera cases and rapid response to contain outbreaks, prevention of recurrence by targeted multi-sectoral approach, and an effective mechanism of coordination for technical support, resource mobilization, and partnership at different levels. Like cholera cases, a number of plague cases are also reduced due to good availability of effective drugs, improvement of sanitation, improvement of housing and quality of life. Primary pneumonic plague caused by aerosolized *Y. pestis* is having high fatality rate. As *Y. pestis* has the capacity to infection through aerosol, it fits into the category of a potential agent of bioterrorism. Its outbreak should be identified as soon as possible and appropriate steps should be followed for its management.

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CHAPTER

166 Cryptococcal Disease: A Review

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Abstract

Cryptococcosis is an opportunistic mycosis which was uncommonly identified before the HIV/AIDS pandemic. It is responsible for high mortality among people living with HIV/AIDS (PLHA) and also among other non-HIV immunocompromised people. Cryptococcus is one of the four fungal species accounting for almost 90% of fungal infection-related deaths in the world, the other three being Candida, Aspergillus, and Pneumocystis. *C. neoformans* is found in high concentrations in bird guano and *C. gattii* in decaying vegetation especially that of the Red River gum trees (*Eucalyptus camaldulensis*). The preferred sites of infection by *C. neoformans* and *C. gattii* are lungs and central nervous system. In an immunocompromised person, cryptococcus can disseminate widely involving skin, bone/joints, prostate, and eyes. The most severe clinical manifestation of cryptococcal infection is meningoencephalitis. There are three mechanisms by which infection can spread from the lungs to brain: one, by disruption of vascular integrity leading to passive hematogenous transport; two, by endothelial cells phagocytosing spores from blood stream and later expulsing them to circulation; and three, by movement of the yeasts from the bloodstream into CNS within macrophages using the Trojan Horse mechanism. Diagnosis of cryptococcosis is based on direct visualization of the yeast, histopathology of tissue specimens, culture, and detection of cryptococcal antigen (CrAg). Cryptococcal meningitis (CM) in PLHA is associated with high mortality. Timely diagnosis and optimal therapy are both required to prevent deaths. Treatment of CM is divided into three phases: induction, consolidation, and maintenance. Three drugs have been traditionally used in the treatment of CM: amphotericin B (AmB) or liposomal amphotericin (L-AmB), fluconazole (FLU), and flucytosine (5FC). A number of strategies have been evaluated and implemented to prevent CM in PLHA with low CD4 cell counts in resource-limited settings like starting preemptive fluconazole therapy in CrAg-positive patients with low CD4 cell count.

Introduction

Cryptococcosis is an opportunistic mycosis which was uncommonly identified before the HIV/AIDS pandemic. It is responsible for high mortality among people living with HIV/AIDS (PLHA) and also among other non-HIV immunocompromised people. The ability to detect cryptococcal antigen (CrAg) has enabled us to estimate the global prevalence of the infection. Cryptococcal antigenemia is prevalent in about 6% (95% confidence interval 5.8–6.2%) of PLHA with CD4 cell count ≤100 cells/μL (severely immunocompromised). In absolute numbers this is a staggering 2,78,000 people. Of these, 2,23,000 developed cryptococcal meningitis (CM) in 2014 and 73% of these cases occurred in sub-Saharan Africa (SSA). It is estimated that 1,81,000 PLHA die of CM every year with 75% of these deaths occurring in SSA.[1] About 50% of PLHA with CM die within a year of contracting infection mainly due to unsuccessful/inadequate treatment.[2] AIDS-related CM causes 20–25% of AIDS-related deaths every year.[3] Cryptococcosis has been increasingly recognized in non-HIV immunocompromised people. In countries with good health-care systems with equitable access to timely care,

25% of all CM-related hospitalizations and deaths occur in non-HIV patients. In the US, CM is the commonest cause of non-viral meningitis now.[4] Different serotypes of *Cryptococcus neoformans* have been associated with CM in PLHA and those without HIV/AIDS. However, the boundaries are getting increasingly blurred now.

Cryptococcus is one of the four fungal species accounting for almost 90% of fungal infection related deaths in the world, the other three being *Candida, Aspergillus,* and *Pneumocystis.*[5] There are 37 species of Cryptococcus in the genus Filobasidiella of the phylum Basidiomycota. Most human infections can be attributed to *C. neoformans* or *Cryptococcus gatti.*[6] Based on the capsular polysaccharide, glucuronoxylomannan (GXM), the yeast form of *Cryptococcus neoformans* is classified into four serotypes, A through D. Serotypes A and D of *C. neoformans* are responsible for most human infections.[7] *C. neoformans var. grubii* (serotype A) accounts for 90% of human infections. It is worldwide in distribution and is especially associated with CM in people with CD4+ T cell deficiency (mainly HIV-infected and also in transplant recipients and those with rheumatological disorders requiring immunomodulatory therapy).[8,9] *C. neoformans var. neoformans* (serotype D) is also global in distribution but is mostly identified amongst human cases in Europe. *Cryptococcus gattii* (serotypes B and C) was for long thought to be a tropical/subtropical fungus but it has now been discovered in high temperate zones like Northwestern US, Vancouver, and other parts of British Columbia in Canada. *C. gattii* causes disease among those with "normal" immune system. It is now also being recognized as a pathogen in PLHA, and people with other immunodeficiencies especially those with autoantibodies against granulocyte-monocyte colony stimulation factor (GM-CSF).[10]

CM in both HIV-infected and HIV-negative with immune deficiencies is plagued by IRIS which causes considerable morbidity and mortality. IRIS as a disease entity came into its own only in the course of the HIV pandemic when highly active antiretroviral therapy was introduced. About 10–25% PLHA without a known opportunistic infection (OI) starting ART develop IRIS.[11,12] Most IRIS events occur within the first 2–3 months of initiating ART. But delayed IRIS has been reported with cryptococcal and CMV infections and these can occur many years later. Approximately 25% of CM patients receiving ART and antifungal therapy will develop IRIS and mortality associated with Cryptococcal IRIS (cIRIS) varies from 0% to 67%.[13-16] In HIV-negative patients with CM, IRIS has been reported with reversal of iatrogenic immunosuppression especially with TNF-α inhibitor therapy.[17] IRIS has triggered a deep study of the immunobiology of HIV-associated OIs and new insights have opened up new immunomodulatory interventions.

Pathobiology

C. neoformans is found in high concentrations in bird guano, especially in the droppings of pigeons and chicken. *C. gattii* is found in decaying vegetation especially that of the Red River gum trees (*Eucalyptus camaldulensis*).[7,18] Cryptococcus survives in the environment as a yeast (sexual form), producing hyphae with terminal basidiospores which may break off and then become aerosolized. Since their average diameter is 3 microns, they are small enough to travel right up to the alveoli. In most hosts, the infection is asymptomatic. A seroprevalence study done among children in New York revealed that 70% had antibodies against cryptococcal antigens. It seems that asymptomatic colonization of airways and latent infection of lungs and airways maybe common.[19,20] Autopsy studies have shown granulomatous lesions in lung parenchyma and sub-pleural nodules containing yeast forms.[21,22] Just as in tuberculosis (TB), a robust immune system keeps the infection from manifesting as clinical disease. The most severe clinical manifestation of cryptococcal infection is meningoencephalitis. There are three mechanisms by which infection can spread from the lungs to brain: one, by disrupting vascular integrity leading to passive integrity leading to passive hematogenous transport, two, by endothelial cells phagocytosing spores from blood stream and later expulsing them to circulation, and three, by movement of the yeasts from the bloodstream into CNS within macrophages using the Trojan Horse mechanism. On crossing the blood brain barrier, the fungal cells are released by vomocytosis. Just as in TB, hematogenous spread can occur during primary infection or due to reactivation when immunity is lowered. Severe disease can develop many years after primary infection.[3,23] Pirofski and Casadevall proposed a mechanism which allows the host to tolerate infection for long periods without manifesting disease. They termed it the disease tolerance and damage response framework (DRF). This system mainly evolved to mitigate and avoid damage to the lungs and brain.[24,25]

The DRF is based on the interplay of microbial and host factors that may either cause disease or produce a net benefit to the host. The highly dynamic and complex interaction between the fungal virulence factors and host's immune response can result in a variety of outcomes ranging from debilitating disease to colonization, latency and commensalism. *Cryptococcus sp*. have an array of mechanisms that enable them to survive, proliferate, and disseminate in a mammalian host. The fungus produces numerous enzymes which cause damage at a molecular level. These include proteases, phospholipase, urease, and nuclease. At a cellular level, cryptococcus can damage host cells by interfering with phagolysosome maturation, increasing permeability of phagosome membrane, interfering with organelle function, causing cytoskeletal alterations, cytoplasmic vacuolation and both lytic and non-lytic exocytosis. The first step in the protective response against cryptococcal infection is the production of proinflammatory cytokines, then followed by generation of an effective Th1/Th17 adaptive immune response and classical activation (M1 type) of macrophages. All these processes lead to fungal clearance. A robust response commensurate with fungal burden can lead to excessive tissue damage. A good example of this is cryptococcal IRIS. In immunocompromised patients, both inflammatory response and immune function are compromised enabling unbridled fungal replication resulting in high fungal burden. The ideal scenario is one where the host resistance mechanisms are balanced by the host tolerance mechanism. This leads to minimal/or no clinical disease and probably fungal latency. The host resistance mechanisms, namely proinflammatory cytokine production, activation of dendritic cells (DCs), generation effective Th1/Th17 response, and M1 type macrophage polarization are balanced by cryptococcal and host disease tolerance mechanisms.

Cryptococcus-associated disease tolerance strategies can be grouped as metabolic adaptions to physiological conditions in the host, evasion, and interference with innate and adaptive immune responses. Cryptococcus can activate gene expression that enables it to survive in human cells at 37°C and also in nutrient-poor environments like the CNS. The fungus van produce meaning using host catecholamines. This reaction is mediated by fungal phenoloxidase. It is this ability to use catecholamines that gains the fungus a niche in the CNS. The capsule serves as a principal defense against innate immune mechanisms. The capsule conceals cell wall carbohydrate antigenic epitopes, inhibits antibody binding to fungal cell wall, and activates and depletes complement factors. The capsule modulates cytokine production and suppresses T cell proliferation. It also induces apoptosis of host cells. During active infection, cryptococcal cell capsule can enlarge leading to formation of giant "Titan" cells. The size of these cells varies from 50 to 100 microns and this large size inhibits phagocytosis. Fungal cells can release their capsular glucuronoxylomannan (GXN) and this causes shedding of L-selectin from neutrophils. Loss of L-selectin inhibits neutrophilic migration, endothelial adhesion, and extravasation into tissues. Other capsular factors can interfere with maturation and activation of neutrophils, DCs, and macrophages. The yeast cells secrete a number of enzymes that enable them to survive in the harsh environment of the phagolysosome. These are mainly involved in nitric oxide detoxification and neutralizing oxidative stress. Other enzymes and substances that enable the fungus to survive intracellularly include urease, phospholipase B1, laccase, melanin, and heat shock protein70 homolog Ssal 1. The ability to escape from host cell without causing its lysis is the most important mechanism for persistence of cryptococcus in host tissue. This non-lytic escape from phagocytes is also called vomocytosis. This enables the organism to prevent the inflammatory response that would be associated with host cell death. *Cryptococcus sp.* are able to swing cellular immune response toward a non-protective Th2 response by two main mechanisms: cryptococcal urease recruits immature DCs to lymphoid tissue in the lungs, and host chiotriosidase cleaves fungal chitin and triggers CD11 b^+ conventional DCs to undergo Th2 differentiation. *C. neoformans* secretes prostaglandin E2 (PGE2) that suppresses Th17 differentiation. A strong Th17 response is critical for a sterilizing immune response. In fact, this process facilitates latent infection.

The host immune response to cryptococcal infection that leads to disease tolerance is due to T regulatory (Treg) cells, IL-10 signaling, DC response, role of tryptophan pathway and T cell exhaustion. Tregs are involved in the production of anti-inflammatory cytokines like IL-10, and transforming growth factor-β. Severe pathology occurs when there are mutations in Treg-associated transcription factor fork head box protein P3 (FOXP3). CrAg-specific

Tregs can colocalize with Th2 effector cells in infected lungs and thereby limit inflammatory damage. IL-10 is an anti-inflammatory cytokine that is secreted by Tregs and DCs. It inhibits production of IL-1, Il-6, IL-23, IFN-γ, TNF-α in fungal infections. In PLHA with cryptococcal infection, high levels of IL-10 correlate with fungemia and dissemination. Therefore, IL-10 levels can be a surrogate marker of progressive or persistent cryptococcal infection. Among the antigen presenting cells, DCs are the ones that can present cryptococcal antigens most efficiently to T cells. Development of a Th1/Th17 immune response greatly depends on classical activation of monocyte-derived DCs (MoDCs). As mentioned earlier capsular characteristics can affect DC activation. The local cytokine and chemokine milieu also affects their activation. Immunomodulatary DCs have been known to evolve in the course of infection and they can lead to Th1/Th17 suppression, reduced macrophage activation and impaired fungal clearance. Indoleamine 2,3-dioxygenase (IDO) is an enzyme involved in tryptophan metabolism. It plays an important role in balancing the activity of Tregs and Th1/Th17 cells. Expression of IDO by DCs leads to a tolerogenic phenotype in experimental models. The same has not been demonstrated in humans with cryptococcal infection. Its significance is still to be explored. A state of chronic immune activation can lead to T cell exhaustion. One of the mechanisms that promotes this is the upregulation of cytotoxic T lymphocyte-associated protein-4 (CTLA-4). T cell activation and function depend on a double signal: the binding of antigen presented by MHC to T cell receptor and binding of CD80 and CD86 on anitigen-presenting cell to CD-28 on T cell. CTLA-4 binds to CD80 and CD86 and thus blocks CD-28. In the absence of this co-stimulatory signal T cells become anergic. In murine cryptococcal infection models, upregulation of CTLA-4 has been demonstrated. Sustained expression of programmed cell death protein-1 (PD-1) on CD4 T cells, DCs and macrophages is also associated with persistence of infection. Modulation of levels of CTLA-4 and PD-1 could be strategies for treating cryptococcal IRIS (cIRIS).[4,26,27]

Cryptococcal IRIS

T cell depletion in HIV infection severely compromises adaptive immune response and this can lead to unbridled fungal dissemination to the meninges. Immune restitution with ART predisposes patients with CM to IRIS. Evolution of cIRIS goes through three stages: pre-ART paucity of inflammatory response, innate cell activation, and immune dysregulation. During the pre-ART phase both innate and adaptive immune responses are compromised. Migration of neutrophils into the meninges and their fungistatic activity is compromised. Poor antigenic clearance and risk for IRIS are linked to decreased levels of IL-6, IL-8 and TNF-α (innate inflammatory cytokines) and IFN-γ (adaptive inflammatory cytokine). Risk of cIRIS increases with higher expression of CCL2 and CCL3. Natural killer cells with increased expression of CXCR3 and CX3CR1 also participate in the initial response to cryptococcal infection in CNS. When ART is started, T cell immunity takes some time to develop. In this interim, antigenic burden causes a buildup of proinflammatory signaling by antigen presenting cells. This is demonstrated by increased IL-6 and CRP levels in weeks preceding development of IRIS. When ART associated immune restitution reaches a critical level, a powerful Th1 response and cytokine storm herald the onset of IRIS. Phagocytic killing of intracellular pathogens is also defective due to absence of IFN-γ signaling from CD4 T cells in the pre-ART phase. But a buildup of partially primed myeloid cells occurs in the CNS during this time. When CD4+ cell reconstitution occurs with ART, activation of these myeloid cells with production of proinflammatory cytokines occurs. Myeloid cells that accumulate in CNS prior to IRIS are mainly proinflammatory intermediate monocytes. The final phase of IRIS is marked by immune dysregulation. In a normal response to a fungal infection classical activation of monocytes leads to increased fungal kill. However, this does not occur in immunocompromised people. Here the buildup is of intermediate monocytes with increased expression of programmed death ligand-1 (PD-L1). Their activity results in a powerful inflammatory response and less efficient fungal kill. Lymphopenia associated with HIV infection results in a homeostatic response to cryptococcal infection regulated by IL-6 and characterized by proliferation of naive T cells which resemble effector memory T cells. Later, during IRIS, these cells ramp up secretion of IFN-γ and push the immune activity toward a powerful Th1 response. Immune restitution also results in a robust increase of highly-differentiated memory $CD4^+$ T cells with no inhibitory control. The net result is severe inflammation, tissue destruction, and functional impairment.[28-32]

Clinical Features

The preferred sites of infection by *C. neoformans* and *C. gattii* are lungs and CNS. In an immunocompromised person, cryptococcus can disseminate widely. They can involve skin, bone/joints, prostate, and eyes. A retrospective study of cryptococcosis in Denver, Colorado, USA, showed that patients with cryptococcosis had, apart from features of CM, respiratory symptoms, hyponatremia, prior lung disease, or history of corticosteroid therapy.[33]

Respiratory System

The main route of entry of cryptococcus is through the respiratory tract. Clinical manifestations are varied and depend on immune status. In an immunoscompetent person it can be just a symptomless colonization of the airways or a pulmonary nodule detectable only on a radiograph. In the immunocompetent, the infection is accidentally discovered on imaging in up to one-third of the cases. The radiological manifestation maybe a solitary nodule or multiple nodules without calcification or pulmonary infiltrates. Hilar lymphadenopathy, pleural effusion, and cavitary lesions are also described. The presentation is more florid and dangerous when the immune system is compromised. In this setting the manifestation can be a severe pneumonia or a life-threatening acute respiratory distress syndrome (ARDS).[34,35] Isolated pulmonary cryptococcosis can occur in the absence of CNS involvement in the immunocompromised. In the presence of cryptococcal meningoencephalitis, pulmonary involvement is seen in 10–55% of PLHA. But here, neurological symptoms usually dominate.[35] A Chinese study in HIV-negative subjects reported slightly different findings. In this study, 49.3% of the subjects with CM had evidence of pulmonary cryptococcosis. They usually presented with fever, cough, expectoration, and lower limb edema rather than with CNS symptoms. Subjects with lung infection were also younger (<30 years) than those who did not have lung infection.[36] Serum CrAg is usually negative in truly isolated pulmonary cryptococcosis. Whenever cryptococcus is isolated from the lungs or other sterile body sites in an immunocompromised individual, a lumbar puncture to exclude CNS disease is recommended regardless of the patient's symptoms or serum CrAg titer results. The only exception for a diagnostic LP would be an immunocompetent person without CNS symptoms. Here, infection can be presumed to be limited to the lungs.

Central Nervous System

The presentation of CM is usually subacute with symptoms developing over weeks. Clinical symptomatology may include fever, lassitude, headache, altered sensorium, and focal deficits like cranial neuropathies. In severely immunocompromised patients, fungal burden in the CSF can be very high (>1 million yeast cells/mL of SF). In these patients presentation is usually acute and features of raised intracranial pressure maybe present. Their CSF will also show high CrAg titers. A study from SSA showed that seizures occurred at presentation in 28% (231/821) HIV positive subjects with CM and 15.5% developed seizures during the course of illness. Seizures at presentation were associated with lower GCS scores, lower CD4 cell counts increased CSF opening pressures when compared to HIV+ patients with CM but without seizures. CSF fungal burden was higher in those with seizures at presentation than in those developing seizures during course of illness.[37] *C. gattii* infections can cause cryptococcomas in the brain and can also cause obstructive hydrocephalus. In the lungs also it can cause mass lesions. Focal neurological deficits and cranial neuropathies due to cryptococcomas are common manifestations. These patients respond poorly to antifungal therapy and decompressive surgery may be required to relieve raised ICP. *C. neoformans* is less likely to cause such lesions.[38-40]

In the absence of a definite microbiological diagnosis, TB meningitis (TBM) is the commonest differential diagnosis for CM. In both, fever, headache, and vomiting are common presenting complaints. Altered mental status is more common in CM than in TBM in HIV-negative individuals. Altered vision and hearing are commoner in CM and cough is more likely in TBM. CM is associated with corticosteroid use, pulmonary infection, hepatobiliary disease and diabetes. Those with TBM are likely to have TB elsewhere outside CNS or disseminated TB.[36,41] In the Denver study, risk factors associated with CM were HIV infection, prior use of corticosteroids, malignancy, transplant status, lung disease, and active smoking.[33]

In HIV negative children with CM, fever, nausea, vomiting, and headache are the commonest symptoms. Meningeal signs, altered consciousness, and fundal changes are common findings. CSF opening pressure is

raised in most. Involvement of other organs is common with the lungs being the commonest.[42]

Among the elderly, those older than 65 years are more vulnerable to developing CM. There is a female preponderance and altered consciousness and cerebral infarction are more common than in the young.[36]

Skin

After pulmonary and CNS involvement, cutaneous manifestations are the commonest presentation of cryptococcosis. Usually the lesions are non-specific and similar to those seen in other infections. Primary cryptococcosis is uncommon and is due to direct inoculation of the fungus into the skin by injury or laboratory accidents. The lesions are single and occur at the site of innoculation. They can present as whitlow, papule, nodule, ulcerated lesion or cellulitis. In immunocompromised patients, dermal cryptococcosis is secondary to disseminated infection. Here the lesions tend to be multiple. Lesions often resemble those of molluscum contagiosum. They are flesh-colored papules/nodules with central umbilications. Pustules, acneiform lesions, abscesses, cellulitis, and gralulomata have all been described. Regional lymphadenopathy and discharging sinuses may occur. Skin biopsy and cultures are required to culture and identify the fungus. Solid organ transplant recipients on tacrolimus are prone to cutaneous cryptococcosis and osteoarticular involvement. Tacrolimus inhibits a protein required for cryptococcal growth at 37°C. It acts by interfering with calcineurin signaling pathway in the fungus. However, at lower temperatures (<24°C), this inhibitory activity is lost making patients on calcineurin inhibitors prone to cryptococcal infection.[43,44]

Immune Reconstitution Inflammatory Syndrome

Antiretroviral therapy leads to immune restitution in PLHA. When this process occurs in a severely immunocompromised person, it leads to a rebound of pathogen-specific immunity. This manifests as a clinical entity called immune reconstitution inflammatory syndrome. When there is a "paradoxical" deterioration of a known OI or appearance of the OI in new sites or "recurrence" of OI while on ART, it is called paradoxical IRIS. In unmasking IRIS, ART leads to an accelerated manifestation of an occult infection. In the context of cryptococcosis another entity is described and that is post-infectious inflammatory response syndrome which is a clinical deterioration in a previously healthy individuals. All of them also have an exaggerated anti-cryptococcal immune response. Cryptococcal IRIS causes severe morbidity and is associated with a high mortality.[14,45-47] Cryptococcal IRIS is a diagnosis of exclusion. Progressive infection secondary to suboptimal antifungal therapy, primary antifungal drug resistance or persistent immune deficits, other coexistent OIs (like TB), malignancy, and drug toxicity need to be excluded. Risk factors for IRIS include severe immune deficiency at baseline with rapid immune restitution with ART, high fungal burden at baseline and ineffective immune repose in the host during initial infection. The commonest time period for cIRIS is within first 3 months of starting ART. Classical features of cIRIS in HIV infected patients with low CD4 cell counts include little or no meningeal irritation despite high cryptococcal load, extremely high serum and CSF CrAg tiires, muted inflammatory response in CSF manifesting as low CSF WBC count, and high yeast burden on CSF microscopy and ease in culturing yeast from CSF or serum.[48]

Laboratory Diagnosis

Diagnosis of cryptococcosis is based on direct visualization of the yeast, histopathology of tissue specimens, culture, and detection of CrAg. Molecular methods, although available and extensively used for research purposes, are not used currently in routine clinical practice.

Direct visualization is traditionally by India ink staining. The fungus appears as a globular, encapsulated yeast cells which may or may not be budding. The yeast cell size varies from 5 to 20 μm in diameter. India ink staining is the most rapid method for diagnosis of CM and has been the method in vogue in low-income countries for a long time. The sensitivity is only 80–85% for AIDS-related CM, meaning that 1 in 7 diagnoses will be missed. Sensitivity falls to about 40% in patients with low fungal burden (<1,000 CFUs/mL of CSF). Detection of yeasts is operator dependent. Lysed WBCs can be mistaken for fungal elements.[49,50]

Histopathology

Cryptococcus can be detected from a variety of tissue samples like lungs, brain, skin, bone marrow, lymph nodes,

and other organs.[51] Histopathology is more sensitive than India ink staining. Special staining techniques are available to visualize different fungal elements. Mucicarmine, Alcian Blue, and Periodic-acid-Schiff stain the fungal polysaccharide capsule. The melanin in the yeast cell wall is delineated by Fontana–Masson stain. Gomorri-methenamine-silver stain also enables visualization of the cell wall. Calcofluor binds to fungal chitin.[52,53]

Culture

Cryptococcus can be cultured readily using routine fungal or bacterial culture media. CSF, sputum, and skin biopsy sample all yield the fungus easily. The sensitivity of CSF and blood cultures in adult PLHA with CM is 90% and 50–70% respectively. Volume of inoculum determines the culture sensitivity. It is 82% for 10 μL of CSF and 94% for 100 μL.[54,55] Fungal culture remains relevant even today for clinical, therapeutic, and research reasons. For the clinician, cultures help confirm clearance of the yeast from CSF after induction therapy, and to distinguish between relapse of CM and paradoxical IRIS. Serial cultures have a log 10-linear clearance. This enables computation of early fungicidal activity (EFA). EFA is a useful marker of drug regimen potency and is also used as an efficacy endpoint in phase II trials. Quantitative cultures allow measurement of fungal colony forming units (CFUs) from CSF. The disadvantages of using culture for diagnosis are that results become available only in 3–7 days, and in a setting of low fungal burden, cultures can be negative.[56]

Serology

Serological tests to detect cryptococcal capsular antigen has made diagnosis of cryptococcal infection easy and fast. CrAg has been detected in CSF and serum using latex agglutination and enzyme immunoassay (EIA) techniques for more than two decades. The sensitivity of CrAg-Latex for serum and CSF is 83–97% and 93–100%, respectively. The specificity for serum and CSF is 93–100% and 93–98%, respectively. For EIA, the sensitivity for serum and CSF is 94% and 100% respectively and the specificity is 96% and 98% respectively.[55,57] Both CrAg-Latex and EIA have some disadvantages. The CrAg-Latex is a manual test and there is a high degree of subjectivity in its interpretation. Both require laboratory infrastructure, and refrigeration of reagents thereby making the tests expensive. CrAg-Latex has lower sensitivity for CrAg of serotype C (*C. gattii*). EIA had a lower sensitivity for serotypes C and D. False positive test results are low but known (<1%). These are due to technical issues, contamination or infection with *Trichosporon beigelli, Capnocytophaga canimorsus,* and *Stomatococcus mucilaginosus*. False negatives can be seen early in infection due to a low fungal burden, due to poorly encapsulated organisms and due to prozone effect in the setting of extremely high antigen titers, which can be overcome with dilution.[58] False-negative results in latex agglutination tests can occur in the early stages of infection when fungal burden is low and also because of improper storage of clinical sample.[49,52,54,59]

The US FDA has approved a lateral flow immuno-chromatographic dipstick assay (LFA) for serum and CSF. The European Union has approved it for serum, plasma, and CSF. It can detect CrAg of all species of cryptococcus. The test uses a combination of two monoclonal antibodies. The first one is reactive one against CrAG of serotypes A, B, and C. The other is highly reactive against CrAg of serotypes A and D. The test can be done in five easy steps **(as shown in Fig. 1)** and and takes 10 minutes to give the result. The test meets the World Health Organization's (WHO) "ÁSSURED" çriteria. It is *a*ffordable (i.e., cheap), *s*ensitive (equal to or better than other CrAg tests), *s*pecific (similar to other CrAg tests), *u*ser-friendly (just as easy as the pregnancy test), *r*apid and robust (done in 10 minutes), *e*quipment-free, and *d*elivered (i.e., it is portable and light-weight with a long shelf-life and requiring no refrigeration).

CrAg LFA can be used both qualitatively and semiquantitatively. A schematic representation of CrAg LFA is shown in **Figures 2A and B**. The test has been validated in a large muticentric study in South Africa and Uganda. The test has a sensitivity and specificity of 99.3% and 99.1% respectively. The data provided by the manufacturers state that LFA has a sensitivity and specificity of 99.5% and 99% respectively and, positive predictive and negative predictive values of 98% and of 99.7% respectively with serum, plasma, urine, or CSF samples when compared to cultures. There is 100% concordance for serum and plasma tested by fingerstick LFA test and 100% negative predictive value for excluding CM. The finger stick LFA can show false negative result in a scenario of asymptomatic patient with a low fungal burden. Pipetting whole blood on to the LFA can increase diagnostic yield over direct application of blood to CrAg

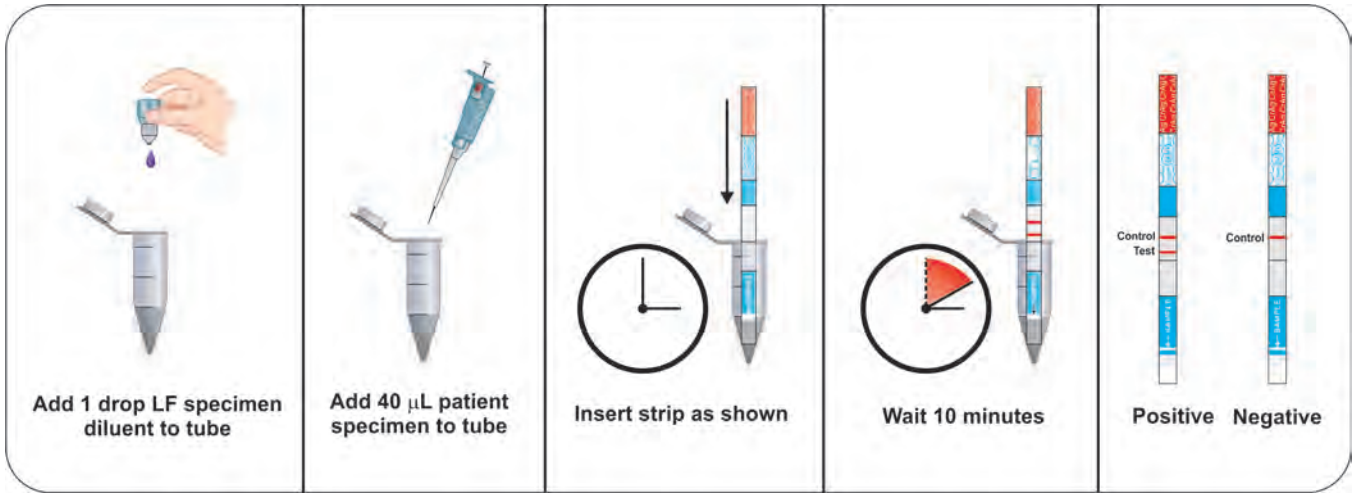
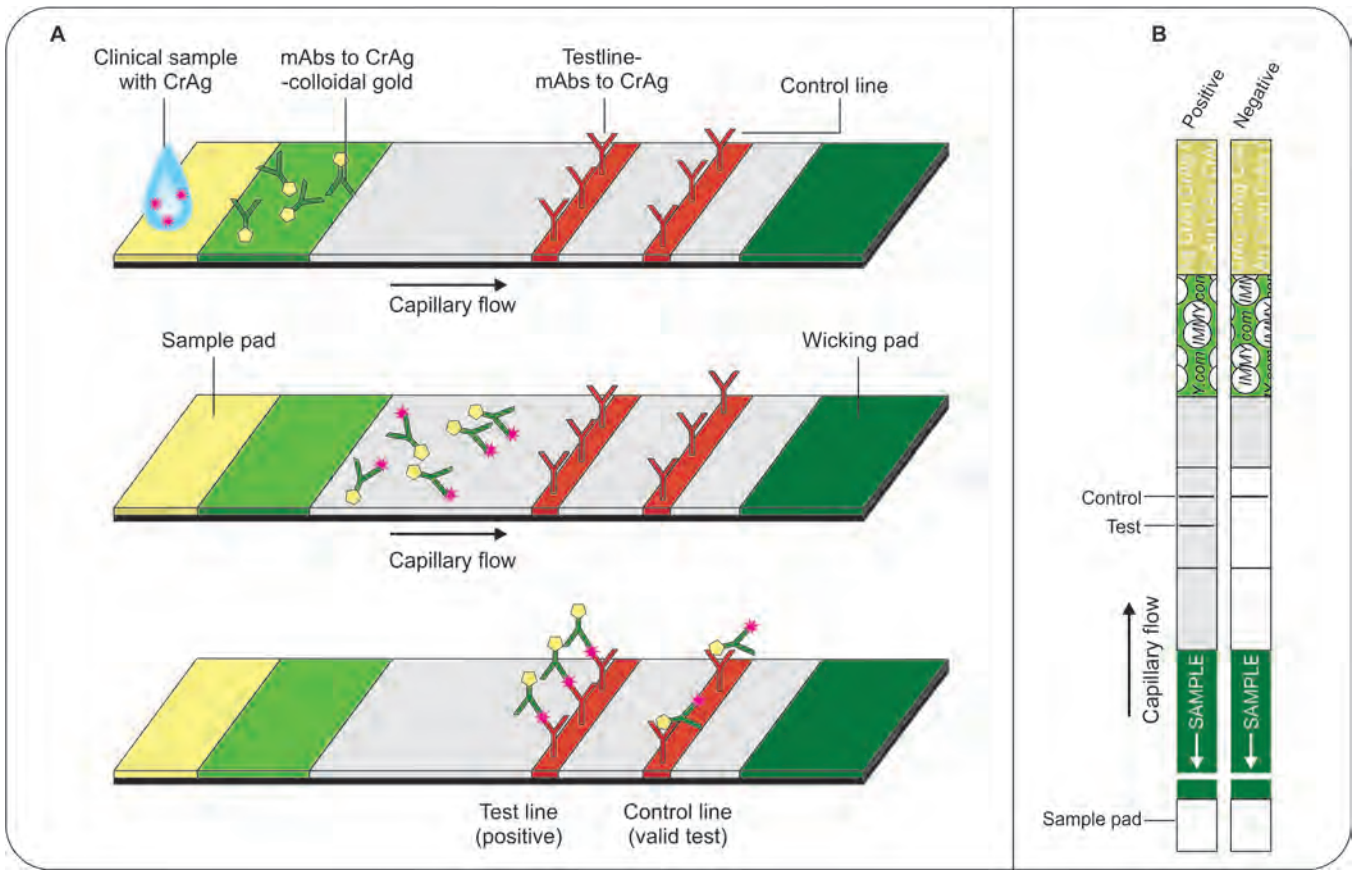


Fig. 1: Five easy steps to detect cryptococcal antigen using LFA. Step 1: add one drop of specimen to a tube. Step 2: add of 40 µL (1 drop) of patient specimen to the tube. Step 3: insert the LFA strip into the tube. Step 4: incubate for 10 minutes. Step 5: interpret results[60]



Figs. 2A and B: (A) Schematic representation of lateral flow immunochromatographic assay for detection of CrAg. (B) Images of positive and positive and negative controls[61]

LFA sample pad.[62] CrAg LFA is about 5 times more sensitive than CrAg-Latex when comparing semi-quantitative titers by serial dilution. This means that a specimen positive by CrAg-Latex at 1:8 dilution will be positive by CrAg LFA at 1:40 dilution. The semiquantitative assay reports the highest dilution that gives a positive result.

CrAg detection is used for detecting early CM, screening PLHA for cryptococcal infection, and for prognostication and therapeutic decision-making (when it is done semi-quantitatively).

Detection of Early Cryptococcal Meningitis

A study in Uganda investigated 1201 HIV positive individuals hospitalized for suspected meningitis. Fifty-six percent of these patients (671/1,201) had CM confirmed by CSF CrAg positivity. Four percent of the subjects with neurological symptoms and CSF analysis negative for CrAG were found to have serum CrAg positivity. Cryptococcus was identified by culture or PCR in 9% of these serum CrAg+ and CSF CrAg- patients. This subset of patients with neurological symptoms, serum CrAg positivity, and CSF CrAg negativity constitute the early cryptococcal meningo-encephalitis' group. In-hospital mortality was 32% in symptomatic cryptococcal antigenemia and 31% in CM. These findings suggest that immunocompromised patients with suspected CNS infections should always have serum tested for CrAg especially when no CSF pathogen is detected and that in early cryptococcal meningoencephalitis, yeasts maybe present in brain parenchyma without meningeal involvement.[63]

Screening for CrAg

CrAg appears peripheral blood many weeks to months before the onset of symptomatic disease. There is thus an opportunity for early detection and pre-emptive action. Serological prevalence studies for CrAg in PLHA have been done in various parts of the world. The serological prevalence of CrAg in ART-naive asymptomatic PLHA with CD4 cell count <100/μL is 6.8% (95% CI: 2.2–21%) and 4–12.9% in Africa and Southeast Asia respectively. In Brazil, the prevalence in hospitalized PLHA with CD4 cell count <200/μL is 3.1% and 11.4% in two different studies. The global average prevalence in severely immunocompromised PLHA is 6%. The mathematics of cryptococcal screening for PLHA has been worked out. There are 110,500 severely immunocompromised PLHA in Uganda at risk of cryptococcal disease. Screening them and pre-emptively treating 15,500 people with fluconazole would cost $822,600 which is 15% cost of treating meningitis that would occur otherwise. It would also lead to 40% better long-term survival.[64] The low cost of LFA makes screening for CrAg compellingly cost-effective even in areas of prevalence as low as 1%. WHO recommends screening of all ART-naive PLHA with CD4 cell count <100/μL for cryptococcosis by CrAg testing in serum/plasma. It also recommends antifungal therapy if CrAg is positive to prevent development of disease.

CrAg Titer

Semi-quantitative estimation of antigenemia can be done by both CrAg-Latex and LFA by serial dilution titers. Unfortunately the test is not standardized and results can vary with kits from different manufacturers. The variability is more for the latex test. The CrAg LFA manufactured by IMMY is considered the gold standard diagnostic.[56] Semi-quantitative assays are clinically useful because antigenic titers correlate with disease severity and mortality. Plasma/serum CrAg titers of <1:80 are unlikely to be associated with CNS disease. The probability of CNS involvement increases beyond a titer of 1:160 and there is near-universal concordance with CNS disease at titers of 1:1,280. It is suggested that laboratories run test at two dilutions, namely 1:160 and 1:1,280. This will enable risk stratification of patients into low risk (<1:160), intermediate risk (1:160 to 1:1,280) and high risk (>1:1,280) of infection. All those in high risk group should be considered to have disseminated disease regardless of symptoms.[10] Rajasingham and colleagues pooled data from four cohorts and found that survival decreased as plasma CrAg titer increased from <1:160 to >1: 2,560 (log rank P <0.0001). Worryingly, mortality rates were high in asymptomatic individuals with CrAg >1:160 despite their receiving pre-emptive fluconazole therapy.[1,50,65]

Programmatic challenges exist to screen severely immunocompromised PLHA for CrAg. The strategy of ordering the test for people who have got a CD4 count report of ≤100/μL is not efficient and many patients will miss the test. This is known as the "provider-initiated testing" strategy. A study from South Africa showed that only 27% of those eligible actually got screened by this strategy.[66] It also increases the work of the clinic staff because they have to raise another investigation form

and draw another blood sample. The best strategy that has evolved is one known as "reflexive screening." Testing for CrAg is a part of the laboratory protocol. Whenever the laboratory finds a CD4 test result of ≤100/μL, it will automatically run the CrAg test on the remaining blood sample. The laboratory will also report it in along with the CD4 count result and will also offer a brief explanation as to what to do with a positive CrAg report.

Other Tests

1-3β-D Glucan (BDG): It has been long believed that Cryptococcus does not produce enough BDG to be detected easily. A study done in Africa showed that BDG can be detected in the CSF of PLHA with CM with a sensitivity and specificity of 89% and 85% respectively. Sensitivity increases to 98% when fungal burdens are high (>10,000 CFUs/mL). Unlike CrAg, BDG levels decline fast with treatment and thus and thus it can potentially be used to monitor therapy, detect relapse, and also differentiate relapse from cIRIS.[67]

Uses of film array system of multiplex PCR have been tried for detecting common pathogens causing meningitis. Cryptococcal infection can be detected with a sensitivity of 96% when fungal burden is high (>100 CFUs/mL of CSF) but only with a sensitivity of 50% at low fungi burdens (<100 CFUs/mL of CSF). The high cost and sophisticated laboratory facilities preclude its widespread use.

Ribosomal DNA genes and their internal transcribed spacers (ITS) have been found to be a good common marker for bacteria and fungi. It is possible to detect inter- and intra-specific variations. Deep sequencing of rDNA amplicons from CSF can diagnose CM. Metataxonomics of ITS amplicons may be the test of the future for rapid diagnosis and genotypic recognition of *Cryptococcus sp.*[68]

Treatment

Cryptococcal meningitis in PLHA is associated with high mortality. Some strategies to decrease morbidity and mortality include: early diagnosis of HIV infection and early initiation of ART; ART adherence and retention in care; CrAg screening and treatment approach; and improved CM care.

Despite the global coverage of ART being about 60%, CM remains a therapeutic challenge. The incidence of CM remains high and more than 50% of CM cases occur in ART-experienced patients. Timely diagnosis and optimal therapy are both required to prevent deaths. Treatment of CM is divided into three phases: induction, consolidation, and maintenance. The induction phase is meant to drastically reduce fungal burden in the CSF within 2 weeks and is critical for good outcomes. Three drugs have been traditionally used in the treatment of CM: amphotericin B (AmB) or liposomal amphotericin (L-AmB), fluconazole (FLU), and flucytosine (5FC). Of these FLU is the cheapest and most widely available drug. FLU monotherapy, even the highest doses, is associated with high mortality (50% during 10 weeks of treatment).[69] Various 2-week induction regimes have been tried. The main aim was to reduce the serious adverse effects (SAEs) associated with AmB. The dose and duration of therapy have both been modified in various studies. For a long time AmB 1 mg/kg/d + 5FC 100 mg/kg/d for 14 days was accepted as standard induction therapy for HIV-associated CM. But delivering a 2-week course of AmB remains a challenge due to SAEs, and cost. Phase II trials have demonstrated that a shorter course of AmB is associated with fewer SAEs than a 2-week course without reduction in rates of fungal clearance by 2 weeks. This is attributed to long half-life of AmB in the brain.[70,71] The Advancing Cryptococcal meningitis Treatment for Africa (ACTA) trial looked at survival rates at day 14 and day 70 of a 1 week course of AmB combined with either high dose FLU or 5FC, 2 weeks of oral therapy with 5FC and high-dose FLU and 2 week AmB combinations. The study showed that 1-week combination of AmB and 5FC had the lowest 10-week mortality of all regimens and that 5FC was superior to FLU as a partner drug to AmB (10 week mortality HR 0.62, 95% CI: 0.45–0.84, p=0.0020).[72] A systematic review and meta-analysis has looked at data from 13 studies with 2,426 patients. It found that at 10 weeks a 1-week course of AmBd plus 5FC was superior to other regimes for induction treatment of HIV-associated CM. In the case of non-availability of AmB a combination of 5FC and high-dose FLU was the next best alternative.[73] These two regimens have now been accepted as the standard first-line treatment regimens by WHO for HIV-associated CM. The standard WHO recommended treatment regimen for HIV-associated CM is shown in **Table 1**. The alternate regimens that can be used during the induction phase are: 5FC + high-dose FLU for 2 week or AmB + high-dose FLU for 2 weeks (high-dose FLU=1,200 mg/d).

TABLE 1 WHO-recommended first-line antifungal therapy for treatment of cryptococcal meningitis

Medication and dose	*Week 1*	*Week 2*	*Week 3 - 10*	
AmB (1.0 mg/kg/d) + 5FC 100 mg/kg/d	X[a]			
FLU 1200 mg/d		X		
FLU 800 mg/d			X	
FLU 200 mg/d				Through 12 months
Treatment phase	Induction		Consolidation	Maintenance

[a]Therapeutic lumbar puncture and electrolyte supplementation are most critical during the first week of therapy.[74]

Efforts to further shorten AmB exposure and thus cut down on cost and minimize SAEs are on. L-AmB is associated with fewer SAEs than AmB. The AMBITION trial was a phase II trial looking at efficacy of different doses and durations of L-AmB in treatment of CM. L-AmB in a dose of 3 mg/kg/d and FLU 1,200 mg/d were administered for 14 days in the induction phase in the control arm. This was compared with LAmB 10 mg/kg on D1 and 5 mg/kg on D3 + FLU 1,200 mg/d for 14 days; LAmB 10 mg/kg/d on D1 + 5 mg/kg on Ds 3 and 7 + FLU 1,200 mg/d for 14 days and LAmB 10 mg/kg on D1 with FLU 1,200 mg/d for 14 days. The primary outcome was early fungicidal activity and it was non-inferior in all the three short course arms as compared to the control arm. The mortalities in all arms were comparable. Encouraged by its results, AMBITION II phase III trial has been rolled out. This study compares the new WHO first-line regimen of AmB 1 mg/kg/d + 5FC 100 mg/kg/d for 7 days followed by high-dose FLU 1,200 mg/d for 7 more days with a single dose of L-AmB 10 mg/kg on day 1 along with 14 days of 5FC and high-dose FLU. The results will be out in mid-2021.[75]

Management of Raised Intracranial Pressure

An intracranial pressure of >250 mm of water is associated with poor short-term survival in patients with CM.[76] Repeated lumbar punctures improved survival in the COAT study.[29] The raised ICP is due to a strong inflammatory response in the CNS. Though dexamethasone is known to decrease levels of TNF-α, it also decreases the rate of fungal clearance and causes poor outcomes.[77] It is thus contraindicated in treatment of CM.

Advances in Initiating ART in PLHA with CM

Cryptococcal meningitis signals a severely immunocompromised state in PLHA. But starting ART precipitately can do more harm than good. IRIS occurs in 15–20% patients initiating ART. The Cryptococcal Optimal ART Timing Trial (COAT) provided some definitive guidance to delaying initiation of ART in patients with CM for a minimum of 4 weeks after starting antifungals. This trial demonstrated improved survival in patients with CM in whom ART initiation was deferred for up to 5 weeks after diagnosis as compared with immediate ART (within 1–2 weeks).[29] A Cochrane Review further concluded that there is higher all-cause mortality if ART is initiated early in CM in HIV-infected people in low- and middle-income countries.[78] The 2018 WHO guidelines recommend that ART should be started 4–6 weeks after starting antifungal treatment.

Newer Adjuvant Therapies for Treatment of CM

Sertraline, tamoxifen, INF-□, and steroids have all been tried. Steroids are associated with slower fungal clearance and increased mortality and are thus not recommended. Sertraline adjunctive therapy led to faster CSF cryptococcal clearance, and decreased IRIS and relapses when compared to historical data.[79,80] Neurapheresis is the extracorporeal filtration of yeasts from CSF in CM. A proof-of-concept study in murine models has demonstrated its efficacy. Human trials have not been encouraging.[81,82]

Newer Drugs

Flubendazole is an imidazole anti-parasitic drug. It acts against cryptococcus by binding to fungal tubulin. Though studies in mice were encouraging, the results in rabbit studies were disappointing due to poor CSF penetration. An oral formulation is under development and could still serve as an adjunctive therapy.[83] VT1129 is a tetrazole which has also demonstrated *in vitro* activity against both susceptible and FLU-resistant cryptococcal species. It

acts by inhibiting fungal cytochrome P450 enzyme Cyp51 thereby inhibiting biosynthesis of ergosterol. The unique feature of this drug is its high selectivity for fungal enzyme and thus its lack of SAEs and drug interactions.[84] Some more exciting drugs are under clinical trials and results should be out in 2021. These include an orally bioavailable form of AmB, and a glycophosphatidylinositol-anchored wall transfer protein (G wt 1) inhibitor which inhibits transfer of mannoprotein from the golgi complex to cell wall.[56]

Prevention

A number of strategies have been evaluated and implemented to prevent CM in PLHA with low CD4 cell counts in resource-limited settings. A widely accepted one is the "screen and treat" approach. Here, serum CrAg testing is used to decide on starting preemptive fluconazole therapy in CrAg-positive patients. Fluconazole is administered in a dose of 400 mg BD for 2 weeks followed by 400 mg OD for 6 weeks. It is continued at a dose of 200 mg OD till CD4 cell count rises to >200 cells/μL.[85] This approach is associated with a decreased incidence of CM and improved survival among those with advanced HIV disease. It has been successfully implemented in several resource-limited settings, with a baseline prevalence of asymptomatic cryptococcal antigenemia of 5–13%.[86-88] The cost saving and survival benefit of screen and treat strategy has been validated by many studies when compared with standard of care or universal fluconazole prophylaxis, even at CrAg prevalences of as low as 0.6%.[89,90] The WHO recommends implementation of CrAg screening and preemptive fluconazole therapy in ART-naive adults with a CD4 count <100/μL before initiating ART in endemic settings.[91] This strategy has been incorporated into existing HIV-care programs of many countries in sub-Saharan Africa. It has been shown that fluconazole monotherapy is inadequate to prevent CM deaths in asymptomatic CrAg positive with undiagnosed cryptococcosis. This is because fluconazole monotherapy is suboptimal for treatment of CM. In all asymptomatic CrAg positive PLHA, every effort should be made to diagnose cryptococcosis. Investigations should include CSF examination and blood cultures. A suggested approach is to give combination antifungal therapy for all CrAg positive patients or at least those with CrAg >1:160.[92,93] A Thai study showed that in settings where ART is widely available and PLHA with CD4 count <100/μL are regularly started on ART and are CrAg negative, primary prophylaxis with FLU offers no mortality benefit and may not be necessary.[94] Primary anti-cryptococcal prophylaxis is not recommended in high-income regions like Europe and the USA, where ART is widely available and CrAg prevalence in population is low.[95] There is some data that "screen and treat" would be cost-effective, even in resource-rich settings, although this is currently not part of standard practice.[96] Another vexing issue that has risen because of the widespread use of primary prophylaxis for CM in Africa is that of emerging fluconazole resistance in Uganda.[97]

Secondary Chemoprophylaxis

Suppressive or maintenance therapy is offered to all CM patients on completion of intensive and consolidation phases of treatment because relapse rate of CM is 50% in the first year.[98] Fluconazole at 200 mg daily is the suppressive therapy of choice. WHO recommends continuing till CD4 count rises to more than 200/μL. IDSA recommends that suppressive therapy can be stopped after 12 months if CD4 count is more than 100/μL and there is virological suppression sustained for ≥3 months (undetectable or very low viral RNA). Therapy should be restarted if CD4 dips below 100/μL.[99]

Outcomes

HIV associated CM has a 3-month mortality of 70% in Africa. The major risk factors for mortality are: longer duration of symptoms, altered mental status, concomitant cryptococcal lung infection, disseminated disease, high fungal burden with low rate of clearance, low CSF WBC count (<20 × 10^6/mm^3, raised ICP on admission and lack of facilities to perform therapeutic lumbar puncture (LP) to control ICP and abnormal brain imaging. Mortality is higher in low- and middle-income countries than in high-income countries because of the high proportion of late testers and late presenters, CM being the presenting illness in HIV disease, severe immunosuppression compounded by anemia, malnutrition, delayed diagnosis due to lack of optimal laboratory services, non-availability of good combination antifungal therapy and lack of facilities for therapeutic LP.[10,36] The study from the USA showed that seizures in HIV+ patients with CM were associated with increased 10 week mortality (adjusted hazard ratio 1.45, 95% CI: 1.11–1.89). Patients with seizures also had more

cognitive deficits after 3 months when compared to those without seizures.[37,100] TB confection with CM is associated with an increased hazard of death (HR 1.75, 95% CI: 1.33–2.32, p<0.001).[101]

A study from Uganda and South Africa showed that the estimated hazard of death at 18 weeks was 10% lower for every 50 cells/μL increase in absolute CD4 cell count at the time of diagnosis. Mortality was lowest when CD4 cell count was between 50–99 cell/μL (mortality 35%) and higher if CD cell count was <50 cell/μL (47%) or if it was >100 cell/μL (40%). These findings were consistent with the DRF theory.[102]

Cryptococcal antigenemia has a strong association with CM/mortality in PLHA with cryptococcosis and CD4 cell count between 100–200 cells/μL (Hazard ratio 10, 95% CI: 2.2–45.3, p=0.003).[103] A high fungal burden of >100,000 CFUs/mm^3 is also associated with increased mortality.[56] The outcome of CM is bad even in Latin America. In one 15 year-follow up study, with 340 enrolled patients, 42% died during follow-up. More deaths were seen after starting ART than in treatment naive HIV-CM.[104] Another study from the USA showed that CM led to hearing impairment, muscle weakness, and cognitive deficits.[33,34]

In elderly patients, mortality directly correlates with age (>65 years). The presence of cryptococcaemia is the most significant prognostic factor in these people.[105]

Conclusion

Cryptococcal disease in PLHA continues to be a big public health problem in low and middle income countries. Routine CrAg screening and pre-emptive antifungal therapy, can significantly reduce CM associated morbidity and mortality in these regions. Exclusion of cryptococcosis in asymptomatic PLHA with advanced disease and high CrAG titers is a good strategy. Combination antifungal therapy has made a significant difference in outcome of HIV-associated CM. The regimes are becoming more affordable, shorter, and safer. cIRIS continues to be a problem in immunocompromised persons with cryptococcosis.

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CHAPTER

167 Enteric Fever—Challenges to Overcome

Rupali Malik, Anupam Prakash

Abstract

Enteric fever is an important resilient community-acquired systemic bacterial infection, commonly seen in resource limited tropical countries with overcrowding and poor sanitation, causing significant morbidity and mortality, and thus posing a grave public health challenge to reckon with. Enteric fever includes infections caused by *Salmonella typhi* (typhoid fever) as well as those caused by *Salmonella paratyphi* A, B, and C (paratyphoid fevers). Its prevention, diagnosis, as well as management pose major challenges with limited options available for empirical treatment. Thus, there is an urgent need to monitor the burden of this disease and antimicrobial resistance to guide empirical therapy and devise newer diagnostic, as well as preventive public health strategies for containment of its spread.

Introduction

Enteric fever is an important differential of acute undifferentiated febrile illness in developing countries. It causes around 14.3 million infections annually with over 135,000 deaths worldwide.[1] Its annual incidence in our country is 493.5/100,000 persons per years with 340.1/100,000 cases per years occurring in children of 2–5 years, the higher incidence in children reflecting active transmission in the community.[2] The burden of typhoid and paratyphoid fever in India as per a meta-analysis in laboratory-confirmed enteric fever cases is estimated to be a prevalence of 7% for *Salmonella typhi* and 0.9% for *Salmonella paratyphi* A.[2-5]

Human beings are the only reservoir of this infection and the transmission can occur either through direct contact or indirectly via contact with fecal contaminated food or water. Sexual transmission between male partners has also been reported. Both genders and all age groups are infected throughout the year with a peak during the summer and rainy seasons, that is, from May to October. Although the gastric acid serves as a barrier to the entry of Salmonella through the oral route, but an excess bacterial load along with the lack of gastric acid in persons on proton pump inhibitors or achlorhydria or *Helicobacter pylori* infection, allows bacteria to traverse through the stomach and reach the small intestine, where these are localized in the Peyer's patches. However, once the barrier of Peyer's patches is passed, these can reach different parts of the body, and cause enteric fever and its varied manifestations, which can involve any organ system of the body. Some factors which predispose to severe infection include—primary immunodeficiencies like chronic granulomatous disease, neutropenia, organ transplant recipients.

Incubation period can range from 6 days to 21 days (usually 2 weeks). The clinical presentation of typhoid and paratyphoid fever is the same except milder manifestations and shorter incubation in paratyphoid fever. Most cases of enteric fever are caused by the gram negative bacilli *S. typhi*; however, incidence of *S. paratyphi* A cases is rising in Asia, perhaps as a result of vaccination for *S. typhi*, and

it now accounts for up to one-third of enteric fever cases in India and Nepal.[1,6,7]

Clinical Features

Fever is the most common presenting symptom in 90%[8] patients and is prolonged (>4 weeks) in untreated patients. It is usually moderate to high grade and remittent nature, without touching baseline or continuous, which rises every 3rd or 4th day, in what is classically defined as step-ladder fashion. However, due to frequent use of antipyretics and antibiotics early in the course, this pattern may not be evident always. High-grade continuous fever is associated with toxemia. Non-specific abdominal symptoms, like vomiting, diarrhea, and occasionally constipation, may also occur during the first week of illness. Soft splenomegaly is characteristic (to differentiate from the firm splenomegaly seen in malaria) and can be easily missed. Patients with enteric fever usually have a coated tongue and relative bradycardia. Patient can also have jaundice because of liver involvement (*enteric hepatitis*), breathlessness, and wheezing (*enteric bronchitis*), obtundation, delirium and coma (*enteric encephalopathy*), bone marrow depression, cholecystitis, loose motions, that is, classically pea-soup diarrhea (*enteritis*), intestinal perforation, and skin rash (*Rose spots*—2–5 mm diameter macular lesions seen transiently during the second week of illness, considered to be due to bacterial emboli). Serious complications usually occur in the second week of illness. Intestinal perforation occurs in about 1–3% of hospitalized patients with enteric fever, with common site being terminal ileum (70–80%) followed by less commonly involved sites like jejunum, ceacum, colon, or gall bladder. Gall bladder may remain a preserved focus in partially treated patients of enteric fever, and lead to a carrier state, wherein the patient may keep shedding bacteria in stools for months or years, becoming a public health hazard. The prolonged asymptomatic carrier state can be seen in about 10–15% of patients.[9]

Atypical manifestations of enteric fever have also been reported including ataxia, sensorineural deafness, meningism, Guillain-Barré syndrome (GBS), myocarditis, acute respiratory distress syndrome (ARDS), osteomyelitis, etc. Complications, like osteomyelitis, mycotic aneurysms, and soft tissue abscesses, are reported more often in paratyphoid infections.[10] Renal complications, like glomerulonephritis, pyelonephritis, cystitis, and mild proteinuria, have also been reported rarely. Hematological involvement can lead to bone marrow suppression, disseminated intravascular coagulation (DIC) and hemophagocytic lymphohistiocytosis (HLH).[9]

Reinfection may occur, if primary infection is terminated using early intervention with antibiotics.

Differential Diagnosis

Various tropical infections, like malaria, dengue, chikungunya, leptospirosis, and scrub typhus, are common differentials. However, continuous high grade fever, coated tongue, relative bradycardia, toxic looks, and soft splenomegaly should definitely be considered a pointer to enteric fever.

Diagnostic Challenge

Diagnosis of enteric fever poses an immense challenge as blood culture, which is considered the gold standard, has a low sensitivity of 40–60%.[11] Moreover, in our country, delayed presentations with pre-exposure to inadequate and unnecessary antibiotic therapy prior to visiting a proper health-care facility hinders its performance. Though it is positive in the first week itself and also provides sensitivity testing for antibiotics, it takes longer time, thus delaying treatment. Newer commercially available rapid serological tests, like TUBEX TF® (IDL, Sweden) and Typhidot® (Malaysian Biodiagnostic Research, Malaysia), can also be used as point of care tests in an emergency setting for early diagnosis. The former is an antibody-based test based on the principle of inhibition reaction between host and in vitro antibodies that compete for *S. typhi* specific lipopolysaccharide, while latter is a qualitative enzyme-linked immunosorbent assay (ELISA) based test that detects immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against *S. typhi* outer membrane protein. They have sensitivity of 55–70% and specificity of more than 85%.[12] These kits perform better among hospitalized patients than those evaluated in the community setting. Serum Widal test provides the titers of antibodies to somatic 'O' and flagellar 'H' antigens, and is helpful in the second week of fever onwards. A titer more than or equal to 1:160 is considered positive in endemic areas as in India, although rising titers in paired sera can be very helpful. Third week stool culture and fourth week urine culture may be helpful; however, untreated patients

are more likely to develop complications in the third and fourth week of fever. In partially treated patients, blood culture may not be positive, but bone marrow culture may still be positive. Directed investigations may be dictated by the suspicion of various complications. Thus, the existing diagnostic tests suffer from limitations regarding time cycle, sensitivity, infrastructure need, *etc*, emphasizing the need for newer, more accurate, and rapid point-of-care diagnostic tests.

Complete blood counts usually suggest leukocytosis, but bone marrow suppression can be associated with normocytic normochromic anemia, leukopenia, and thrombocytopenia. Transaminitis with mild elevation of serum bilirubin levels may be observed. Kidney functions are normal, but insensible losses due to high fever and anorexia because of toxemia can result in prerenal azotemia.

Management Challenge

Mainstay for management of enteric fever is to give antibiotics along with use of antipyretics and maintenance of hydration and adequate nutrition. Conventionally, chloramphenicol 1–2 g IV 8-hourly used to be the gold standard of treatment; however, with advent of newer potent antibiotics in the 1990s and due to idiosyncratic complication of chloramphenicol, like aplastic anemia, its use was abandoned. Cotrimoxazole and ampicillin were other agents used. Use of aminoglycosides was precluded as they were injectable drugs with well-known neurotoxicity, nephrotoxicity, and ototoxicity. Multidrug-resistant (MDR) strains resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, soon became prevalent worldwide, though they are now decreasing with wider use of other antibiotics, but development of increasing resistance to fluoroquinolones as well as even cephalosporins is a growing challenge now.

Quinolones are an effective group, and ciprofloxacin, ofloxacin, lomefloxacin, and levofloxacin were all rampantly used with great effect. But due to rising fluoroquinolones resistance, ciprofloxacin is no longer the empirical choice of treatment in our country.[13]

Ceftriaxone and cefixime are currently considered the treatment of choice, but there are also reports on increased minimum inhibitory concentration (MIC) to ceftriaxone causing delayed defervescence and even reports on the full resistance.[14]

Oral azithromycin 20 mg/kg once daily (to a maximum of 1 g daily) for 7 days has been recommended for treatment of uncomplicated enteric fever, and is considered to be equiefficacious to intravenous ceftriaxone (75 mg/kg/day to maximum 2.5 g/day) given for 7 days, with less chances of relapse and similar adverse effect profile.[15] A 5-day course of azithromycin has also been reported to be efficacious.[16]

In a study from Delhi, India,[15] resistance to co-trimoxazole, chloramphenicol, ceftriaxone, and azithromycin were reported to be 6.1%, 13.8%, 16.1%, and 5.78%, respectively over a 7-year period. Multidrug-resistant *S. typhi* and *S. paratyphi* A were reported to be 2.73% and 1.91%, respectively. In a recent systematic review and meta-analysis, multidrug-resistant *S. typhi* was reported to be 9% and multidrug-resistant *S. paratyphi* as 2% in South Asia. Besides, fluoroquinolone non-susceptible *S. typhi* and *S. paratyphi* were pegged at 70% and 53%, respectively in South Asia.[17] Resistance rates for various agents are highly variable from study to study and region to region, but resistance rates to azithromycin appear lowest among all the antibiotics.

There is a decrease in culture positive cases these days, which may suggest a decrease in the burden of disease, but can also be a reflection of the early empirical antibiotic use to treat typhoid fever in the community. There is a possibility that due to the emerging antibiotic resistant strains, under the selective pressure of antibiotic use, only patients who fail to respond to empirical therapy visit tertiary care hospitals. Thus, culture positive cases may represent only a small proportion of total number of cases in a community and this may lead to skewing of antimicrobial susceptibility data toward resistance.

Some treating physicians prefer to use two agents simultaneously to treat enteric fever. But this seems justifiable only in patients who have enteric fever with complications and in patients having no clinical improvement with monotherapy. It may be prudent to start with a single agent in uncomplicated enteric fever, and once susceptibility report is obtained decision on adding a second agent or switching to another agent can be taken. Role of various fixed drug combinations available still needs further evaluation.

Prevention and Control Challenge

Three vaccines are commercially available for typhoid fever, one live attenuated oral vaccine and two injectable

inactivated vaccines, with limited efficacy (50–72%). Ty21a, is an oral live attenuated *S. typhi* vaccine (given on days 1, 3, 5, and 7, with a booster every 5 years). It is not given in children less than 6 years. Vi CPS is a parenteral vaccine consisting of purified Vi polysaccharide from the bacterial capsule (given in one dose, with a booster every 2 years). It is not given in children less than 2 years. Third, is an injectable typhoid conjugate vaccine (TCV), consisting of Vi polysaccharide antigen linked to tetanus toxoid protein. It can be used in children from 6 months of age and adults up to 45 years of age. No vaccine for paratyphoid fever is presently available.[12]

Public health measures like availability of safe food and *wa*ter, adequate *s*anitation services, and proper personal *h*ygiene (WASH) are important to prevent enteric fever.[12] The challenge of controlling typhoid fever is often compounded by the lack of adequate nationwide surveillance in the affected countries. Recently in India, a study titled "National Surveillance System for Enteric Fever in India (NSSEFI)" is being done to estimate the incidence of typhoid fever in age-specific manner in children between 6 months and 15 years.[18]

Conclusion

In this era of emerging antibiotic resistant strains, with no new drug in the horizon, there is an imperative need for continuous surveillance to inform clinicians regarding early diagnosis and better management of infections with use of effective antibiotic policies and also government policymakers for strengthening preventive strategies like adequate sanitation with safe food and water supply, along with development of new vaccines that are effective against both *S. typhi* as well as *S. paratyphi* A infections. Though challenges persist in all these aspects hindering implementation of facilities available, an integrated approach with a comprehensive policy framework is required for prevention, control, and elimination of enteric fever.

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CHAPTER

168 Leptospirosis and Brucellosis—Can These Be Difficult to Diagnose?

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Abstract

Zoonotic diseases are important for humans as they may cause disease in them and are recognized as important public health issue. Brucellosis and leptospirosis are important zoonotic diseases of public health importance. The clinical presentation of these disorders mimics many other common diseases. The present chapter summarizes the important manifestation of these disorders and there differentiating aspects with other diseases.

Introduction

Zoonoses are diseases transmitted from animals to man have been recognized as important public health issues for centuries. Brucellosis and leptospirosis are important infections in animal handlers causing wide range of similar clinical manifestation. Butchers and slaughterhouse workers are at high risk of contracting zoonotic diseases due to handling of animals or by ingestion of unpasteurized milk or milk products. Non-specific symptoms including fever lead to chronic disease due to misdiagnosis. Zoonoses should be suspected if there are infection's protean manifestations along with appropriate exposure history. Hence, in this chapter, we seek to summarize brucellosis and leptospirosis infection in human.

Brucellosis

Livestock animals are mainly affected by brucellosis. It is caused by the small, Gram-negative coccobacilli of the genus *Brucella*. Main species causing disease in humans are *Brucella melitensis* (sheep and goat), *Brucella suis* (pigs), and *Brucella abortus* (cattle). The disease has worldwide distribution and is mainly seen in rural areas. Relapses can occur after primary infection and disease can also be chronic.

Pathogenesis and Modes of Transmission

Human transmission in brucellosis occurs through direct contact with infected animal, ingestion of unpasteurized milk and milk products, or carcasses of infected animal.

Human brucellosis is usually associated with domestic or occupational exposure to infected animals or their products. Veterinarians, shepherds, farmers, goatherds, and employees of meat-processing plants and slaughterhouses in endemic areas are occupationally exposed to infection. Laboratory workers who handle cultures or infected samples are also at risk. Travelers and urban residents usually acquire the infection through consumption of contaminated foods. The most frequently implicated sources of infection are dairy products, especially soft cheeses, unpasteurized milk, and ice cream, under exceptional circumstances raw meat and bone marrow can also be source of infection. Infections acquired through cosmetic treatments using materials of fetal origin have been reported. Person-to-person transmission is extremely rare, as is transfer of infection

by blood or tissue donation. No evidence of increased severity and prevalence of *Brucellosis* in immunodeficient individuals and persons infected with human immunodeficiency virus, even though it is a chronic intracellular infection.[1]

Clinical Features

The severity of brucellosis is related to infecting species, biotype, and host factors. *B. melitensis* and *B. suis* can cause severe disease in humans, with *B. abortus* usually being associated with milder disease. Human infection with *B. canis* is rare. Human brucellosis can be associated with acute, sub-acute, relapsing, and chronic manifestations. The incubation period is normally between 2 and 4 weeks, but it may be months.

Acute brucellosis can present as a non-specific febrile illness characterized by intermittent or remittent fever (39–40°C). The fever may be associated with chills, night sweats, joint and muscle pain, weight loss, fatigue, malaise, headache, and adenopathy mainly in children.

It may also be associated with non-specific gastrointestinal disorders, hepatomegaly and/or splenomegaly, cough, arthritis (knee), and orchitis.[2]

Waxing and waning type of fever is characteristic of sub-acute brucellosis and is also known as undulant fever. It is often low grade, persists for weeks, accompanied by arthralgia, arthropathy and diminished well-being. Undulant fever is more common in adults than in children and can involve specific organ systems. Intrauterine infection, miscarriage, premature delivery, and spontaneous abortion are common during infection of human brucellosis in pregnancy.[3]

Localized Form

Primary infection may progress to localized infection (even several months or years later):

- *Osteoarticular:* Sacroiliac joint, lower limbs joints, spine (vertebral osteomyelitis, intervertebral disk infection)
- *Genitourinary:* Orchitis, epididymitis
- *Pulmonary:* Bronchitis, pneumonia, pleurisy
- *Neurological:* Meningitis, encephalitis, polyneuritis

Complications of Brucellosis

- *Osteoarticular complications:* Affect 20–40% of patients. Sacroiliitis is the most common reported complication, especially when *B. melitensis* predominates.[1,4]
- *Pulmonary complications:* Respiratory symptoms are reported by 15–25% of patients but radiological changes are seen in less than 10%.[5] They range from flu-like symptoms to bronchitis, lobar pneumonia, interstitial pneumonitis, lung abscesses, hilar lymphadenopathy, and lung effusions.
- *Genitourinary complications:* Complications from the genitourinary tract are rare. Acute orchitis or epididymo-orchitis with signs of systemic infection can occur in males and there can be pyelonephritis resembling tuberculosis, particularly in females.
- *Neurologic complications:* Depression is a common complaint, but invasion of the central nervous system occurs in only 2–4% of cases. It usually presents as acute or chronic meningitis. Encephalitis, polyradiculopathy, psychosis, and meningovascular complications have also been described, as well as rarer complex abscesses.[6]
- *Cardiovascular complications:* Endocarditis, although rare, is the main cause of death related to brucellosis.[1,4] The aortic valve is more often involved than the mitral valve. Other complications include mycotic aneurysms, myocarditis and pericarditis.
- *Cutaneous involvement*: Cutaneous manifestations of brucellosis consist mainly of transient nonspecific lesions including erythema nodosum, petechiae, vasculitis, papules, and rashes.

Diagnosis

The diagnosis should be considered in a case of chronic febrile illness having epidemiological risk factors along with osteoarticular involvement (axial spine or sacroiliac joints), uveitis or other focal lesions described earlier. Confirmatory diagnosis is usually based on microbiologic culture of blood, tissues, or bone marrow.[7] Blood culture, which is gold standard for diagnosis, is positive only in the acute phase and has sensitivity of less than 50–70%.[2] Bone marrow cultures are more sensitive than blood cultures in acute brucellosis and remain positive even in later course of the infection, along with antimicrobial treatment.[8,9]

Body fluids, such as cerebrospinal fluid (CSF) or joint fluid, show lymphocytosis, low glucose levels and high protein concentration. Elevated CSF adenosine deaminase levels are also present. Biopsied samples of tissues such as lymph node or liver may show noncaseating granulomas without acid/alcohol-fast

bacilli. In recent years, matrix-assisted laser desorption ionization time-of-flight spectrometry (MALDI-TOF MS) has emerged as a powerful tool in bacterial identification. The peripheral blood-based polymerase chain reaction detects bacteremia, to predict relapse, and to exclude "chronic brucellosis."[10]

Serologic tests are more sensitive than culture. The serum agglutination test (SAT) remains the best standardized and most widely used serologic test.[8] Other serological tests are indirect immunofluorescence, Wright agglutination test, Rose Bengal, ELISA, etc. and provide presumptive diagnoses.

Malaria and tuberculosis are to be ruled out in endemic regions.

Radiography

Small erosions or destruction or joint space narrowing is seen in ankles, knees, hips, vertebrae, and sacroiliac joint. Chest radiograph is often normal but sometimes pleural effusion can be present.

Management (Table 1)

The goal of medical therapy is to control symptoms quickly, in order to prevent complications and relapses.

High relapse rates reported with monotherapeutic approaches so multidrug antimicrobial regimens are the mainstay of therapy. The risk of relapse is not well understood and resistance is not a significant issue in treatment of brucellosis.[11]

Same treatment is to be given for localized forms of the infection, but for a period of 6 weeks to 4 months depending on the focus.

Leptospirosis

Leptospirosis is an important zoonotic disease globally caused by spirochetes of the genus Leptospira. Leptospirosis affects almost all domestic and wild animals worldwide except Antarctica. Rodents (rat), dogs, and cattle are mainly affected. It is a disease of public health importance in tropics and is seen in agricultural workers[14] as well as urban slum residents.[15] Disease is endemic throughout the world; however, outbreaks superimposed on endemic disease activity are regularly linked to severe hurricane and flooding events.

Pathogenesis and Modes of Transmission

Human transmission of leptospirosis occurs by contact of moist soil or freshwater contaminated with urine of

TABLE 1 Management of brucellosis

Children under 8 years[12]	Rifampicin + Co-trimoxazole or Gentamicin + Co-trimoxazole
Children 8 years and over	Rifampicin + Doxycycline or Gentamicin + Doxycycline
Adults[13]	Rifampicin + Doxycycline or Doxycycline + Streptomycin or Gentamicin
Pregnant/breastfeeding women	Rifampicin occasionally Rifampicin + co-trimoxazole
Sacroiliitis	Doxycycline + Rifampin + Gentamicin—2–3 weeks Then Doxycycline + Rifampicin for 6 weeks
Nervous system infection	Doxycycline + Streptomycin + Rifampicin or Doxycycline + Co-trimoxazole + Rifampicin
Co-trimoxazole: PO for 6 weeks Children < 8 years: 20 mg SMX + 4 mg TMP/kg 2 times daily **Doxycycline:** PO for 6 weeks Children ≥ 8 years: 1–2 mg/kg 2 times daily Adults: 100 mg 2 times daily **Rifampicin:** PO for 6 weeks Children: 15–20 mg/kg once daily (max. 600 mg daily) Adults: 600–900 mg once daily **Gentamicin:** IM for 2 weeks Children and adults: 5 mg/kg once daily **Streptomycin:** IM for 2 weeks Adults: 1 g once daily	

an infected animal (indirect contact) or direct contact of blood, urine, and other body fluids or tissues of an infected animal through skin lesions or mucous membranes.

Leptospires are shed in urine as they colonize proximal renal tubules of mammalian hosts. They can survive for several months in the environment under moist conditions; factors affecting survival are the presence of warmth (above 22°C) and neutral pH (pH 6.2–8.0). Rodents are a particularly important reservoir. Some serovars appear to be preferentially adapted to select mammalian hosts; examples are the serovar *Icterohaemorrhagiae* which is primarily associated with the Norway rat, *pomona* with swine and cattle and *canicola* with dogs. However, a particular host species may serve as a reservoir for one or more serovars, and a particular serovar may colonize different animal species. Transmission of infection in humans usually occurs through contact with contaminated water or moist soil. Organisms enter humans through the mucosal surface of the nasopharynx, mouth, eye, or esophagus or through abrasions of the skin. Risks of leptospirosis transmission and exacerbation are increased due to migration of the rural poor to urban slums. Intense exposure to leptospires has been documented in workers of sugarcane, rice, and rubber plantation. Leptospirosis is also acquired by direct contact with the urine, blood, or tissues of infected animals but is less frequent.

Clinical Features

Severe, icteric illness occurs in less than 10% of symptomatic infections; however, subclinical infection is very common. Majority of cases of leptospirosis are mild, presenting as febrile illness, but disease can be potentially fatal leading to multiorgan dysfunction. The incubation period is usually 1–2 weeks but ranges from 1 to 30 days.[16]

Leptospirosis is classically described as biphasic.

Acute phase (leptospiremic/septic/anicteric phase): characterized by:

- High fever with chills of sudden onset (3–10 days duration)
- Headache
- Muscle pain (especially calf pain)
- Photophobia
- Ocular pain
- Bilateral conjunctival hemorrhage is very frequent
- Organism can be cultured from blood and detected by polymerase chain reaction
- May be associated with:
- Gastrointestinal symptoms (abdominal pain, nausea, anorexia, vomiting)
- Non-productive cough
- Adenopathies
- Hepatomegaly

Immune phase:

- The signs of the acute phase regress after 5–7 days then reappear for a few days but are usually mild (milder fever, less severe myalgia) and then disappear.
- Coincide with the appearance of antibodies, and leptospires can be cultured from the urine.
- Aseptic meningitis is the hallmark of immune phase of leptospirosis but is not associated with mortality. Cerebrospinal fluid pleocytosis can be demonstrated in 80–90% of patients during the second week of illness. Clinical signs and symptoms of meningitis are seen in only 50% cases.
- Uveitis is a late manifestation of leptospirosis. It is generally seen after 4–8 months of illness. Most frequently affected area is anterior uveal tract. Common symptoms of uveitis are photophobia, pain, and blurring of vision.

Severe or Ictero-hemorrhagic Form (Weil's Disease)

The onset is the same but a few days later the symptoms worsen:

- Renal disorders (oliguria or polyuria or anuria)
- Hepatic disorder (jaundice—appears 5–9 day of illness, hepatomegaly)
- Widespread hemorrhages (ecchymoses, haemoptysis, purpura, epistaxis, etc.)
- Pulmonary signs (chest pain)
- Cardiac signs (myocarditis, pericarditis)
- Refractory shock
- Death occur from subarachnoid hemorrhage or gastrointestinal bleeding
- Eye signs: Conjunctival hemorrhage, scleral icterus, and conjunctival suffusion
- Leptospirosis-associated severe Pulmonary Hemorrhage Syndrome is as a widespread public health problem having a case fatality rate of about 50%
- Apparent critical threshold for severe outcomes such as SPHS and death is leptospiremia of 10,000 or more bacteria per milliliter of blood

Diagnosis

Leptospirosis may be difficult to distinguish from other infectious causes of fever, and a high index of suspicion is required based on the local epidemiology. Modified World Health Organization (WHO) Faine's criteria (with amendment) 2012 Criteria for Diagnosis of Leptospirosis is summarized in **Table 2**.[17]

Laboratory diagnosis is difficult to obtain. The routine investigation demonstrates:

- *Complete blood count:* Anemia, polymorphonuclear leukocytosis, or thrombocytopenia.
- *Urine:* Leukocyturia, proteinuria, possible microscopic hematuria.
- Enzyme markers of skeletal muscle damage are elevated in the sera of 50% of patients during the first week of illness, such as creatine kinase, aldolase, etc.
- Hyperbilirubinemia, prolongations of the prothrombin time, and modest elevations of serum alkaline phosphatase are typical. There is mild hepatocellular necrosis in Weil's disease.
- Elevated markers of inflammation (C-reactive protein level, procalcitonin level, and erythrocyte sedimentation rate).

Serology

- *Between 0 and 7 days:* Real-time PCR (early diagnosis)
- *After 7 days:* Microscopic agglutination test (MAT); IgM ELISA test provides presumptive diagnosis
- *After 10 days:* MAT and IgM ELISA tests only.
  - *Culture:* Limited use (bacteria grow slowly, specific culture medium)

Radiography

The most common radiographic finding is a bilateral patchy alveolar pattern that corresponds to scattered alveolar hemorrhage. These abnormalities predominantly affect the lower lobes. Other findings include pleura-based densities (representing areas of hemorrhage) and diffuse ground-glass attenuation typical of acute respiratory distress syndrome (ARDS).

Management (Table 3)

Management should be started on high index of suspicion as early intervention may prevent the development of multiorgan failure and antibiotics are less likely to benefit once organ damage has occurred.[10]

TABLE 2 Modified World Health Organization (WHO) criteria for diagnosis of leptospirosis

Part A: Clinical data	
Headache	2 Points
Fever	2 Points
Temperature >39*C	2 Points
Conjunctival suffusion	4 Points
Myalgias	4 Points
Meningeal signs	4 Points
Conjunctival suffusion + meningism + myalgia	10 Points
Jaundice	1 Points
Albuminuria /Nitrogen retention	2 Points
Haemoptysis / Dyspnea	2 Points
Part B: Epidemiological factors	
Heavy rainfall	5 Points
Contact with contaminated environment	4 Points
Animal contact	1 Points
Part C: Bacteriological and laboratory Findings	
Isolation of leptospira in culture	Diagnosis certain
PCR	25 Points
Positive IgM ELISA	15 Points
Slide Agglutination test (SAT) Positive	15 Points
MAT single high titer	15 Points
MAT Rising titer/seroconversion (Paired sera)	25 Points
Presumptive leptospirosis if score • Part A or Part A & Part B score: 26 or more • Part A, B, C (Total): 25 or more **Possible leptospirosis if score between 20-25 points**	
ELISA—enzyme linked immunosorbent assay IgM—Immunoglobin M MAT—Microscopic agglutination test	

TABLE 3 Management of leptospirosis

Indication	*Regimen*
Mild leptospirosis	• Doxycycline 100 mg twice a day or • Amoxycillin 500 mg thrice a day or • Ampicillin 500 mg thrice a day
Moderate/Severe leptospirosis	• Penicillin 1.5 million units IV or IM 6 hourly or • Ceftriaxone 2 gm/day IV or • Cefotaxime 1 gm IV 6 hourly • Doxycycline 200 mg IV loading followed by 100 mg IV 12 hourly
Chemoprophylaxis	• Doxycycline 200 mg PO once a week or • Azithromycin 250 mg PO once or twice a week

All regimens to be given for 7 days. Aggressive supportive care in leptospirosis essential and can be lifesaving.

TABLE 4 Differentiating clinical features of various diseases

Disease	Symptoms											Physical and laboratory findings	Chest radiograph
	Fever	Cough	Sputum	Headache	Dyspnea	Rash	Sore throat	Joint pain	Myalgia	Confusion	Diarrhea		
Brucellosis	++	++	–	–	+	+	–	+	+	+	–	Hepatosplenomegaly, painful lymphadenopathy	Soft miliary mottling, Parenchymal nodules, consolidation, hilar or paratracheal lymphadenopathy, pneumothorax
Leptospirosis	++	++	+	+++	++	Hemorrhagic rash over legs	+	+	++	++	_	Hepatomegaly Icterus Hemoptysis Conjunctival suffusion	Multiple ill - defined nodules in both lungs
Malaria	++	–	–	+	–	–	+/–	+/–	+	++	+	Hepatosplenomegaly Icterus	Normal
Influenza	+	++	++	++	++	–	+/–	+	+	+/–	+	–	Bi-basal air space opacities, perihilar reticular and alveolar infiltrates
Mycoplasma pneumonia	++	++	++	-	++		–	–	–	–	–	Abnormal LFT	Bronchial wall thickening, Centrilobular nodules, Ground glass attenuation, consolidation
Dengue	++ biphasic fever	–	–	+++	+	++ purpuric rash	–	++	+	+	–	Hepatosplenomegaly Pleural effusion lymphadenopathy	Usually normal Sometimes pleural effusion
Enteric fever	++ continuous fever	–	–	+/–	–	Blanching erythematous maculopapular lesions	–	+/–	+	+/–	+	Hepatosplenomegaly	No changes
Tuberculosis	+ evening rise	++	+	+/–	+/–	–	–	+/–	+	+/–	+/– abdominal tuberculosis	Hepatosplenomegaly Pleural effusion lymphadenopathy	Consolidation Infiltrates Pleural effusion Military shadows
Legionellosis	+	+	+	–	+/–	–	–	+	+	+/–	+	Renal and hepatic dysfunction	Consolidation Infiltrates
Rickettsial Disease (Scrub Typhus)	+	+	+/–	+	+/–	Eschar for lower part of body	–	+/–	++	–	+	Renal and hepatic dysfunction Splenomegaly lymphadenopathy	Mostly normal

Differentiating Brucellosis and Leptospirosis with Other Diseases

The differential diagnosis of these infections is broad, reflecting the diverse clinical presentations of the disease. When fever, headache, and myalgia predominate, influenza, and other common and less common viral infections (e.g., dengue and chikungunya) should be considered. Malaria, typhoid fever, Rickettsial diseases may mimic the early stages of disease and are important to recognize. Dual infections have been reported. In this light, it is advisable to conduct testing for other diseases also. Some common features to differentiate these infections with other common infections are shown in **Table 4**.

Conclusion

Brucellosis and leptospirosis have diverse clinical presentations, so these diseases have to be differentiated from many common disorders like influenza, malaria, dengue, typhoid, and rickettsial diseases. Although, management of these diseases is not difficult but early diagnosis is key to better outcome.

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CHAPTER

169 Growing Threat of *Klebsiella*—How to Counter?

Aditya Prakash Misra

Abstract

Klebsiella pneumoniae is an important pathogen that belongs to family *Enterobacteriaceae*. Incidence of extended spectrum beta lactamases (ESBL) producing Gram-negative bacteria has gradually increased in last 2–3 decades. Problem is further compounded by carbapenemase producing Gram-negative bacteria. Carbapenem-resistant Enterobacteriaceae (CRE) has become a global threat recently. WHO in a policy statement in 2017 had mentioned that future development of antimicrobial agents should focus on CRE.[1] Klebsiella is the most important pathogen of CRE family encountered all over the world.

Introduction

Edwin Klebb in 1875 had described Klebsiella, as a Gram-negative bacterium belonging to family Enterobacteriaceae. *Klebsiella* is part of microbiome in healthy individuals and colonizes mainly gastrointestinal system. It can cause severe infections in critically ill and immune-compromised patients. Klebsiella causes urinary tract infection, pneumonias, blood stream infections, liver abscesses, necrotizing fasciitis, meningitis and surgical site infections, mainly. Kaur et al. from a single tertiary care center in Delhi reported 69.3% mortality in patients suffering from colistin-resistant K pneumonia infections.[2] Another study from South India reported high rates of resistance to Carbapenem, Minocycline, and Tigecycline in isolates of *Klebsiella* blood stream infections.[3] Carbapenem resistance had increased during the study period. High resistance of Klebsiella to various antibiotics is also reported from China, Korea, Greece, other European countries, and the USA. Falagas et al. have shown that mortality due to carbapenem-resistant *Klebsiella pneumoniae* exceeds 60% despite the combination therapy.[4]

Klebsiella pneumoniae is the main pathogenic organism in the genus. In some cases K oxytoca have been isolated from human clinical specimens. *Klebsiella* can be differentiated into various types by biotyping, serotyping, phage typing, bacteriocin typing and molecular typing. Serotyping is most commonly used and is based on capsule antigens.

Pathogenicity

Pathogenicity of *Klebsiella* depends upon these factors—

Capsular antigens: Klebsiella has a capsule made of complex acidic polysaccharides. Capsular antigens are essential to virulence and have been divided into 79 serotypes. Klebsiella strains of K1, K2, K4, and K5 are more virulent.

Fimbriae: Fimbriae (Pili) are filamentous projections on bacterial surface by which it attaches to the host surface.

Fimbriae help in developing biofilms and also help organism to adhere to medical devices.

Lipopolysaccharide: Helps in evading host's defense mechanisms.

Siderophores: Iron is an essential factor in bacterial growth. The level of free bioavailable iron is too low for bacteria growth. Klebsiella secretes high affinity, low molecular weight iron chelators, called siderophores. These siderophores in Klebsiella belong to two different groups. More common, the phenolate group with best known representative enterobactin, and hydroxamate type siderophores with best known representative, as aerobactin and ferrioxamine.[5]

Some terms like hypervirulent Klebsiella pneumoniae (hvKp) and hypermucoviscous K pneumoniae are also being used recently. hvKp was first recognized in Taiwan in 1986,[6] although genomic studies suggest that it existed unrecognized as early as 1920s.[7] Approximately 70% of hvKp isolates are capsular types K1 or K2. Fortunately less drug resistance has observed in hvKp. The siderophore, aerobactin accounts for more than 90% of hvKp's total siderophore production. Clinical laboratories are unable to differentiate between classical K pneumoniae and hvKp. There is no commercially available assay that reliably differentiates the two. However, several biomarkers, including peg 344, iroB, iucA, MPa, mpA2, and quantitative siderophore production greater than30 mg/mL predict hvKp strains.[8]

Hypermucoviscous phenotypes may also show increased virulence, as it may prevent them from host's defense mechanisms.

Role of Clinical Microbiology

In isolates suspected to be carbapenemase producer Klebsiella, a double disc synergy test (DDST) on Muller-Hinton agar media may be done. Tests using inhibitors such as boronic acid or EDTA are being used more frequently to detect KPC or Metallo Beta Lactamase (MBL) carbapenemase respectively. The modified carbapenem inactivation method (Mcim) has replaced modified Hodge test recently, as it is easy to perform and is less expensive. Various automated systems may be employed to detect KPC producers. Various molecular methods, for example molecular antibiogram, have been used in identification of pathogens and most common resistant genes. Molecular assays though expensive, but help clinicians in de-escalation of therapy, avoiding unnecessary antibiotics, reducing length of stay and mortality.[9]

Mechanisms for Antibiotic Resistance

As early as 1970s, aminoglycoside resistant Klebsiella were noted. Since 1982, strains that produce ESBL, making them resistant to extended spectrum cephalosporins (hallmark being resistant to ceftazidime). These ESBLs were, SHV-5 in Europe and TEM-10 & TEM-12 in the USA. The first report of carbapenemase-resistant Klebsiella pneumonia in the USA was in 1996. Since then it has been widely reported in various countries of Europe, South America, and Asia. Carbapenemase produced may belong to Ambler class A (K pneumoniae carbapenemase) or class B (metallo-β-lactamases, MBL, New Delhi metallo-β-lactamases, NDM) and class D (OXA-48 like carbapenemases).[9]

Polymyxins serve as a last resort for treatment in CRE. Lately resistance to polymyxins is being encountered all over the globe. Polymyxin resistance has been reported as an independent marker for 14-day mortality in patients with KPC producing K pneumoniae. Polymyxin resistance is chromosomally mediated and takes place by addition of cationic groups to bacterial outer membrane. More recently a plasmid mediated gene (mcr-I) has been discovered, which confers resistance to polymyxins.[10] As per clinical laboratory standards institute/European committee on antimicrobial susceptibility testing (CLSI/EUCAST) both microdilution should be used as a reference model for polymyxins susceptibility testing.

The SENTRY[11] and SMART study[12] reported that in India, most common gene foe encoding carbapenemase was NDM-1 followed by OXA-48 variants. However, a study from South India, done later reported equal distribution of NDM-1 and OXA-48 like genes.[13]

Treatment

The worldwide spread of multidrug resistant Klebsiella and KPC producing strains are causing a serious threat. In our country resistance to various antibiotics is steadily increasing. Problem is further aggravated by absence of a central collating body, ineffective antibiotic stewardship program, and rampant misuse of available antibiotics. Major pharmacological companies are not doing enough

research for discovering newer antibiotics. There is no gold standard treatment for KPC producing Klebsiella. The choice of treatment depends upon site and severity of infection, local antibiogram, and host factors. Various strategies to effectively treat these infections are discussed below.

Combination Therapy

Most of the retrospective studies have found that combination therapy is associated with lower mortality. Choice of the combination should be guided by local antibiogram. For KPC producing Klebsiella, it will be prudent to use polymyxins with carbapenems. However, this combination may not show good results, if MIC levels are more than 16 µg/mL. A study from ICU patients in North India showed polymyxins resistance in Klebsiella isolates in blood, urine, and sputum samples as 8.75%, 4.26%, and 4.4%, respectively.[14]

Dual Carbapenem Therapy

It refers to the use of ertapenem with either meropenem or doripenem. Ertapenem has highest affinity for carbapenemase and may consume most of it and allowing larger part of the other carbapenem to exert its bactericidal effect.[15]

Triple Combination Therapy

Triple combination of polymyxins, carbapenem, and tigecycline has been found to significantly reduce the mortality in infections due to KPC producing Klebsiella strains. The emergence of polymyxins resistant strains during the treatment is a serious concern.[15]

Newer Agents

Avibactam is a non-beta-lactam beta-lactamase inhibitor that has activity against class A and C beta-lactamases including KPC and AmpC. Its combination with ceftazidime has been approved by FDA in 2015 for complicated UTI including pyelonephritis. It may not be effective if MIC levels are more than 8 µg/mL. Meropenem with another beta-lactamase inhibitor vaborbactam is also being tried. Imipenem-cilastatin along with relebactam, another new beta-lactamase inhibitor is also being used. Plazomicin a new aminoglycoside with efficacy against multidrug resistant Enterobacteriaceae bacteria is also available now. Eravacycline, a semi-synthetic tetracycline with efficacy against KPC and NDM carbapenemase, is showing promise.[15]

Conclusion

To conclude, the management of multidrug and pan-drug resistant Klebsiella is a serious challenge to health care. Klebsiella is a major source of carbapenemase resistance in various species through horizontal transfer of plasmids and transposons, leading to emergence of multidrug and even pan-drug resistance. We need good infection control program, antibiotic stewardship, environmental cleaning, hand hygiene, and contact precautions to prevent spread of these deadly bacteria. Tracing carriers of KPC Klebsiella and eradicating through selective digestive decontamination may be an exciting option.[16]

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CHAPTER

170 Infection with *Acinetobacter*—A Challenge for the Physician

Krishna Padarabinda Tripathy

Abstract

Acinetobacter species has emerged as one of the most significantly resistant pathogens causing heath-care associated infections. *Acinetobacter baumannii*, a Gram-negative coccobacillus constitutes 85% of the infections caused by Acinetobacter species in human beings. Prolonged length of hospital stay, invasive procedures, use of third-generation cephalosporins, etc. are some of the risk factors contributing toward the infection with this resistant organism. It has been increasingly recognized as an important cause of pneumonia, septicemia, meningitis, urinary tract, and wound infections and is associated with high mortality. Due to its inherently resistant property and aptitude to develop MDR and XDR strain, it has proven to be a therapeutic challenge for the physicians. This chapter highlights the infection and disease producing factors, mechanism of antibiotic class resistance and its treatment, and an unpublished data about *A. baumannii* in brief.

Introduction

In the modern health-care system, Acinetobacter has undoubtedly emerged as one of the most significant pathogens accountable for health-care associated infections involving multiple organs. It is also known to cause community acquired infections in combat zone and disaster associated infections because of its ubiquitous nature. In 1911, Acinetobacter species were isolated from soil and first described as Micrococcus calcoaceticus. Thereafter, the genus was renamed multiple times for several years, and since 1950, it is referred as Acinetobacter. Earlier Acinetobacter was an organism of unconvincing pathogenicity, which during the last three decades has emerged as a serious infectious agent to the hospitals around the globe.

According to many studies worldwide, it has been found that *Acinetobacter baumannii* develops resistance to antimicrobials rapidly, resulting in multidrug-resistant and pan-drug-resistant strains, which may cause large outbreaks of health-care associated infections. The World Health Organization declared that the ESKAPE organisms (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, A. baumannii, Pseudomonas aeruginosa, and Enterobacter species*) are known to effectively escape the outcome of antibacterial drugs. *A. baumannii* is amongst the most serious ones in the group. This Gram-negative coccobacillus because of its inherent mechanism of resistance and pathogenicity has become a threat to mankind and one of the significant therapeutic challenges for the physicians.

Bacteriology

These species are strictly aerobic, Gram-negative, non-motile, oxidase negative, catalase positive, non-fermenting coccobacillus that grows at 20–30°C and could be easily recovered on standard culture media. Amongst the Acinetobacter species causing infections in human beings, *A. baumannii* constitutes about 85% of the infections in humans. Other species in the genus causing occasional infections in human beings are *Acinetobacter nosocomialis, Acinetobacter pittii*.[1] Molecular methods like Matrix assisted laser desorption-ionization-time-of-flight

TABLE 1 Risk factors for colonization and infection with the pathogen

Risk factors for colonization and infection with A. baumannii	
Health-care associated infections in ICU patients	• Prolonged length of hospital/ICU stay • Mechanical ventilation • Invasive procedures • Tracheostomy, central venous catheterization • Nasogastric tube feedings • Recipient of third-generation cephalosporins, fluoroquinolones, and carbapenems
Health-care associated infections in hospital	• Hands of the health-care worker • Respiratory therapy equipment • Infusion pumps • Fomites like bed rails, door handles, tabletops
Community-acquired infections	• History of alcohol abuse • Diabetes mellitus • Smoking • Chronic lung disease, Chronic kidney disease • Cancers

mass spectrometry (MALDI-TOF-MS) and quantitative real-time polymerase chain reaction (RT-PCR) are often required to detect *A. baumannii* because it is difficult to identify it just based on phenotype.

Acinetobacter species that have been isolated from foods, arthropods, the environment, soil, and water are known to be its natural habitats. In our day-to-day practice, Acinetobacter culture positivity should be analyzed as colonization which is the presence of bacterium on a body surface (like on the skin, oral cavity, airway, or intestines) and not causing disease in the individual, in contrast to infection, where there is invasion of a host's body tissues by disease-causing organisms. There are various risk factors for colonization and infection with the pathogen that is summarized in **Table 1**. It is hypothesized that *A. baumannii* species are ubiquitous in nature[2] as they survive in dry as well as damp environment which promotes its environmental desiccation for weeks and causes fomite contamination in hospitals.

In the United States, the Centre for Disease Control have estimated 12,000 Acinetobacter infections every year out of which multidrug-resistant strains causes 7,300 cases with high mortality.[3] The Indian Council of Medical Research estimates Acinetobacter species as the second most common isolated pathogen (45%) causing hospital-acquired infections after Pseudomonas species (52%). *A. baumannii* was found resistant to most antibiotics except colistin, it showed 70% non-susceptibility to almost every antibiotics tested. Invasive specimens from lower respiratory tract and blood had higher non-susceptibility rates against different categories of antibiotics in comparison to other specimens.[4]

TABLE 2 Virulence factors and their role in pathogenesis of *A. baumannii*

Virulence factors	*Role in pathogenesis*
Porin (OmpA, Omp33-36, Omp22, CarO, Opr D-like)	Adherence and invasion, induction of apoptosis, biofilm formation
Capsular polysaccharide	Growth in serum, prevent complement activation and delays phagocytosis, biofilm formation
Lipopolysaccharide (LPS)	Serum resistance, survival in tissue infection, evasion of the host immune response
Phospholipase (PLC and PLD)	Exert cytotoxic effect on epithelial cells and facilitate their invasion
Iron-acquisition systems	Ability to grow in iron deficiencies in human host through secretion of siderophores

Pathogenesis

A. baumannii intrinsically is more virulent in humans as compared to other Acinetobacter spp. as it grows better at 37°C and resists macrophage uptake than other species. The important virulence factors and their role in pathogenesis is summarized in the **Table 2**.

Mechanism of Resistance

Acinetobacter infections have proven to be a therapeutic challenge to physicians as it is one of the most resistant organisms known and its treatment centers upon controlling the antibiotic resistance. It is an inherently resistant organism which has the aptitude to develop multidrug-resistant and extensive drug-resistant strains. This is one of the vital contributory factors in its capability to adapt itself to changes in environmental pressures. The common mechanisms of resistance are explained in **Figure 1**.

AmpC cephalosporinase: Acinetobacter-derived cephalosporinases (ADCs) are the genomic variants of *A.*

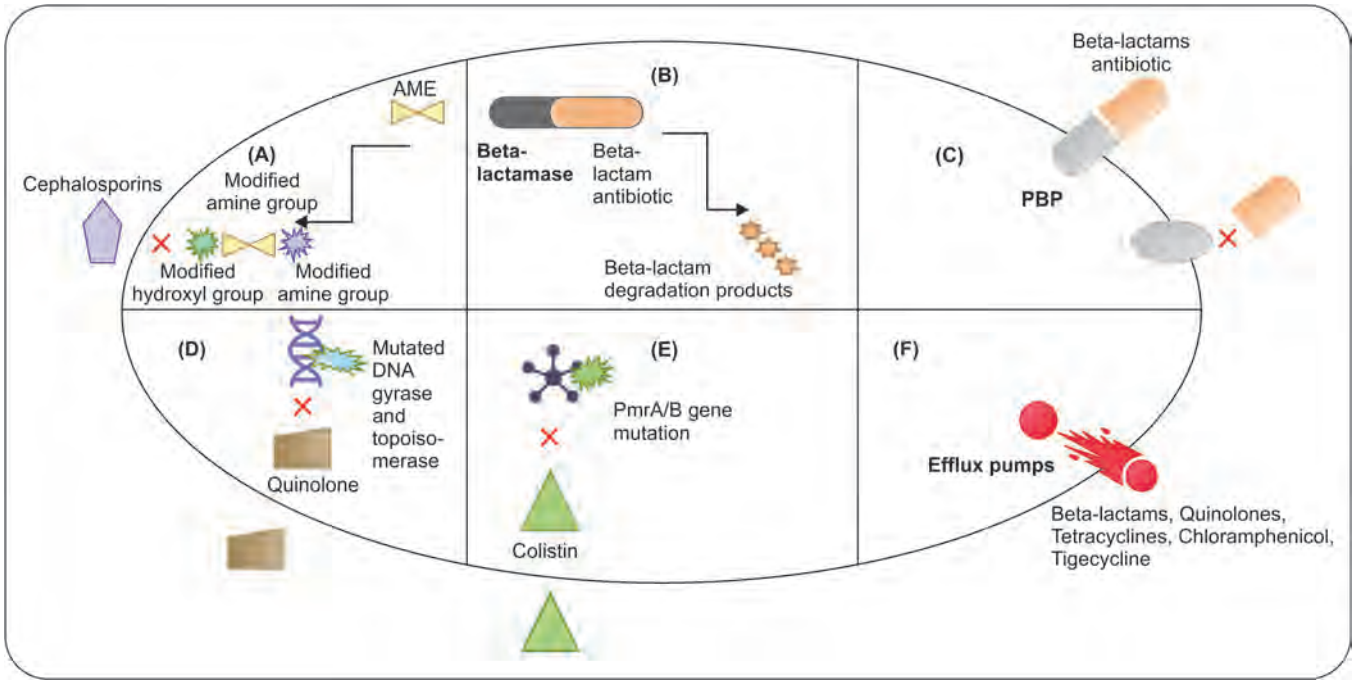

Fig. 1: Mechanism of resistance in *Acinetobacter baumannii*

baumannii which contains a non-inducible chromosomal AmpC cephalosporinase. Addition of promotor insertion sequence known as ISAba1 regulates the AmpC gene. Overexpression of AmpC cephalosporinase/ Aminoglycoside modifying enzyme (AME) and the presence of ISAba1 is intrinsically responsible for resistance to extended spectrum cephalosporin. Antibiotics like Cefepime and carbapenems, so far seems to have a stable response to these enzymes.

- *Porin channels:* Amongst the list of various mechanisms causing carbapenem resistance, the commonest are absence of penicillin binding protein 2(PBP2) and production of naturally occurring oxacillinase (OXA). Some isolates have been observed to have added downregulation of porin expression, leading to reduction in entry of carbapenem.
- *Efflux pumps:* Overexpression of bacterial efflux pumps decreases the concentration of β-lactam antibiotics in the periplasmic space. Efflux pumps usually act in association with overexpression of AmpC β-lactamases or carbapenemases causing resistance in Acinetobacter. Efflux pumps not only remove β-lactam antibiotics, but can actively remove chloramphenicol, quinolone, tetracycline, tigecycline, and disinfectants.
- Serine and metallo-β-lactamases: It confers resistance to carbapenems as they as they exhibit strong hydrolytic activity against all β-lactam antibiotics except monobactams (i.e., aztreonam).
- *DNA topoisomerase mutations:* Resistance to aminoglycosides and quinolones in Acinetobacter infections is due to the point mutations in the gyrA and parC topoisomerase enzymes which are the bacterial targets.
- *PmrA and PmrB proteins:* Due to its overexpression, resistance to colistin occurs.

Definitions in Antimicrobial Resistance[5]

- *Multidrug resistant (MDR):* When the isolate is resistant to at least three classes of antimicrobial drugs, that is, all penicillin and cephalosporins (including inhibitor combinations), aminoglycosides and fluoroquinolones, it is said to be "MDR Acinetobacter species."
- *Extensively-drug resistant (XDR):* When the Acinetobacter isolate is resistant to carbapenems and shall also be resistant to three classes of antimicrobials mentioned above (MDR), it is said to be "*XDR Acinetobacter species*."

- *Pan-drug resistant (PDR):* When the XDR Acinetobacter isolate is also resistant to tigecycline and polymyxin, it is said to be "*PDR Acinetobacter species*."[6]

Clinical Manifestations

Pneumonia

Nosocomial pneumonias occur due to aspiration, prolonged hospital stay, and mechanical ventilation, which create an ideal environment for transmission of bacteria like Acinetobacter. It adheres and forms biofilms on the tube. The clinical manifestation is fever and increased sputum production. It is diagnosed through respiratory cultures. Imaging findings are non-specific and can include lobar consolidations, pleural effusion, or rarely cavitation.

Community-acquired pneumonia is not as common as nosocomial pneumonia but a serious manifestation when caused by *A. baumannii*. Majority occurs in regions with hot and humid climates. It is caused by a diverse range of strains and is distinct from hospital strains. Symptoms and signs are similar in both the types. Without appropriate initial antibiotic therapy, mortality rate has been reported to be as high as 64%.[7]

Bloodstream Infections

Bloodstream infections due to *A. baumannii* occur mostly in the presence of central venous catheter or due to dissemination secondary to extensive pneumonia. Patients may present with septic shock and disseminated intravascular coagulopathy.

Skin and Soft Tissue Infections

Acinetobacter species are known to colonize the skin flora and it is important to differentiate colonization from nosocomial infections. Trauma-associated *A. baumannii* skin and soft tissue infections may be due to orthopedic external fixator devices, gunshot wounds, etc. There have been several recent reports regarding the occurrence of necrotizing fasciitis due to *A. baumannii*. The skin infection due to this species may evolve from an edematous peau d'orange appearance to sandpaper like, to a necrotizing process with hemorrhagic bullae.

In war-zones or after a traumatic injury to soldiers, Acinetobacter has been a significant cause of skin & soft tissue infections. These infections are also found following natural disasters (floods, earthquakes, etc.).

Urinary Tract Infections

Health-care associated urinary tract infection which is a major source of *A. baumannii* isolates occur mainly as catheter-associated infections or with percutaneous nephrostomy tubes. Community-acquired *A. baumannii* urinary tract infections are reported in post-renal transplant and nephrolithiasis patients.

Other Miscellaneous Infections

Meningitis: Majority of the cases of *A. baumannii* meningitis have been reported in post-traumatic injuries and post-neurosurgical procedures.

Osteomyelitis: Occurs typically postsurgical or trauma related. Acinetobacter can cause keratitis due to use of contact lenses, and few cases of native and prosthetic valve endocarditis have been reported.

Our institutional experience (unpublished): In our institute KIMS Bhubaneswar, a recent study was done for 1 year (July, 2018–June, 2019). Around 455 patients grew *A. baumannii* infection in various cultures, out of which 348 (76.4%) found in ICU patients and 107 (23.6%) in non-ICU patients. Respiratory tract infection was the commonest infection in ICU as well as non-ICU settings, followed by septicemia in ICU and skin and soft tissue infection in non-ICU settings. In ICU setting, 8% of isolates were pure MDR, 68% were XDR, 7% PDR, and 17% were sensitive to all classes of antibiotics while in non-ICU patients, 14% of isolates were pure MDR, 52.3% XDR, 9% PDR, and 24% were sensitive to all classes of antibiotics. This states the seriousness of infections caused by MDR and XDR *A. baumannii* organisms in a health-care setting and the spread of pan drug resistance even in non-ICU areas. **Figure 2** depicts the pattern of drug resistance as per the isolates obtained from different site of infections.

Treatment

Acinetobacter is considered amongst the most resistant organisms and initiating effective empirical therapy is challenging to the physicians. Definitive therapy should be based on antimicrobial susceptibility test results.

Empirical Therapy

Antibiotic susceptibility pattern is an important factor, which guides clinicians regarding the therapy in an intrinsically resistant organism. In *A. baumannii*

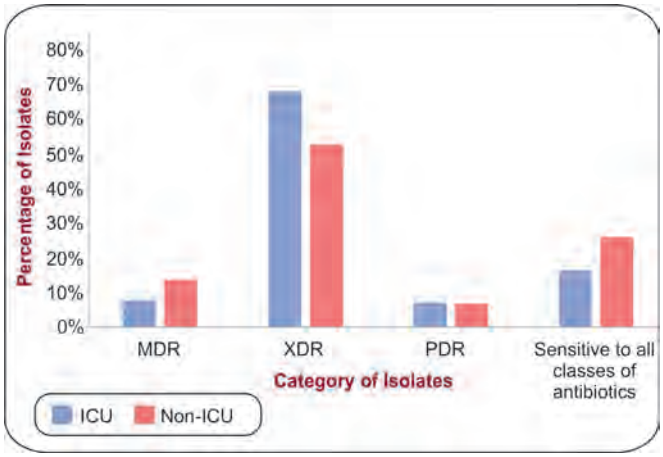

Fig. 2: Pattern of drug resistance in *A. baumannii* infection in ICU and non-ICU patients

infections, empirical therapy is advisable to initiate with carbapenems, as the probability of *A. baumannii* being resistant to cephalosporins (a common first-line antibiotics) is more. After the sensitivity reports therapy is modified accordingly.

Treatment of MDR *Acinetobacter* Species

Here the preferred drugs are Carbapenems, if susceptible.[8] Usually, imipenem is given at the dose of 500 mg q6h and meropenem at the dose of 2g q8h. The prolonged infusion over 3–4 hours is better than bolus injections.

Treatment of Extensive and Pan-drug Resistant *Acinetobacter* Species

The resistance rates of carbapenems in *A. baumannii* infections have been rising substantially globally. However, there is no consensus suggesting optimal anti-microbial treatments for such strains. The options available are: Tigecycline is a glycylcycline antibiotic and is another drug that can be used clinically against MDR *A. baumannii*; Tigecycline is usually found to have a low MIC (2 g/mL) for *A. baumannii* strains, the serum concentration of the drug is also low, and the outcome of ventilator-associated pneumonia and bacteremia associated with *A. baumannii* clinical trials have shown inferior results compared to other alternative agents.

Minocycline is a tetracycline that has good antimicrobial activity and it may even act against the strains resistant to other tetracyclines (including tigecycline). Cross-resistance has been reported with minocycline. Minocycline therapy has high treatment success once given in combination therapy.

Aminoglycosides (amikacin and tobramycin) are not of abundant use against *A. baumannii* due to its toxicity and lack of lung penetration. Inhaled tobramycin can be an adjunct as inhalational therapy in *A. baumannii* pneumonia.

Polymyxins (Colistin and Polymyxin B) being a cationic detergent disrupts bacterial cytoplasmic membranes. It was previously abandoned for its nephrotoxicity and neurotoxicity. Currently the nephrotoxicity rates are reportedly 36%, and neurotoxicity is rarely seen these days due to modified formulations. Although the dosage differs from patient-to-patient, polymyxin can be given at the dose of 1.5–3 mg/kg q12h in MDR-Acinetobacter infections.

Colistin can be given inhalational and intravenous route. For combination therapies, colistin is a key component. An important side effect of inhalational colistin is bronchoconstriction.

The rising rates to resistance are to the last-line drugs, that is, tigecycline and polymyxin against *A. baumannii* are highly reported and is of substantial concern. There is a critical need to find alternative therapeutic options for this.

Combination antimicrobial therapy: Combination therapy appears to be promising in prevention of emergence of resistance and in improving clinical outcomes. Its key component to treat MDR *A. baumannii* is Colistin. Many colistin-based combined therapies, including colistin-rifampicin, colistin-minocycline, colistin-carbapenem, colistin-sulbactam have been found to act synergistically in vivo or in vitro against *A. baumannii*.

Although polymyxin causes dose-related nephrotoxicity, Polymyxin B combination therapies when used with amplified doses of antibiotics such as carbapenem, minocycline, and tigecycline have been found to attenuate the development of polymyxin resistance.

Future treatment options: In view of increasing rates of emergence of multidrug resistance and lack of newer class of antibiotics, alternative strategies are in pipeline to control and treat *A. baumannii*.

- *Bacteriophage:* Bacteriophages therapy is being re-evaluated as an alternative management option to help counteract antibiotic resistance due to its high

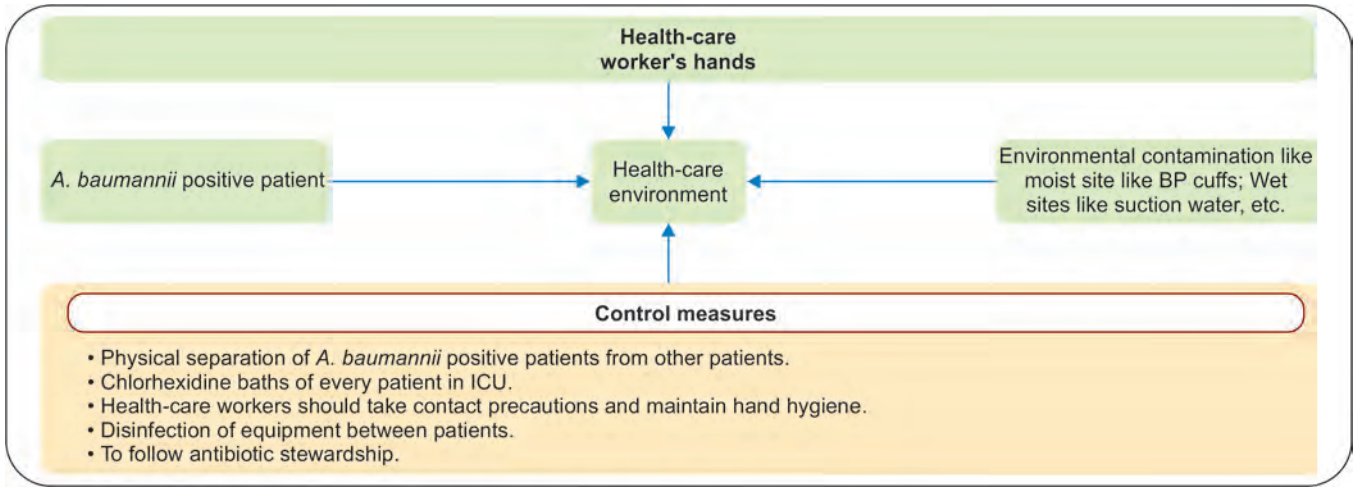

Fig. 3: Source of infections and the control measures to prevent infections

specificity and ability to work quickly. Examples—vB_Ab-M-G7 and B#-C62[8] for MDR *A. baumannii*.

- *Cathelicidins: (antimicrobial peptides):* There were positive results from a cathelicidin known as "Tammar Wallaby WAM1." It has a probability for parenteral use in Acinetobacter infections in humans.
- *Radioimmunotherapy:* It is emerging as a therapeutic possibility due to its ability to kill microorganisms as effectively as cancer cells.[9]
- *Photodynamic therapy:* A photosensitizer is topically applied into the infected tissue, followed by red or near infra-red illumination is given which penetrates and kill the infected tissue. It is used to treat localized bacterial infections.
- *Nanoparticle technology:* This novel and inexpensive technology[9] has shown effective resu[l]ts with its stable nitric oxide-releasing nanoparticle platform and it is potential option for treatment of *A. baumannii* induced complex cutaneous infections.

Infection Control and Prevention

Source of infections and the control measures to prevent infections is summarized in **Figure 3**.

Conclusion

Acinetobacter species have emerged as one of biggest challenge to physicians because of its inherent resistant strains and ability to cause extensive resistance to even the newer antimicrobials. To decrease the spread and emergence of resistance of *A. baumannii* infections, it is important to promote rationale use of antibiotics, and take adequate control measures to prevent the establishment of drug resistant endemic strains.

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CHAPTER

171 Scrub Typhus—Clinical Manifestations and Management

Sudhir Kumar, Govind Kumar, Arshad Ahmad, Amit Kumar Mishra

Abstract

Scrub typhus is an arthropod born acute infectious disease that is caused by intracellular Gram-negative organism Orientia tsutsugamushi. This disease is mainly reported from states of the Himalayan terrain, Eastern and Western Ghats, and the central part of India. Scrub typhus is transmitted by some species of trombiculid mites which are found in areas of heavy scrub vegetation. The mites feed on infected rodent hosts and subsequently transmit the parasite to other rodents and humans. The main target tissue of O. tsutsugamushi is the vascular endothelium in human, leading to generalized vasculitis and perivascular inflammatory changes, and results in end-organ damage of many vital organs including nervous system, cardiovascular system, kidney, lung, and other organ. Scrub typhus presents with fever, headache, myalgia, cough, abdominal pain, conjunctival redness, altered consciousness, apathy, shin pain, lymph node enlargement, hepato-splenomegaly, macula-papular rash and eschar. Currently, the drug of choice for treatment of scrub typhus is doxycycline. Other drugs used to treat scrub typhus, includes tetracyclines, chloramphenicol, rifampicin, azithromycin and quinolones.

Introduction

Scrub typhus is an arthropod born acute infectious disease that is transmitted to humans by *Trombiculidae* family. It is caused by intracellular Gram-negative organism *Orientia tsutsugamushi*. This disease was first described in 1899 in Japan. People of all ages are affected by this disease including those at extreme of age. The term "scrub" is related to the vegetation (land between woods and clearings) where vectors are proliferating. The name *scrub typhus* is misleading, as the disease can be contracted in many other habitats, including forest, beaches, large gardens, and plantations. The word "typhus" is a Greek word which means "fever with stupor" or smoke.[1] "Tsutsuga" means small and dangerous and "mushi" means insect.

Scrub typhus is mainly distributed in the tsutsugamushi triangle, which is bounded by Australia in the south, Japan in the east, Afghanistan in the west and southern parts of the Russia in the north. The disease is mainly prevalent to south-eastern and eastern parts of Asia including India, Myanmar, Nepal, Sri Lanka, Thailand, and other areas in the region.[2] More than hundred crore people of world are at risk for scrub typhus and an estimated ten lakhs cases occur annually.[3] In India, scrub typhus is reported from states of the Himalayan terrain, Eastern and Western Ghats and the central part of India. Number of *Leptotrombidium deliense* is affected by rainfall, which may be the cause for a higher case during the Monsoon time as shown by Gurung *et al*.[4] In India, the agent of scrub typhus is *O. tsutsugamushi*. Its antigenic structure is different from other Rickettsiae. Although our country India is a part of tsutsugamushi triangle, Scrub typhus grossly remains under diagnosed owing to the non-specific variable clinical presentation except eschar, poor specific diagnostic facility and very low index of suspicion by the physician.

Vector and Host

L. deliense and *L. akamushi* are the main vectors of scrub typhus, which are found in countries of the Southeast Asian region including India. This disease is spread through the larval mites or "chiggers." The natural hosts for scrub typhus are small rodents including *Rattus* subgenus. The field rodents and the vector mites act as a reservoir and because of these two the infection continues in nature.

Transmission and Pathogenesis

The causative organism of scrub typhus is *O. tsutsugamushi*, which is an intracellular Gram-negative bacterium. Humans are accidental hosts and the infectious agent is transmitted through the skin by the bite of larval stage of infected trombiculid mites or chiggers.[5] Disease occurrence is more in rainy season and commonly seen among persons who engage in occupational or other work related to contact with mite-infested area. The mites have a life cycle of four stages: adult, egg, larva and nymph. Only stage that can transmit the disease to humans is the chigger or larva. The chigger takes up tissue fluid and lymph. Very high number of *O. tsutsugamushi* are there in the salivary glands of the chigger and these are transmitted into their host when they take up tissue fluid.[6]

Transovarial transmission is seen in mite where they pass the infection on to their eggs. Likewise, transstadial transmission is also seen in which the infection transmitted from egg to the chigger and adult.

The strain of organism and condition of the host are two most important factors that decide the severity of disease. The pathophysiology of scrub typhus is not fully understood, though in general it is thought to be due to vasculitis either localized or disseminated. The principal target site of *O. tsutsugamushi* is the vascular endothelium in human. This organism acts at vascular endothelial cells leading to generalized vasculitis and perivascular inflammatory changes, and results in end-organ damage of many vital organs.[7] Both humoral and cellular immune response are seen against *O. tsutsugamushi.*

Clinical Features

The average incubation period of *O. tsutsugamushi* in humans is around 10 days and can vary between 6 and 21 days.[8] Main symptoms of scrub typhus are pyrexia, headache, muscle pain, dry cough, and abdominal discomfort. Patients may present with subacute/chronic pyrexia and fever of unknown origin.[9] The severity of the symptoms varies widely, depending on the strain of organism and condition of the host.

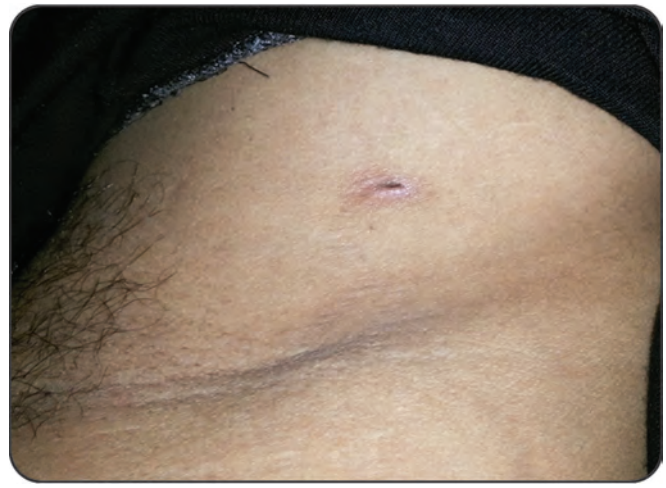

Fig. 1: Eschar at axilla

A small vesicular lesion at the chigger feeding site is usual first sign of scrub typhus, which usually changes into an eschar or an ulcer with local lymph node enlargement. An eschar is a typical lesion with black necrotic center and an erythematous border and is mainly located in the groin, axilla, genitalia, and neck **(Fig. 1)**. The eschar is found in patients suffering from scrub typhus ranges from 7% to 80% in different study. Eschar is the single most important clue for diagnosis on physical examination. The detection rate of eschar depends on multiple factors like the skin color of the infected person and site of the lesion.

Sudden onset fever is the most common symptom accompanied with conjunctival redness, severe headache, altered consciousness, apathy, myalgia, shin pain, and more characteristically lymph node enlargement and hepatosplenomegaly. Fever is usually of high grade and may be with shaking chills.

A maculopapular rash appear at end of first week which initially seen at the trunk and later on spread to the limbs. This rash is not well appreciated among dark skinned individuals.

Systemic symptoms and signs related to major organ system like the central nervous system, cardiovascular system, kidney, pulmonary, and digestive systems become evident by end of second week. Major organ system involvement may produce serious complication in the

form of myocarditis, pneumonia, meningitis/encephalitis, acute renal failure, and gastrointestinal bleeding. Acute respiratory distress syndrome development is more commonly seen in patients of scrub typhus who have high leukocyte count and late treatment. Meningitis, meningoencephalitis, or encephalitis is common form of neurological involvement seen in scrub typhus.[10]

According to Kim et al., older age (≥60 years), scrub typhus patients without an eschar, and laboratory parameters such as leukocyte counts >10,000/mm and serum albumin level ≤3.0 g/dL are potential indicators of complications.[11] Untreated patient remains febrile for about 2 weeks and have a long convalescence of around 6 weeks thereafter.

Differential Diagnosis

Differentiated and undifferentiated fever are two form of acute febrile illness (AFI). In differentiated fever there is obvious presence of focus of infection or inflammation, while in undifferentiated fever there is no obvious focus of infection and the symptoms and signs are quite nonspecific. In patient with undifferentiated fever several diagnostic possibilities are considered, especially in the tropics.[12] The differential diagnosis of scrub typhus includes typhoid fever, dengue fever, malaria, other rickettsioses, anthrax, leptospirosis, and hemorrhagic fevers. It is considered as one of the causes of fever of unknown origin (FUO) in endemic areas.

Diagnosis

Febrile illness along with eschar on physical examination almost confirms the diagnosis. Leukocytosis and decreased platelet count may be seen. Altered liver function and kidney function test may be seen in large number of cases. Ultrasonography may reveal hepatosplenomegaly.

The lab diagnosis of scrub typhus is either confirmed or supported by identifying the microbe in cell culture, presence of antigen by immune-histochemical methods or the antibodies by the indirect immunofluorescence assay (IFA) and detecting organism's nucleic acid using polymerase chain reaction (PCR).

As antigen identification tests have low sensitivity/specificity and require tissue specimens, serological tests to identify antibodies are the better diagnostic tool in real clinical scenario as they are simple and easy to perform.[13] After infection IgM antibodies against *O. tsutsugamushi* appear in the body at the end of first week while IgG antibodies appear at the end of the second week. The Weil-Felix (WF) test has better specificity but poor sensitivity and is based on the identification of antibodies to various *Proteus* species, which contain cross-reacting antigenic epitopes to antigens from members of the genus *Rickettsia*. The WF test is said to be positive when there is high titer of 1:320 or more or a fourfold rise in titer.

The standard serological test is the indirect IFA for the detection of IgM antibodies. This test has many demerit which consist of retrospective nature, availability of trained technician and equipment which may not be possible in many labs.[14] At present most lab use the enzyme-linked immunosorbent assay (ELISA) for the presence of IgM antibodies in scrub typhus as it gives an objective result and has sensitivity almost equal to that of IFA.[13] Rapid diagnostic kit to detect scrub typhus IgM antibodies have sensitivity in range of 34.7–96.7% and specificity between 93.3–99.7%.[15]

The samples from which causative microbe of scrub typhus is isolated are buffy coat of blood, defibrinated whole blood, plasma, tissue, skin biopsy, and arthropod samples. It takes around 4 weeks to detect rickettsia in cell culture. Molecular methods using PCR is possible from skin rash specimen, eschar, lymph node biopsies, or blood and is less time consuming. Nested PCR method is more sensitive than doing single PCR. This is a less time-consuming method and takes around 1 day.[16]

A positive IgM ELISA in the suspected patient with defervescence within 2 days of prescribing doxycycline or scrub IgM ELISA seroconversion on convalescent sera with other causes of acute febrile illness ruled out after proper investigations also favors scrub typhus infection.[12]

Management

There are several drugs to treat scrub typhus, including tetracyclines, chloramphenicol, rifampicin, azithromycin, and quinolones. Currently, the drug of choice is doxycycline, a member of the tetracycline family, and several studies have proved its effectiveness. The recommended therapeutic dose for scrub typhus in adult is doxycycline 200 mg/day for 7–15 days and tetracycline 2 g/day for 7–15 days in divided doses. But many case reports of natural resistance make it difficult to prescribe suitable antibiotic.[17] The use of azithromycin in pregnant

women is believed to be safe for both mothers and fetuses, and it is classified as category B by the US FDA Pregnancy Category. Azithromycin is an effective drug for the management of scrub typhus as it efficiently penetrates human white blood cells and macrophages, which are target area for of *O. tsutsugamushi*. It should be given as short course because of its longer half-life.[18]

Chloramphenicol can also be given in adults and its dose is 500 mg qid orally for 7–15 days. Rifampicin is also effective against *O. tsutsugamushi.*

Doxycycline is the drug of choice for prophylaxis and the usual prophylactic dose is 200 mg per week. Killed vaccines against scrub typhus was disappointing because of results in human studies were not as successful as they were in animal studies.

Current Status in India

Earlier Scrub typhus was an endemic disease in many pockets of our country. But because of large scale use of insecticidal later, scrub typhus cases were reported in very low number from India. Recently there had been increase in number of cases of scrub typhus in India. Resurgence may be due to changes in the human behavior, unplanned urbanization, and deforestation, which result in displacement of vectors as well host rodents. Human in town may get bitten by the disease-causing mite larvae while moving in parks or during any other recreational activities such as camping in the affected vegetation area.[19]

Conclusion

Scrub typhus is an important differential diagnosis of undifferentiated fever cases. Eschar is most important clinical sign. High index of suspicion is needed to diagnose it as India is a part of endemic zone "Tsutsugamushi triangle".

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CHAPTER

172 *Burkholderia* Species

Shubhransu Patro

Abstract

Burkholderia species contain the most versatile organisms that occupy a surprisingly wide variety of ecological niches. These infections can be very difficult to treat and, in some cases, lead to death as it is considered to be one of the most antimicrobial-resistant organisms found in the clinical laboratory. These bacteria are used for the purpose of biocontrol, bioremediation, and promotion of plant growth, but safety issues regarding human infections, particularly in patients with compromised immunity, are still questionable. This chapter provides an overview of the genus *Bukholderia*, its ecological diversity, the clinical manifestations observed, and the management protocols that will guide the physician to effectively treat this infection.

Introduction

Burkholderia species continues to be one of the notorious multidrug resistant organisms among the nonfermenting gram-negative bacilli (NFGNB). First described by William Burkholder, the species majorly include plant pathogens and soil bacteria with two important exceptions, *Burkholderia mallei* and *Burkholderia pseudomallei*, which are known to be notorious pathogens in humans and animals.[1,2] Apart from being a primary pathogen in patients of Cystic fibrosis (CF), *Burkholderia* cepacia complex (BCC) has been found responsible for bacteremia in immunocompromised and chronically debilitated patients. There have been numerous documented outbreaks of BCC septicemia in intensive care units and patients with renal failure.[3] Similarly, *B. mallei* and *B. pseudomallei* have been reported as the causative agent of diseases known to be Glanders and Melioidosis, respectively, both of which carry significant mortality and morbidity.[4]

Taxonomy

William Burkholder, an American microbiologist, first discovered the organism responsible for bacterial rot of onion bulb at Cornell University in the year 1950 and was named as *Pseudomonas cepacia*.[1] In the year 1992, Yabuuchi et al. created a new genus "*Burkholderia*," and transferred *P. cepacia* and six other species belonging to rRNA group II of the genus *Pseudomonas* under the new genus.[5] Since the discovery, the taxonomy of the new genus has undergone considerable changes and presently the genus *Burkholderia* consists of 22 species.[6] All the members of the species possess a very large genome ranging between a size of 6 and 9 Mb, which renders the organism versatile and ubiquitous. In the subsequent years, Vandamme and colleagues described *Burkholderia cepacia* as a complex of closely related genomovars and genomic species and referred them collectively as BCC, which included ten different unique species. The members of the BCC are *B. cepacia, B. multivorans, B. cenocepacia, B. stabilis, B. vietnamiensis, B. dolosa, B. ambifaria, B. anthina, B. pyrrocinia, and B. ubonensis.*[2] Based on comparative 16S ribosomal RNA and recA sequencing, multilocus sequence typing (MLST), and intermediate DNA-DNA binding values, recently seven novel species of *Burkholderia* have been identified and are proposed to be included under BCC.[7] The seven new

members are; *B. latens, B. diffusa, B. arboris, B. seminalis, B. metallica, B. contaminans, and B. sabiae*.

Epidemiology

The ability of *Burkholderia* species to survive in extreme environmental conditions makes it ubiquitous. Because of minimal nutritional requirements, it can survive for months in media and solutions like antiseptics, sinks, water, and intravenous fluids. They also tend to reside on indwelling catheters, IV cannula, and nebulizers.[8] Commercial use of BCC in agriculture as a biocontrol agent, in the bioremediation of toxic agents and plant growth promotion contributed to the increased incidence of human infection by the organism. Various reports have documented person-to-person transmission by a few strains of BCC and *B. pseudomallei*.[9] Studies have shown that by the age of 18 years, 3.5% of patients suffering from CF harbor BCC.[10] Among all other *Burkholderia* species, BCC is the most frequently isolated clinical pathogen followed by *B. mallei* and *B. pseudomallei. B. pseudomallei*, the causative agent of Melioidosis, is predominantly found in the regions of Asia, Africa, Northern Australia, and South America and is isolated from soil and water. It is also known to cause outbreaks in Thailand causing significant mortality and morbidity. *B. mallei* also share the same geographical territories as *B. pseudomallei* and primarily affects horses, causing equine glanders. It was one of the first used agent as biological weapon by Germany in the World War I.[11] Human transmission occurs by percutaneous inoculation, ingestion, or inhalation from environment, contact with infected animals and even laboratory acquired infections have been reported.[12] Few other strains like *B. gladioli* and *B. pickettii* have also been reported to cause nosocomial infections and multidrug resistant outbreaks in certain communities and hospitals posing an emerging threat to the society. However, little is known about the epidemiology of these particular species.

Clinical Manifestations

BCC Infection in Cystic Fibrosis

Owing to increased life expectancy in patients with CF, BCC has emerged as a major cause of morbidity and mortality. There is chronic colonization of the major airways with BCC in these patients and it may persist for months to years. Up to 20% of the infected patients rapidly deteriorate due to necrotizing pneumonia and sepsis, which may result in death.[13] This fatal clinical decline in patients with CF is known as "Cepacia Syndrome" and it has not been observed with any other pathogens. This explains the varied outcomes amongst CF patients who are infected with same strain. Reports of "Cepacia Syndrome" have also been documented in non CF patients.[14] There has been reported mortality of 75% in patients with CF who undergo transplantation.[15]

BCC Infection in Non-CF Patients

BCC is recognized as an important pathogen in patients suffering from chronic granulomatous disease where there is inability of macrophages to produce reactive oxygen species due to mutations in NADPH oxidase complex. Mostly, it is a nosocomial infection via contaminated hospital equipment like disinfectants, antiseptics, topical anesthetics, and respiratory therapy equipment. BCC bacteremia in non-CF hospitalized patients is most often seen in patients with comorbidities such as diabetes mellitus, congestive heart failure, malignancy, and hemodialysis along with indwelling urinary catheters, central venous catheters, and endotracheal tubes. BCC pulmonary infection is mostly observed in intensive care patients who are on prolonged mechanical ventilation **(Fig. 1)**.[16] Besides this, skin, soft tissue, and genitourinary infection have been reported in patients with burns or surgical wounds, after prostate biopsy, urethral instrumentation, and exposure to contaminated solutions.

Melioidosis

It is a disease of human and animals caused by *B. pseudomallei*. Every year approximately 1,65,000 people are infected by melioidosis, resulting in death of approximately 89,000 infected patients.[17] The incubation period for the disease has been recorded to be as less as 1 day to up to a period of 62 years.[18] Because of its prolonged incubation period the disease has also been referred as "Vietnamese time bomb."[19] One or more risk factors for the disease are found in up to 80% patients. Well-known risk factors for melioidosis include diabetes mellitus, heavy alcohol use, chronic pulmonary disease, chronic renal disease, glucocorticoid therapy and cancer.[20] The spectrum of clinical manifestations is greatly varied ranging for acute fulminant septic illness to a chronic infection that may be confused with tuberculosis or

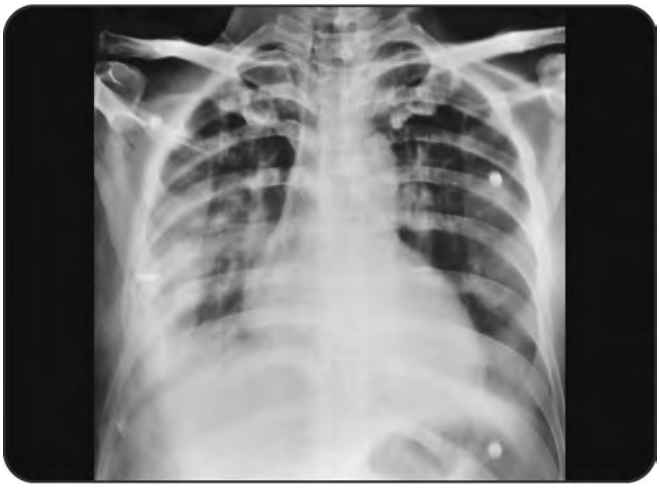

Fig. 1: Chest X-ray showing a right lower lobe pneumonia in patient with BCC infection

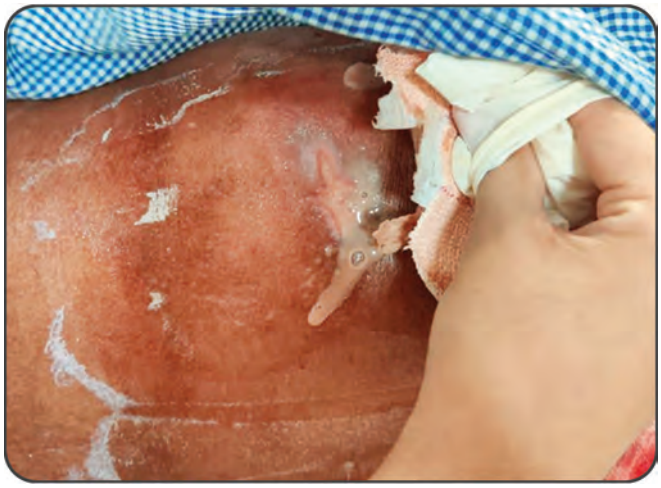

Fig. 2: Pus draining from a localized abscess in a diabetic patient with melioidosis

malignancy for which it has been nicknamed as "The Great Imitator."[21] The disease can manifest as an acute infection seen in 85% of the patients as pneumonia, sepsis or localized abscess **(Fig. 2)**; as chronic infection seen in 10% of the affected group, where it mimics symptoms of tuberculosis; and as a latent infection in 5% of the patients who are immunocompetent. The most common presentation is pneumonia **(Fig. 3)**, while others are genitourinary infection, skin infection, overwhelming sepsis with abscesses disseminated in multiple internal organs **(Fig. 4)**, septic arthritis **(Fig. 5)**, and osteomyelitis. Mortality rates for melioidosis are approximately 40% in Northeast Thailand (35% in children) and 14% in Australia.[22]

Glanders

Glanders is a highly contagious and fatal disease of the equine. It is caused by the organism *B. mallei*.[23] In India, it is a notifiable disease and more than 50% cases of equine glanders have been reported from Uttar Pradesh.[24] The incubation period for the acute form of disease is 1–14 days, while for the chronic form, the incubation period may be to 12 weeks. Clinically, it may manifest as a local infection with nodules and lymphadenitis when transmitted by skin inoculation. Pneumonic forms are usually transmitted through inhalational route. Patient may develop septicemia with shock when organism disseminates from the skin or lungs causing significant mortality. The mortality of pulmonary form and the septicemic form of glanders has been as high as 95% without treatment and about 40–50% with treatment.[24]

Others

Other members of the *Burkholderia* species like *B. gladioli* and *B. pickettii* have been rarely found to cause infections in CF patients and hospital outbreaks. However, a little is known regarding the clinical features and etiopathogenesis of these two species.

Diagnosis

Identifying *Burkholderia* species has been a tedious task because of poor laboratory proficiency throughout the world. A combination of selective media, biochemical analysis along with commercial kits, is being routinely used for species identification. For identifying BCC, three selective media are used; the *P. cepacia* agar (PCA), the oxidation-fermentation polymyxin bacitracin lactose agar (OFPBL), and the *B. cepacia* selective agar (BCSA). BCSA is the most recent and preferred selective media used. Apart from BCC, other members of the species like *B. gladioli*, Ralstonia spp., and Pandoraea spp. can also be grown in BCSA. Similarly, out of various culture medias used for identification of *B. pseudomallei*, the Ashdown's selective agar (containing gentamicin), is the most commonly used. The characteristic "safety pin" appearance on Gram's staining in a histopathological specimen also helps in identification of *B. pseudomallei*. Use of automated

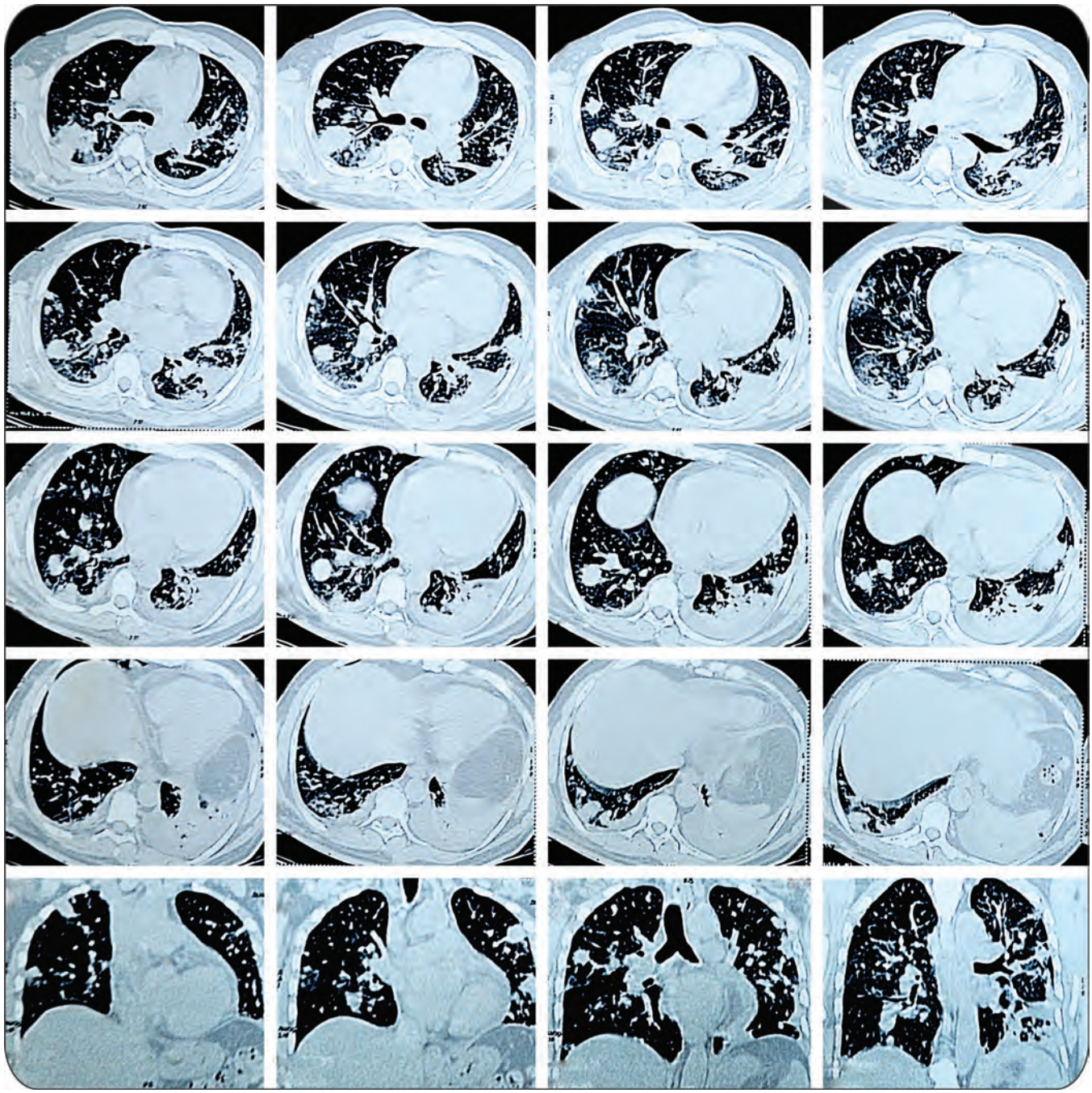

Fig. 3: HRCT thorax revealing multiple bilateral opacity in a patient suffering from melioidosis

identification systems like API 20, Phoenix, Microscan, and Vitek 2 to identify BCC complex is also on the rise nowadays, but the identification is not trustworthy as many of the species of NFGNB are misidentified as BCC. Distinguishing *B. pseudomallei* from *B. mallei* on the basis of morphology and serologic tests is also a tedious task. Molecular identification has been a breakthrough recently where identification is performed by DNA based polymerase chain reaction, which identifies the differences in sequence of 16S rRNA gene or recA gene,

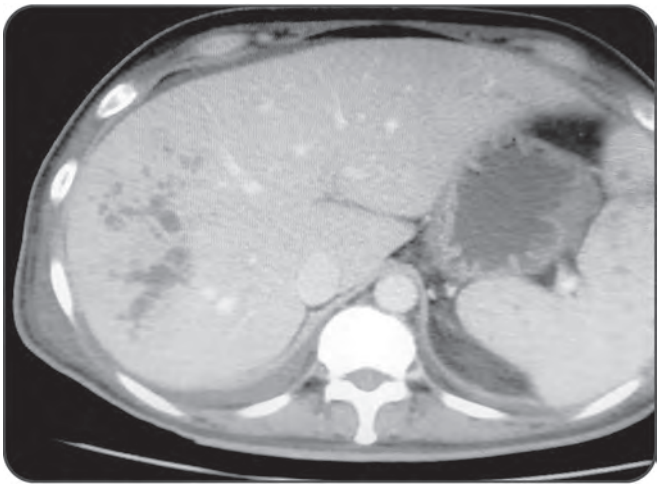

Fig. 4: CT abdomen showing multiple abscesses in liver and spleen in a immunocompromised patient suffering from melioidosis

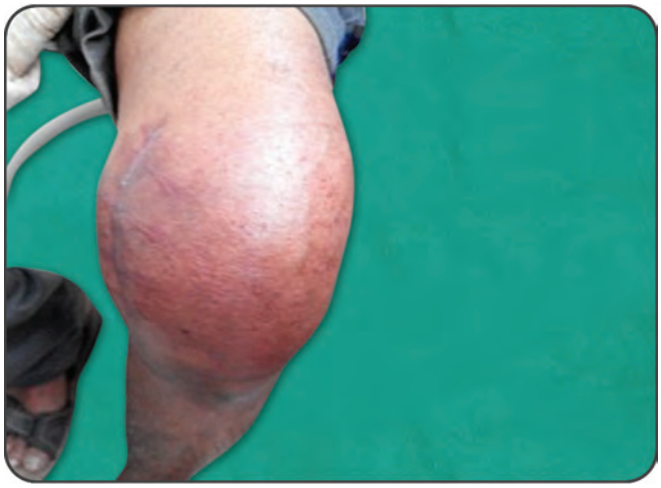

Fig. 5: Septic arthritis involving knee in a patient with melioidosis (*Source:* Patro S, Panda SS, Mishra D, et al. *Burkholderia* infections in diabetic patients emerging as a challenge for physicians: a case series. J Clin Diagn Res. 2019;13:OD04-07.)

that help in distinguishing the species. Other methods of molecular identification like MALDI-TOF MS, multilocus restriction typing, pulsed field-gel electrophoresis, and BOX-PCR have been equally found effective in identifying species.[25]

Management

Burkholderia cepacia Infections

This organism is intrinsically resistant to many of the antimicrobial agents, which pose the greatest challenge in its management. The BCC isolates from CF patients have shown to be substantially more resistant. Therefore, combination drug therapy for serious infections has been suggested. Antimicrobials that are most effective and considered first line are Trimethoprim-sulfamethoxazole (TMP-SMX), Meropenem, and Doxycycline. Some strains are also susceptible to third-generation ureidopenicillins, advanced cephalosporins, and fluoroquinolones.[16]

Burkholderia pseudomallei Infections

Treatment is divided in two phases: the "induction phase" for 2 weeks with intravenous ceftazidime or a carbapenem (either Meropenem or imipenem), and the "eradication phase" with 12 weeks of oral antibiotics such as trimethoprim-sulfamethoxazole to eradicate the infection and prevent relapse. Alternative eradication therapies include doxycycline and co-amoxiclav but both therapies have a higher rate of relapse.[21]

Burkholderia mallei Infections

This organism causes human infection rarely, so there is limited information available regarding choice of antibiotics. Because of its similarities with *B. pseudomallei*, it is postulated that the drug susceptibility would be same. Susceptibility to macrolides, azithromycin, and clarithromycin have also been reported.[16]

Conclusion

Most of the *Burkholderia* species infections are hospital acquired and potentially pathogenic in individuals with impaired host defense, which can lead to septicemia and acute respiratory distress syndrome (ARDS) with requirement of ventilator and perfusion support if not intervened at the earliest. Treatment of this infection is really a challenge to physicians as patient needs long-term antibiotic therapy and recurrence of infection is very common even after prolonged treatment. As these infections carry a very grave prognosis, hence, high risk of suspicion is required in all cases of septicemia and ARDS particularly with impaired host defense. Prompt management of the infection and the underlying conditions will definitely reduce the mortality and morbidity to a great extent.

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CHAPTER

173 Managing Dermatophytosis (Tinea Infections) in Today's Scenario

Basavana Gowdappa Hathur, Garehatty Rudrappa Kanthraj

Abstract

Dermatophytosis is common fungal infection in human population. These keratinophilic fungi are restricted to the stratum corneum. The frequent strain causing infection earlier was Trichophyton rubrum; but at present, Trichophyton mentagrophyte is found to be common pathogen. Dermatophytosis requires prolonged treatment. Change in the fungal species, resistance, and steroid abuse leading to reinfection make the condition refractory to treatment. Details of treatment taken and family history are important. Appropriate combination of oral and topical antifungal agents and counseling for better adherence to treatment are needed in resistant and steroid misuse cases.

Introduction

"*Ringworm*" infection is frequently used terminology for dermatophytosis. This infection basically involves the keratinized tissue of the superficial layers of skin. There are three genera among dermatophytes: Epidermophyton, Microsporum, and Trichophyton. These fungi are keratinophilic and have capacity to invade the keratinous tissue of living animals. The involvement of epidermis, especially stratum corneum and tissue with higher keratin contents like hair and nails is common. These organisms are unable to penetrate deeper layers of skin or organs in immune-competent individuals and commonly confine to superficial non-living cornified layers. The clinical manifestations are basically dependent on response of the infected individual to dermatophytosis, which can vary between milder to significant clinical expression. These are mainly caused by reaction of host to the metabolic products of the organism, degree of virulence, anatomic location of the infection, and prevailing environmental factors.[1]

There can be lot of geographical variation in incidence and prevalence of these fungal infections. Several factors, like high humidity, hygienic practice of the individual, and risk proportion of individuals to acquire infection, can change from region to region. The dermatophytosis can have seasonal influence, with higher incidence in summer and lower in other seasons. Nearly quarter of global population is expected to have dermatophytosis as per WHO estimates. There can be 30–70% of general population who are asymptomatic carriers.[2]

Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis and *Trichophyton tonsurans* are frequently seen pathogens to cause cutaneous fungal infection. Tinea capitis is commonly caused by *Trichophyton tonsurans*. Tinea pedis, Tinea unguium, Tinea corporis, and Tinea cruris[2] are commonly caused by *T. rubrum*.

These cutaneous fungal infections can produce significant impact on quality of life. They can be responsible for lot of social embarrassment, psychosocial discomfort, and impact on their work environment and hamper efficiency. The best way to reduce morbidity and restrict transmission is by diagnosing early and providing proper health education for prevention and adherence

to treatment. Therapy can be protracted and produce financial concerns. Disrupted therapy can be one of the important causes for relapses. There can be frustrations among treating clinician due to inadequate therapeutic response and relapse.

Changing Scenario of Dermatophytes

There is an epidemiological transition of dermatophytosis in India. *T. rubrum* was found to be common pathogen in the past by many observers in India; however, at present it is significantly less prevalent. *T. mentagrophyte* is presently found to be frequent when compared to past.[3]

Antifungal Drugs: Mode of Action

See **Table 1**.

Treatment of Dermatophytosis

Common topical antifungal cream used **(Table 2)**.[4]

Duration of treatment is given for 4–6 weeks or longer, depending on clinical severity and therapeutic response (Modified and reproduced with permission from Poojary SA).[4]

Common clinical situations for use of topical preparations:

- Infections during conception and first trimester
- Patients with renal, hepatic, and cardiovascular diseases
- Patients who are taking compelling medications for comorbidities with potential interaction

Common guidelines for improved therapeutic outcomes of using topical preparations:

- Medication should be applied over the lesion and surrounding skin, starting from outer aspect
- Choice of formulation can be variable, based on the region of the disease:
  - *Liquid preparations:* Web spaces, axilla, external genitalia, wet-lesions, and larger area of involvement
  - *Creams:* Dry lesions, lesions with prurigo
  - *Ointments:* Hyperkeratotic lesions
  - *Gels:* Over the facial region
  - *Nail lacquers:* Subungual lesions
  - *Shampoos:* As additional component in tinea capitis

TABLE 1 The Mechanism of action of antifungal drugs

Class	*Mechanism of action*
Alkylamine e.g., Terbinafine	Inhibition of squalene epoxide
Azoles	Inhibition of 14–α-demethylase
Griseofulvin	Disruption of mitotic spindle
Amphotericin B	Bind to fungal cell membrane ergosterol
Flucytosine	DNA–RNA inhibitors

TABLE 2 Common topical antifungal creams used

Antifungal class	*Formulations with concentrations*
Azoles-Imidazoles	• Clotrimazole 1% cream • Ketoconazole 2% cream • Miconazole 2% cream • Bifonazole 1% cream • Oxiconazole 1% ream • Sertaconazole 2% cream • Luliconazole 1% cream • Eberconazole 1% cream • Fenticonazole 2% cream
Triazoles	Fluconazole 0.5% gel
Alkyl amine	Terbinafine 1% cream
Benzylamine	Butenafine 1% cream
Morpholine	Amorolfine 0.25% cream, 5% nail laquer
Hydroxypyridinones	Ciclopirox 1% cream, naillaquer

Source: Modified and reproduced with permission from reference 4.

Advantages of topical versus oral antifungals:

- Insignificant side effects
- Less chances of interaction with other drugs
- Can have better psychological effect with pharmaco-economy

Disadvantages of topical preparations:

- Difficult to use in extensive infection
- Poor response due to inadequate quantity of application
- Inability to apply in difficult to reach areas, which leave a residual focus of infection[4]

Adverse Effects of Topical Antifungals

Topical applications are well tolerated with few adverse effects like pruritus, burning sensation, irritation, erythema, maceration, and fissuring.[4]

TABLE 3 Common oral antifungals used

Condition	*Drug*	*Dosage and duration*
Tinea corporis/cruris	• Terbinafine • Itraconazole • Fluconazole • Griseofulvin (microsize) (ultra-micro size)	• 250 mg/day od, 3–6 mg/kg for 2–3 weeks • 200 mg/day for 1–2 weeks • 150–300 mg/week for 3–4 weeks • 500 mg/day (10–20 mg/kg) for 2–4 weeks • 300–375 mg/day (5–10 mg/kg)
Tinea pedis	• Terbinafine • Itraconazole • Fluconazole • Griseofulvin	• 250 mg od for 1–2 weeks • 100–200 mg/day for 2–4 weeks • 150 mg/week for 1 month • 750–1000 mg/day 4–8 weeks • 660–750 mg/day

(Modified and reproduced with permission from Reference 5.)

Common oral antifungals used are summarized in **Table 3**.

Clinical situation where the systemic antifungals are required:

- Involvement of scalp (Tinea capitis)
- Involvement of the nails
- Fungal infection at many areas of the body
- Tinea corporis with extensive involvement
- Tinea pedis with extensive involvement[5]

Adverse Effects of Oral Antifungals

Gastrointestinal disturbances, altered LFT, headache, pruritus, and cutaneous allergic reactions are common. Erythema multiforme and toxic epidermal necrolysis can occur. Lupus erythematosus and psoriasis can be exacerbated.

Drug Interactions of Oral Antifungals

Terbinafine is predominantly metabolized by CYP2D6. Caution should be exercised while prescribing tricyclic antidepressants, SSRI, beta-blockers antiarrhythmics, MAO inhibitors, warfarin, cyclosporine, and rifampin. These are common drug interactions of oral antifungal agents.

Antifungals in Elderly

The presence of comorbidities and higher drug interactions warrants caution for antifungals for the elderly. Fluconazole and itraconazole being CYP3A4 inhibitors can cause several drug interactions and terbinafine is safe in elderly and can be the drug of first choice. Topical terbinafine, ketoconazole, or clotrimazole cream is preferred.

Fluconazole is the safest oral antifungal in hepatic and renal disorders. Topical terbinafine, ketoconazole, or clotrimazole cream is preferred in hepatorenal disorders.

The following are the challenges encountered in the treatment of dermatophytosis:

- Resistance
- Recurrence
- Reinfection
- Misuse of topical steroids
- Associated comorbidities
- Immunosuppression

Antifungal Resistance

Antifungal resistance can be either microbiological resistance or clinical resistance. Resistance as assessed by in vitro susceptibility testing shows resistance, with exceeding of MIC from susceptibility breakpoint. The resistance, which occurs naturally, is primary where the organism is not exposed to the drug previously. The genetic mutation basically contributes to secondary resistance and the organism would have been susceptible to the same agent previously.

Several factors can contribute to inadequate clinical response, it could be due to inadequate dose, improper adherence to therapy or altered genetic profile of pathogen, or the therapeutic agent selected may be

wrong. The resistance to griseofulvin and terbinafine in some dermatophytes have been reported in India. The clinical response and susceptibility assessment may not correlate; hence, it is not appropriate to use the term, "*resistant*" in the absence of these definitive criteria for these fungal infections. Assessment of in-vitro susceptibility to terbinafine, fluconazole, and griseofulvin as reported in many studies does not imply that there is an absolute resistance, the clinicians should think of using better dosage or prolonged treatment for adequate response. The antifungal drug susceptibility is said to be different in Indians, hence there is need to establish dose determination and MIC breakpoint guidelines by the Clinical Laboratory Standards Institute (CLSI).

Steroid Abuse in Tinea

Steroid modified tinea is a common problem in India. Permutation and combination of various antifungals, antibacterials, and topical potent corticosteroids are used. Nearly half of the sales of these combinations in India are due to self-medication or advice by unqualified persons. The combination of clobetasol propionate, ornidazole, ofloxacin, and terbinafine are frequently used in India. Irrational and non-supervised use has aggravated the problem. Long time and intermittent use result in erythema, telangiectasia, and atrophy. The clinical picture variable due to altered T-cell mediated immunity suppression. Ineffective elimination of the dermatophyte results in chronic, wide-spread, and ill-defined lesions. Constant itching and scratching result in lichenification. Improper central clearing due to topical steroid abuse results in various bizarre shapes mimicking Tinea pseudoimbricata. Supervised short duration of topical steroid is required to treat lichenification followed by antifungal treatment. Prolonged treatment needs counseling for adherence to the treatment.[6]

Recurrence

There is lack of uniformly acceptable definition of "*recurrent dermatophytosis*." Whenever there is a protracted course with variable degree of persistence of lesions, these patients contribute for easy spread of infection to family members and other closely associated people. Common contributing factors are overcrowding, living together in congested accommodation, the use of tight footwear, tight-fitting clothes, and sharing of community bath and sports facilities.

Future Directions for Prevention of Refractory Dermatophytosis

The primary factor for emergence of antifungal resistance appears to be inadequate dose and improper combination. There is need of clear guidelines for dose recommendation for prevention and treatment.

Ghannoum and Rice[7] suggested for intense clinical correlation with appropriate medication combination and acceptable dosage by using the pk/pd data and surveillance inputs. Early diagnosis with correct combination will help in reducing resistance and refractoriness.

Measures improve hand hygiene: Hand wash; clipping of nail; regular bathing, keeping the skin dry, use of proper shoes, cotton socks, and absorbent powder; avoidance of sharing of bathing facilities and cloths; avoidance of walking barefoot in public bathroom are important in preventing spread.[8]

Using appropriate combination of drugs will increase the fungicidal effect and increase the spectrum of activity and reduce refractoriness. Choose a combination of oral and topical antifungal with different mechanism of action for better clinical outcome.

Antifungal drugs in the pipeline that are active against azole-resistant isolates, like cationic peptide histatin will be important for revised treatment strategies. The combined use of azoles and cytokines will be useful in treatment of fungal infections in immune-compromised individuals.

Conclusion

- Cutaneous fungal infections are very common in humans. Dermatophytes have higher affinity to stratum corneum. The common strain is T. mentagrophytes among dermatophytes. Tinea corporis and cruris require 3–4 weeks of treatment.
- Fingernail requires 6–8 weeks; however, toenail requires 10–12 weeks of treatment.
- Patients with renal, liver, and cardiovascular diseases are treated with topical antifungal.
- Resistance, recurrences, reinfection, topical steroid misuse, and associated comorbidities pose a clinical challenge in antifungal treatment.

Contd...

Contd...

- Steroid modified tinea in India is a result of topical antifungal used in combination with potent topical steroids and antibacterial that account for about 50% of the sales of all topical steroids in India.
- Careful history taking-treatment history, combination of oral and topical antifungal with different molecules that have varied mechanism of action and counseling is needed in resistance and topical steroid misuse cases.
- Drug interactions must be considered before starting any oral antifungals.

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CHAPTER

174 Rickettsial Infection

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Abstract

Rickettsial infections are important public health problems and are often underdiagnosed or misdiagnosed leading to the burden of morbidity and mortality due to nonspecific symptoms and signs and absence of specific diagnostic tests. The present review addresses the epidemiology, clinical features, diagnosis, complications, and management of these infections, primarily for a practicing clinician.

Introduction

The rickettsioses represent one of the important causes of febrile thrombocytopenia worldwide. Rickettsial infections which were initially seen more often had reduced in incidence with extensive use of pesticides to control vectors. Tetracycline was one of the most commonly used antibiotics which also contributed to reduction of prevalence of rickettsial infections. However, the indiscriminate use of tetracycline has declined due to adoption of better antibiotic policies.[1] Additionally, the urbanization of rural areas has exposed more of the population to potential sources of infection. These two factors have coincided with the re-emergence of this deadly scourge.[1]

These diseases can be incapacitating and difficult to diagnose in resource-poor settings. Potential cases are often under-recognized or under-tested. Adding to the burden of morbidity and mortality is the dearth of adequate laboratory testing facilities and uniformity of reporting systems.[2]

Rickettsioses present with non-specific signs. However, certain clinical features are indicative when present in a constellation, such as the presence of high-grade continuous fever, centripetal/centrifugal rash, generalized lymphadenopathy, decreased platelets, and the pathognomonic eschar (tachè noire) which is rarely seen in our setup. However, atypical presentations are also more prevalent in hyperendemic areas.[3] Clinical presentation along with positive Weil Felix test is employed to make the diagnosis of rickettsiosis.[4]

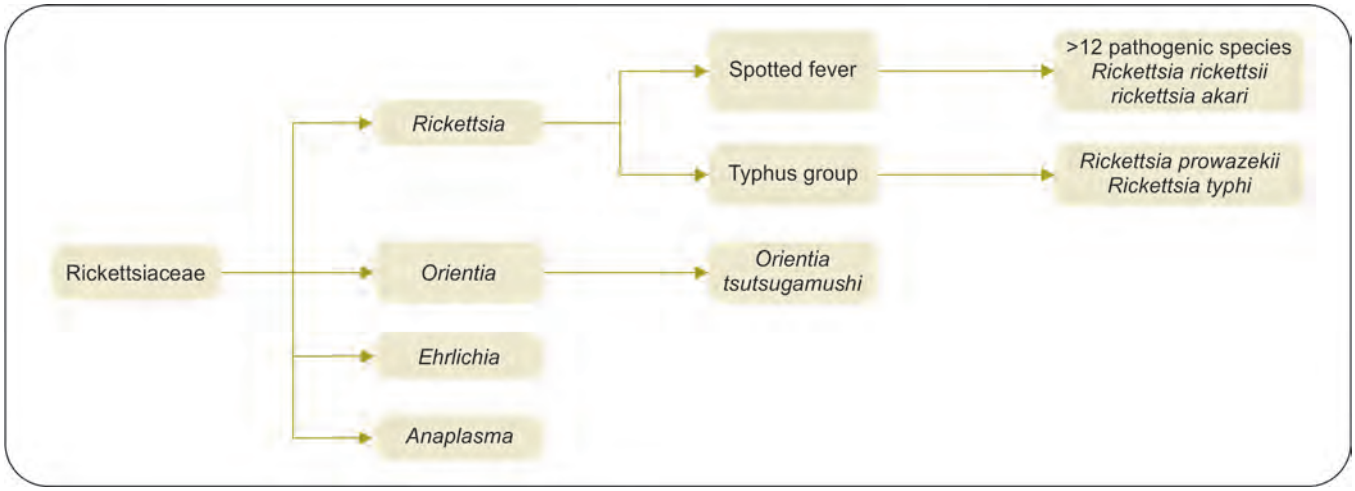
Structure and Genome

Rickettsia is small, Gram-negative coccobacillary form adapted to obligatory intracellular parasitism and transmitted by arthropod vector (lice, flees, ticks, and mites) found in their alimentary canal. In vertebrates especially humans they infect vascular endothelium and reticuloendothelial cells.[5] Rickettsiae are not evident on blood smear and do not stain with most of the conventional stains; however, it stains red with Giemsa stain.[3] Rickettsial genome is 1–1.5 Mb and is a single circular genome.

The Rickettsiaceae Family

Family Rickettsiaceae is divided based on lipopolysaccharide group antigen into four genera **(Flowchart 1)**.

Flowchart 1: Classification of rickettsial infections



Vectors

Transmission is by arthropod vectors like lice, fleas, ticks, and mites.

Distribution

The distribution is dependent on the arthropod host/vector. Tick vector dependent infections have limited geographic spread (except Antarctica).[1,2]

Risk Factors

People staying near mountains, bushes, and equatorial rain forests are at risk. Improper hygiene and rearing of domestic animals are also risk factors.[3]

Pathogenesis

Endothelial cells are primary target (exception Rickettsia akari). They cause damage to the cell causing cellular detachment. The cells in circulation when lodged in distal capillaries become the source of infection. Through antibody, mediated opsonization rickettsia can enter phagocytic cell.[3]

Clinical Features

The incubation period varies 2–21 days. Signs and symptoms are non specific. *Fever is the most common presentation which starts abruptly and is of high grade* in association with headache, muscle ache, apathy, drowsiness, photophobia, conjunctival suffusion, generalized lymphadenopathy (abdominopelvic, para-aortic, porta hepatis, splenic hilum), and hepatosplenomegaly.[6,7]

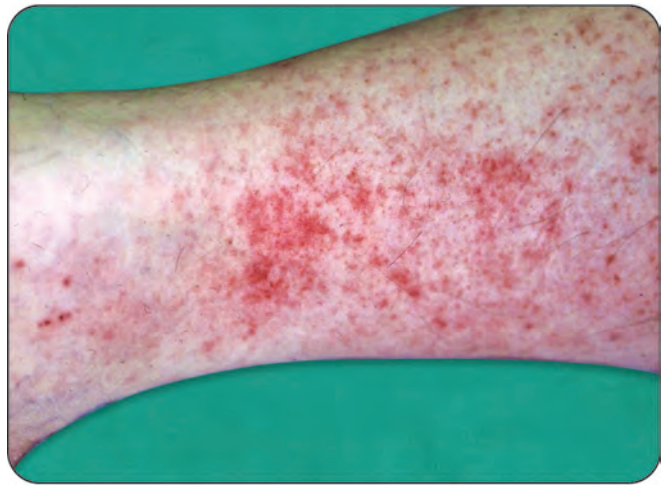


Fig. 1: Rickettsial rash

The rash: Though considered as characteristic feature of rickettsioses is not seen in all patients. It occurs on the third or fifth day of illness. It may be typical with macules, papules, hemorrhage, or petechiae or atypical asymmetrical localized to small area **(Fig. 1)**. It may be centripetal or centrifugal in distribution mainly seen over the soles of the feet and palms of the hand.[3,8]

Eschar: It is vesicular lesion at the site of inoculation which ulcerates, heals with development of black necrotic scar associated with regional lymphadenopathy. Necrotic

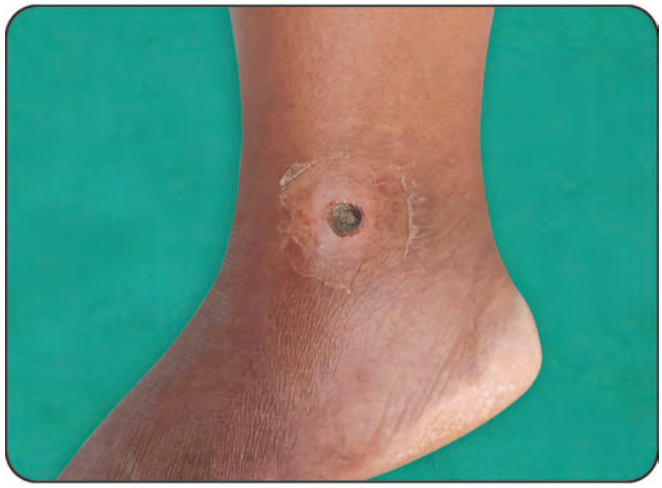


Fig. 2: A classical eschar

eschar **(Fig. 2)** is seen in belt area, in groin, under the arms, sometimes over the neck. Even though it is the single most important clue for the diagnosis it is recognized in less than 50% even by an experienced physician. Sometimes multiple eschars are seen under the trouser belt. Scrub typhus patients with virulent strains have lower incidence of rash/eschar, and hence severity of clinical features depend on serotype and genotype of rickettsia.

In India, three common groups of infections are seen the spotted fever group (e.g., *R. akari*), the typhus group (e.g., *R. typhi*), scrub typhus (*Orientia tsutsugamushi*). The significant clinical differences between them have been studied by the author's team.[9,10]

Scrub typhus was more likely to present with fever 7–14 days (p=0.03); splenomegaly (p=0.023), and eschar (p=0.014) were significant examination findings; in the laboratory, it presents with increased SGOT/SGPT (p=0.024), and decreased albumin (p=0.021). Spotted fever group had a preponderance toward fever less than 7 days (p=0.043), vomiting (p=0.03), and joint pain (p=0.049). Macular rash (p=0.04) was observed clinically. Pleural effusion (p=0.021) was a significant complication. Typhus group had fever more than 14 days (p=0.04), associated with cough (p=0.019), and abdominal pain (p=0.039). Hepatomegaly (p=0.045) was a significant clinical finding.[10]

Atypical presentation that may be seen in hyperendemic areas are: acute abdomen without fever, nausea, vomiting, diarrhea, and constipation.

Neurological complications of ricketsioses are encephalitis, aseptic meningitis, meningoencephalitis; respiratory symptoms like cough and breathlessness associated with ARDS and pneumonia and non-cardiogenic pulmonary edema (30–60%), gastrointestinal manifestations presenting as acute gastroenteritis, severe pain abdomen often mistaken for surgical abdomen; transaminitis with acute hepatitis and hepatic encephalopathy, coagulation factor consumption results in a DIC-like syndrome.[7]

Differential diagnosis of aseptic meningitis should include rickettsial meningoencephalitis in endemic areas, especially when associated with altered renal or hepatic functions. Acute kidney injury is associated with poor prognosis.[3]

Retinal vasculitis is commonly seen amongst females. It is asymptomatic in the early stage, resolves by 6 months. The prognosis is favorable.[3]

Without medications uncomplicated infection might recover within 14 days. Untreated cases carry a mortality rate of 30%. Persistent subclinical infection in convalescent patients occurs with *Rickettsia prowazekii*, which later presents as recrudescent typhus or Brill-Zinsser disease.[2,9]

People travelling from disease endemic region might present with symptoms within few days of return. Since the incubation period for most rickettsial infections is from 2–21 days, symptoms which begins 20 days after travel from a disease-endemic area has less probability to be a rickettsial infection.[8]

Investigations

Early stages—lymphopenia; late stages—lymphocytosis (30%), Elevated ESR, decreased platelet count in less than 50% of cases.

Later—Deranged liver function test (50%): Increased serum bilirubin, increased ALT, AST (75–95%), reduction in albumin less than 3 gm% (seen in significant number of patients); reduced sodium, increased blood urea, and serum creatinine.

Chest X-ray: Pneumonitis, bilateral infiltrates, pleural effusion, and ultrasound abdomen: Hepatosplenomegaly.[11]

Diagnosis

Early stages: It is challenging to diagnose these infections and differentiate them from other infections like dengue,

malaria. The clinical manifestations of most rickettsioses present as a continuous spectrum. In the absence of definite pathognomonic signs, there are signs and symptoms highly suggestive of the etiology. However, not all cases present with the set of typical clinical manifestations that aid in prompt recognition. As such the clinical acumen and awareness of the treating physician has a great role in the diagnosis and management of these cases. In resource poor country, fever with rash, fever with thrombocytopenia and rash Weil Felix test clinches the diagnosis.[11]

When to Suspect Rickettsial Infection?

Any patient presenting with fever and rash, fever and eschar, aseptic meningitis, acute renal failure with eschar, increased vasculitis should be suspected of having rickettsial infection.

Weil-Felix Test

This test is easily available, cheap, and easy to perform. The results are available on the same day. The sensitivity is 46%, specificity is 100%, is positive in second week. OX2, OX19, and OXK strains of agglutinins of proteus bacteria are used in the test.[3,8,11] Results must be interpreted in the correct clinical context **(Table 1)**. Value of testing two sequential serum or plasma samples together with fourfold rise in antibody level is more important in confirming acute infection.[3,8,11]

Indirect Immunofluorescence Assay/ Immunoperoxidase Assay

It is the gold standard investigation. Sensitivity is 89–100%, specificity is 100%, but major constraints being, the test is not easily available, costly, and takes more than 7 days for results. Immunoglobulin M rises at the end of first week; Immunoglobulin G rises at the end of second week.

TABLE 1 Interpretation of Weil-Felix test

Diseases	*Weil-Felix*		
	OX-19	*OX-2*	*OX-K*
Rocky mountain spotted fever	+	+	–
Rickettsial-pox	–	–	–
Epidemic typhus	+	–	–
Endemic typhus	+	–	–
Scrub typhus	–	–	+

Immunohistologic Examination

The only diagnostic test proved useful during acute illness is immunohistologic examination from cutaneous biopsy sample of a rash or biopsy of a lymph node. It is 70% sensitive, 100% specific. However, high expertise is needed to interpret biopsy result.[3,11]

Polymerase Chain Reaction

It is species specific and is positive in initial 7 days**.** It can be done on whole blood, eschar, or skin biopsy. It has a specificity of 100% for both PCR and Rt-PCR and sensitivity of 22–36% for PCR and 45–82% for Rt-PCR. Tissue sample shows higher sensitivity compared to blood sample.

Culture

Organism is grown on tissue culture Vero cell of kidney, egg yolk sac and isolation needs biosafety level III labs. However, culture is unnecessary, laborious and hazardous to lab personnel. Median time for reporting is 27 days.

Treatment

If cases are left untreated fatality may go up to 30%.[1,3] When diagnosed properly it can be treated easily, but the difficulty lies in diagnosing rickettsial infection during initial phase of the disease when antibiotic use is very effective.[12]

Doxycycline is the treatment of choice. Dose 100 mg two times a day should be used for 7–10 days. Within 24–48 hours after initiation of antibiotic, patient improves drastically. If patient fails to respond within 48 hours, it is unlikely to be Rickettsial infection.[12] Extremely sick patients (especially with MODS and ARDS) may require 10–14 days to respond to treatment. Relapse is usually seen if treatment is discontinued as soon as fever subsides. Discoloration of teeth is more common in children and depends on duration of treatment,[13] other side effects are hypoplasia of the enamel, depression of skeletal growth, and limb hypoplasia. As such, doxycycline should not be used in children less than 8 years because of these above side effects. In pregnant women due to the adverse effects on the skeletal growth of fetus. Azithromycin 500 mg once daily is used instead in this setting.[7]

If patients respond poorly to doxycycline or drug resistant serotypes: combination of doxycycline with rifampicin for 6–8 days or azithromycin with rifampicin (600 mg once a day) to be used. Rifampicin should always be used in combination as it leads to resistance when used alone. In India, rifampicin is avoided due to the prevalence of tuberculosis.

Treatment in pregnancy: Chloramphenicol is also an alternative drug and can be recommended for use in pregnancy in dose 500 mg four times a day for 7–14 days but has to be avoided in last trimester due to fear of bone marrow suppression and gray baby syndrome. Azithromycin is safer alternative in pregnancy. A macrolide, Josamycin, has been used with success in spotted fever group in pregnancy in a dose of 3 gm/day orally for 5 days. Doxycycline can be used in late pregnancy.

Vaccine

No vaccine is available for Rickettsial infection. An ideal vaccine should give protection to all biogroups in order to give acceptable level of protection. This complexity continues to hamper efforts to produce effective viable vaccine due to enormous antigenic variations among the biogroups.

Recent Developments

Rickettsiae have specific regions of oompA and oompB surface proteins and measures to detect antibodies against them, might prove beneficial in future treatment of rickettsiae.[3]

Prevention

Preventing exposure to a vector infested habitat, wearing closed-toed shoes, long pants, long sleeved clothes, topical application of insect repellents, protected pets may help in prevention.

Conclusion

Rickettsial infections are some of the covert re-emerging infections of present times generally incapacitating and notoriously difficult to diagnose. Untreated cases have fatality rate up to 30%. When diagnosed properly it is often easily treated. Greatest challenge is difficult diagnostic dilemma posed by these infections early in clinical course when antibiotic therapy is most effective; hence, physicians and pediatricians have to include rickettsial infection in differential diagnosis of acute febrile thrombocytopenia.

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CHAPTER

175 Adult Vaccination

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Abstract

Adult immunization is less talked about area of health-care practice needing regular updation and implementation. It is an easy means of disease prevention which should find place as a separate topic in the medical curriculum. While the Guidelines for Immunization of Children are routinely updated and practiced clinically, the same is not true for adult immunization. The slowly waning immunity gained from vaccination in childhood, risk of exposure from frequent travels, changing lifestyles, age related immunosenescence, increasing comorbidities like diabetes and chronic kidney disease, organ transplantation and increasing use of immunosuppressive further necessitate implementation of adult vaccination measures. API guidelines recommend routine vaccination for Pneumococcal infection, Influenza, Human papilloma virus, Measles, Mumps Rubella, Diphtheria, Pertussis, and Tetanus in Adult Indian subjects. It is imperative for the related health-care associations to work together and devise a common adult vaccination schedule which can be followed by clinicians all over the country. Physician realization, public health education about its need and government initiatives in implementation would go a long way in strengthening the infection control measures and improve the communicable disease health-related indices.

Introduction

The recent pandemic of COVID-19 has exposed the vulnerability of human race to infectious diseases and re-emphasized that prevention is an essential part of management of communicable diseases worldwide. Vaccination forms an important part of primary prevention for control of morbidity and mortality related to infectious diseases. With increasing age, adult immunity declines (immunosenescence) and therefore there is need to address it through adult immunization.[1] The susceptibility of populations has increased due to changing work environment and culture involving international travels and explorations. The increasing numbers of organ transplant recipients, diabetics, chronic kidney disease (CKD) subjects, indiscriminate antimicrobial use, emerging resistance, and growing susceptible population of subjects on chemotherapeutic agents or radiation therapy, further adds to these concerns. As on date the status of adult vaccination in India is mostly inadequate or incomplete. In contrast to pediatric vaccination guidelines, little importance is laid on Adult Vaccination in India, even when the mortality from vaccine preventable diseases is 350 folds higher in adults in comparison to children.[2] Lack of awareness amongst general public, physician's apathy, meager resources, and lack of political will are impediments to implementation of adult immunization in routine clinical practice. Organizations like API have stressed the urgent need to develop adult vaccination guidelines in India and its revision periodically.

Determinants of the vaccination needs of an individual are age, prior vaccination status, mutations in infectious agents, health or comorbid illness, lifestyle, travel, occupation, infection trends, disease burden in the

population and related health-care/immunization costs. Vaccine induced immunity is neither long lasting nor broad spectrum and declines with time, implying that childhood vaccination may need to be bolstered in adulthood to provide lasting protection. In countries where last dose of Diphtheria vaccine had been administered at less than 6 years of age, a resurgence of Diphtheria in adults more than 15 years age has been noted. Similar, increase in average age of many vaccine preventable diseases in to adult life has been observed. Further, adult individuals act as reservoirs of disease and pose a risk to the unvaccinated children and other family contacts in the household. Likewise, the role of adult vaccination gains importance in hostel facilities, residential institutions, factories, and organizations with residential campuses.

India contributes to 60% of Diphtheria, 40% of tetanus, and 44% of Japanese encephalitis cases of the world.[3] However, age wise epidemiological data relating to burden of vaccine preventable diseases and efficacy of adult vaccination strategies in India is scant. Recent outbreaks of Measles (University in Karnataka, 2013-2014), Japanese Encephalitis (West Bengal 2014), Influenza A (Rajasthan 2015), Varicella (Tamil Nadu 2016-2017), Diphtheria (Assam 2015-2016), Hepatitis A (2015-2016) have alerted us to the relevance of adult immunization in India. In early 2018, around 133 outbreaks of measles, varicella, food poisoning, and diarrhea were reported. To aggravate the issue further, there is a lack of proper disease surveillance and under reporting of outbreaks of vaccine preventable disease in India. Herein we discuss the adult vaccination guidelines as recommended by various organizations for Indian population. The recommended vaccination schedules for clinical practice are mentioned in **Tables 1 and 2**.

TABLE 1 Summary of adult immunization guidelines[7-10]

Organism/Disease	*Vaccine*	*Age of administration*	*Dosage recommendations*
Influenza	Trivalent/Quadrivalent	>19 years onward; 0.5 mL IM 1 dose annually; can be given during pregnancy (FOGSI)	
Streptococcus pneumoniae	PCV 13 PPSV 23	>50 years or <50 years in high risk; PCV followed by PPSV 23 at 1 years, repeat every 5 years	
Human papillomavirus	0.5 mL IM Merck4strain/2strain GSK	9–14 years 2 doses 0 day and 6 months (IMA) 15–45 years at 3 doses 0 day, 1 and 6 months, defer if pregnancy	
Herpes zoster	0.5 mL SC	Individuals >60 years (ISN); 2 doses 2–6 months apart	
Diphtheria, pertussis, tetanus	(Tdap/Td) 0.5 mL IM	Age group >19 years; immunized Tdap once at 10–18 years; then Td 10-yearly (IMA, API, CDC), Non-immune 3 doses, 2 does 4 weeks apart followed by third at 6–12 months Tdap during each pregnancy (API & CDC) IMA adds TT/Td early during pregnancy (2 doses); Tdap during 3rd trimester of pregnancy (1 dose)	
Measles, mumps, and rubella	MMR 0.5 mL SC	19–60 years; 2 doses 1 month apart (ACIP); 1 dose if previously immunized Pregnancy should be deferred for 3 months after immunization	

TABLE 2 Immunization schedule in special situations (routinely not used)[7-10]

Organism/Disease	*Vaccine dosage recommendations*
Hepatitis A	1.0 mL IM; 2 doses in Adults (0 & 6 months)
Hepatitis B	1.0 mL IM; 3 doses (0, 1–2, & 4–6 months) FOGSI recommends in preconception or at high risk during pregnancy
Hepatitis A+B	1.0 mL IM; 3 doses (0, 1–2, & 4–6 months)
Typhoid	0.5 mL IM; 1 dose every 3 years
Cholera	2 separate doses of oral vaccine 1–6 weeks apart for those aged over 6 years
Meningococcal	0.5 mL SC Bivalent/Quadrivalent; Adults (1 dose); At risk/asplenia 2 doses (ACIP and IMA)
Varicella	0.5 mL SC; >13 years of age; 2 doses 4–8 weeks apart

Pneumococcal Vaccination

Pneumonia and invasive pneumococcal disease are two dreaded complications of pneumococcal infection, which account for significant morbidity and mortality, especially in the immunocompromised and the elderly (subjects >50 years of age) with a case fatality of 28%. The common serotypes accounting for 55% of inpatient admissions are 1, 3, 5, 19F, 8, 14, 23F, 4, 19A, and 6B. Further emerging resistance to penicillin and macrolides has underlined the importance of adult pneumococcal vaccination. The incidence of pneumococcal disease per lakh population is 8.8 in healthy adults, 51.4 in adult diabetics, 62.9 in subjects with chronic lung disease, and 93.7 in subjects with chronic heart disease.[4] To reduce morbidity in high risk groups pneumococcal vaccination is recommend in subjects less than 50 years of age with chronic heart disease, lung disease, chronic liver disease (CLD), diabetes mellitus, chronic smokers, and alcoholics.

There are two vaccines available, viz. a PCV13 and PPSV23 name denoting the number of serotype antigens contained. The PCV13 carries a greater response, longer immuological memory, protection against nasopharyngeal carriage, but a lower protection against invasive pneumococcal disease in elderly.

A single dose of PPSV23 is recommended in immunocompetent adults over 65 years of age, to be repeated at every 5 years interval. An early institution of second dose is noted to produce hyporesponsiveness. Initial administration of PCV13 vaccine has been shown to amplify the response to subsequent administration of PPSV23. ACIP 2015 recommends a space of 1 year between the two vaccines irrespective of their order. In individuals who have already received PPSV23, vaccination with PCV13 can be undertaken after 1 year interval. A prior pneumococcal conjugate vaccine (PCV13) vaccination followed by unconjugated capsular polysaccharide vaccine (PPSV23) vaccination is recommended for high risk group with cochlear implant, CSF leaks, sickle cell hemoglobinopathy, asplenia, congenital, or acquired immunodeficiency syndromes.

Influenza Vaccination

Annual influenza vaccination by itself has been shown to reduce cardiac mortality by 19–45% and hospital admissions by 54%, which is comparable to benefit gained from CV risk reduction by smoking cessation or statin therapy. Influenza vaccines are available as trivalent (two strains of Influenza A and one strain of influenza B), quadrivalent (two strains of influenza A and two strain of influenza B) or live attenuated (lyophilized) nasal spray vaccines. Influenza vaccination is recommended in high risk subjects, viz. CKD, chronic obstructive pulmonary disease, heart disease, immunosuppressed subjects, diabetics, and hematological disorders. Single dose needs to be administered annually to gain protection. The timing has to be 2 weeks before the peak season for influenza from October to May.

Measles, Mumps, and Rubella

In 2018, around 55,000 cases of Measles and 1000 cases of Rubella were reported in India.[5,6] Around 16% of Indian population was found to be susceptible to Rubella infection. Incidence of Mumps outbreaks has been reported mainly from hostel facilities, colleges, and schools in poor socioeconomic settings. A single dose of triple vaccine MMR in already immunized individuals and two doses separated at interval of 1–2 month in unimmunized subjects is noted to provide adequate protection.

Diphtheria, Pertussis, and Tetanus

Childhood protection through vaccination is not lifelong and has been found to increase the proneness of adults to Diphtheria Pertussis and Tetanus. India accounts for the majority of these cases in the world. A single dose of triple antigen vaccine followed by booster every 10 years is noted to provide adequate protection in already vaccinated individuals.

Human Papillomavirus Vaccination

Cervical cancer is the second most common cause of cancer and second leading cause of mortality in India. Human papillomavirus (HPV) virus accounts for 90% of cervical and anal cancers, 70% of vulval and vaginal cancers, and 60% of penile cancers. HPV serotypes 16 & 18 are noted to account for 77% of cervical cancers in India.[4] HPV vaccine is recommended before the onset of sexual activity in the age between 9 and 24 years. In the age group of 9–14 years two doses of HPV vaccine are to be administered at 6 months interval. In those over 15 years of age three doses at 0, 1, and 6 months are advocated.

Hepatitis A and B Vaccination

While Hepatitis A virus (HAV) accounts for 10–30% of acute hepatitis and 5–15% of acute liver failure cases, hepatitis B virus (HBV) accounts for 20–30% cases of Cirrhosis and 40–50% cases of hepatocellular carcinoma.[4] The high prevalence of chronic Hepatitis B carrier state in the population also increases the risk of transmission. Hepatitis A vaccination is indicated for candidates for kidney or liver transplant with chronic hepatitis B/C to decrease the risk of fulminant liver failure. Also vaccination for Hepatitis A is indicated in illicit drug users, homosexuals, animal handlers, persons with CLD or other hepatitis virus infections, recipients of clotting factor concentrates. Two doses of Hepatitis A vaccine administered at 6–12 months interval gives adequate protection. Hepatitis B vaccine schedule is 20 µg at 0, 1, and 6 months. Booster dose is not recommended in immunocompetent adults. Combination vaccines for HAV and HBV can also be administered in a three dose (0, 1, and 6 months) or four dose (0 day, 7 days, 21–30 days, and booster at 12 month) schedule.

Meningococcal Vaccination

Three Meningococcal vaccine are available, viz. two quadrivalent vaccine (against four antigens A, C, Y, and W135) for polysaccharide (MPSV4) and conjugate (MCV4) or a bivalent vaccine (antigen A and C). While MCV4 produces lasting immunity, and reduces nasopharyngeal carriage it cannot be used in adults more than 55 years of age and does not provide protection against Meningococcus B strain. Therefore, MPSV4 may be preferred in subjects more than 55 years of age or those requiring single dose, viz. travelers.

Conclusion

The common perception that vaccination is meant only for children has to give way to the understanding that vaccination has to be continued well in to adulthood. Most of adults above 40 years of age have not received universal childhood vaccination, which was started in 1978 and could attain 65% coverage only in 2014.[7] Hence, the realization that adult vaccination is urgently required needs to creep in to the community and a national program has to be carved to reduce the menace of vaccine preventable diseases. As much as two-thirds of Indian population is still unaware of need of vaccination in adulthood.[1] Further the introduction of adult vaccination is cost effective as demonstrated in cost benefit analysis of HPV vaccine in India.[11] The cost of adult vaccination is lower than the cost for childhood vaccination and implementation of many other secondary preventive measures (lipid lowering therapy, antihypertensives, antidiabetics, and bisphosphonate treatment). For the adult vaccination to be successful it needs to overcome the barriers of vaccine hesitancy (4Cs of complacency, convenience, confidence, and cultural acceptance) which can be achieved by widespread health education, evolving consensus on national guidelines and incorporating them in routine clinical practice. Although, as on date adult immunization is not being routinely observed in clinical practice, achieving complete adult vaccination to vaccine preventable diseases through widespread implementation by medical professionals, society's acceptance, government realization, and making vaccines affordable would make this dream come true.

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CHAPTER

176 Neurocysticercosis—Clinician Recap

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Abstract

Neurocysticercosis (NCC) is most common central nervous system parasitic infection caused by Taenia solium. NCC is a common cause of adulthood epilepsy with signification disease burden in developing country like India. The precise knowledge of epidemiology, clinical features, radiological correlation with stage of parasite is very helpful in effective management and reducing the burden of disease. Relational use of anti-parasitic drugs and steroids are effective in cure of NCC. This chapter is focused on clinical and radiological finding and guideline on management of NCC.

Introduction

Neurocysticercosis (NCC) is caused by *Taenia solium* and this is the most common helminthic infection of the central nervous system (CNS). *Taenia solium* is a parasite and transmission of larva stage from pig is responsible for infection in human.[1] NCC is most severe form of cysticercosis and this is a most common cause of acquired epilepsy in adult.[2] NCC is associated with substantial morbidity due to epilepsy, strokes, and associated side effects of long-term drugs therapy for seizures. This disease is a major health problem in India and its prevalence in epilepsy with NCC is around 3.48/1,000 persons.[3] Prevalence of NCC is higher in northern part of India as compare to southern part of India, particularly in urban population.[4] The health and economic impact of disease have not been assessed in depth. Past study has shown that Rs. 5,916 is the direct cost of treatment of solitary cysticercus granuloma per patient.[5]

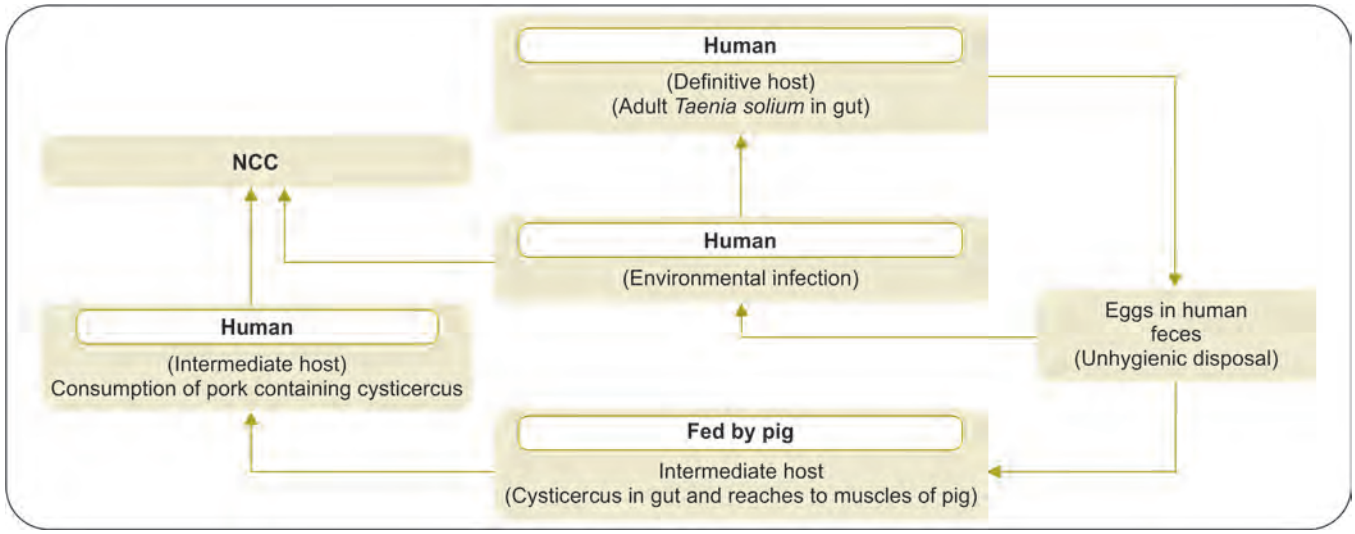
The important factors responsible for occurrence of disease in India are poor personal and social hygienic conditions. This increases scavenging pigs with use of partially cooked unhygienic pork.[6] Further studies will require for measuring the impact of this disease on economy and human health in India. Worldwide estimation of NCC prevalence has relatively less studied and the disease is common in India, Indonesia, most of Southeast Asia, part of China, many sub-Saharan Africa, and regions of Eastern Europe.[7,8]

Even with advancement still there is gap between basic and practical aspects of disease focusing, especially diagnosis of active lesion and appropriate timing of antiparasitic treatment in NCC. This chapter is especially focused on better understanding of disease, diagnosis, and treatment in clinical scenario.

Etiopathogenesis

Taenia solium, also called tapeworm, is the causative parasite of NCC. Both human as well as pig both act as intermediate host for *Taenia solium*. Adult tape worm releases the thousand of eggs in human feces. The pig fed the eggs contenting feces due to poor hygienic condition. The eggs lose their covering in pig's intestine and converted into oncospheres. These oncospheres distributed in muscles of pig via blood after penetrating intestine and form cysticercus. Consumption of uncooked pork that contained cysticercus in muscle of pig leads to

Flowchart 1: Life cycle of *Taenia solium* and etiology of NCC



infection in human. In human stomach digestive enzyme leads evagination of their scolices. These scolices penetrate the gut and reach in brain and produce parenchymal cystic lesion **(Flowchart 1)**. Recent studies also showed that there are person-to-person transmission of human cysticercosis is also equally important as environmental source.[9] Distribution of cysts in brain parenchyma occurs mainly at watershed areas between gray and white matter. Other common sites of cyst lodgment in brain are choroid plexus and 4th ventricle, that give rise ventricular cyst.[10]

In brain parenchyma, cyst has two components, first is vesicular and second is scolex. The first vesicular part is a viable phase consists of a transparent membrane and clear vesicular fluid and with transposed scolex. The initial phase of cysticerci in brain is a colloidal stage, which may survive for many years and finally due to immune response scolex get mineralized and converted into calcification nodule. Inflammatory response of parenchymal cyst is very less and generally limited to only surrounding tissue. But meningeal cyst mostly provokes a severe inflammatory response in subarachnoid space and land up with thickened leptomeninges.[11]

Clinical Manifestation of Neurocysticercosis

Clinical manifestations of NCC are varied from asymptomatic state to life threatening seizure and encephalitis-like stage due to cerebral edema.[2,12] Symptomology is primarily depended up on location and number of lesion as well as parasite load. Higher the parasite load associated with strong immune response and more severe symptoms.[12] Population-based studies have been shown that a substantial number of patients in endemic area were asymptomatic with lesion on imaging of brain.[13]

Most common clinical presentation of NCC is seizures and detected in up to 80% of symptomatic individual.[14] NCC is the leading cause of epilepsy in adult age 25 years and more. Initially it was postulated that only viable cystic stage is responsible for symptoms and not due calcified nodules. The recent studies have been suggested that seizures could occur in any stage of cysticerci. Headache may be associated with or without seizure and may mimic the migraine. **Table 1** is depicted the stage of parasite and possible mechanism of clinical manifestations.

Focal neurological signs may be a presenting feature of NCC. This has been seen up to 20% cases of NCC. The disease course in focal neurological deficits is commonly subacute or chronic and may resemble brain tumor. Pyramidal tract signs are the commonest, but other signs like sensory disturbances, involuntary movements, abnormal muscle tone, signs of brainstem dysfunction, and aphasias may occur in few patients.[17] Acute stroke is uncommon manifestation and occurs due to infraction in internal capsule, corona radiata,

TABLE 1 Mechanism of clinical manifestations in NCC[15,16]

Stage of parasite	*Clinical manifestations*	*Pathogenesis*
Viable cysts	Seizures, hydrocephalus, focal neurological defect	Mass effects cyst on the brain parenchyma
Colloidal and granular cysts	Seizures, encephalitis like stage due to cerebral edema	Degeneration of parasite and host inflammatory response
Calcified nodule	Epileptogenic focus	Gliosis formation around dead parasites

TABLE 2 Pathognomonic finding according to stage to parasite in neuroimaging

Stage of parasite	*Neuroimaging finding of brain parenchymal lesion*
Viable cysts	A well outlined small and rounded cyst with no abnormal enchantment on contrast imaging. Invaginated scolex has seen as eccentric hyperdense nodule and called "hole-with-dot" appearance
Colloidal and granular cysts (degenerating)	The lesions are ill-defined and may be single or multiple with surrounding edema. Contrast imaging showed a ring enhancing or a nodular pattern of enhancing
Calcified nodule	Non-enhancing hyperdense nodule (better detected in CT)

and/or brainstem.[18] Intracranial hypertension is a rare but dreaded manifestations; either due to mass effect or host immune response leading to arachnoiditis or encephalitis.[19] Neurocognitive manifestations are though rare and ranging from psychiatrics symptoms to severe dementia.[20]

Diagnosis

Diagnosis of NCC is improved significantly with increased availability of computed tomography (CT) and magnetic resonance imaging (MRI). These investigations can be able to differentiate the stage of parasite in brain parenchyma and this may be helpful for selection of antiparasitic therapy. **Table 2** shows the pathognomonic finding according to stage to parasite in neuroimaging.[21]

The MRI imaging delineates better subarachnoid NCC, and hydrocephalus is the most common finding. The cause of hydrocephalus is due to diffuse leptomeningeal inflammation and thickening and occlusion of the foramina of Luschka and Magendie.[17] Diagnosis of ventricular cyst is also better MRI imaging and this easily missed in CT scan. Contrast in MRI imaging shows the mobility of cyst within the cavities and this is called "ventricular migration sign."[17]

Serological method of detection of *Taenia solium* specific antibody by enzyme linked assay may be helpful in diagnosis of NCC. The major disadvantage of serological assay is high false negative results. Due to poor sensitivity this cannot be used as diagnostic test but this is a very useful for monitoring of therapy, if positive in NCC.[22]

Even with the advances in neuroimaging and laboratory immunological test, the diagnosis of NCC is still a challenging task for clinician. To improve the diagnosis accuracy of NCC, Del Brutto et al. developed a criteria based on clinical, radiological, immunological, and epidemiological data **(Table 3)**. The diagnostic accuracies of NCC are classified on the basis of these criteria into definitive diagnosis and probable diagnosis. Presence of major criteria is highly suggestive of the diagnosis but minor criteria though non-specific but required.

Treatment

Because of variable presentation of the disease, a single approach is not possible for treatment. The factors affected the tailoring of treatment in NCC are location, numbers, and stage of cysticerci in nervous system.[23] The basis of NCC treatment consist both antiparasitic treatment and symptomatic treatment. The preferred antiparasitic drugs are albendazole (15 mg/kg/day) or praziquantel (50 mg/kg/day) with standard duration of treatment is 10–14 days.

In **Table 4** there are some peculiar point in treatment guideline given by Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH).[24]

TABLE 3 Diagnostic criteria for NCC

Absolute criteria:
• Parasite visualization either by histopathology or funds examination of retinal or neuroimaging (scolex in cystic lesions)
Major criteria:
• Radiology imaging of CNS or spine strongly suggestive of neurocysticercosis • Positive immunoblot serology for parasite • Resolution of suspected cystic lesion either spontaneously or after anti-parasitic therapy
Minor criteria:
• Radiology imaging of CNS or spine strongly suggestive of neurocysticercosis • Clinical features are indicative of neurocysticercosis • Positive parasitic antibody or antigen in CSF • Presence of extra-neuronal cysticercosis
Epidemiologic criteria:
• Patient from high prevalent area of cysticercosis • History of frequent travel to high prevalent area of cysticercosis • History of household contact with Taenia solium infection
Definitive diagnosis (any one):
• One absolute criterion • Two major plus one minor or one epidemiologic criteria • Probable diagnosis (any one): – One major plus two minor criteria – One major plus one minor and one epidemiologic criteria – Three minor plus one epidemiologic criteria

TABLE 4 Summarized treatment guideline of NCC given by IDSA and ASTMH

Location of NCC	***Treatment recommendation***
Viable Intraparenchymal NCC	• In patients with hydrocephalus or diffuse cerebral edema, treat raised intracranial pressure (ICP) (Corticosteroids) and **NOT** use antiparasitic treatment • If ICP not raised, use antiparasitic treatment with adjunctive corticosteroid therapy
Solitary cysticercus granuloma	• Antiparasitic treatment with adjunctive corticosteroid therapy (Albendazole preferred)
Calcified parenchymal neurocysticercosis	• Symptomatic therapy alone, **NOT** use antiparasitic drugs and adjunctive corticosteroid
Intraventricular neurocysticercosis	• Surgical removal and/or shunt surgery with use of corticosteroids for treatment of brain edema in the perioperative period • Antiparasitic drugs only in failure cases
Subarachnoid neurocysticercosis	• Strong recommendation of antiparasitic treatment with adjunctive corticosteroid therapy till resolution of cyst (methotrexate could be use as steroid sparing therapy)
Spinal NCC	• Surgery with strong recommendation of antiparasitic treatment with adjunctive corticosteroid therapy

Conclusion

- Neurocysticercosis is caused by helminthic infection due to *Taenia solium*.
- Most common cause of adulthood epilepsy.
- Environmental human-to-human transmission is also important mode of transmission.
- Diagnosis is improved with neuroimaging, but accuracy required diagnostic criteria.
- Effective antiparasitic treatment with adjuvant corticosteroid therapy is most effective treatment.
- Detection of stage of parasite by neuroimaging is very helpful in selection of treatment.

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CHAPTER

177 Rabies: A Comprehensive Overview

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Abstract

Rabies is one of the most typical zoonotic, fatal, and acute progressive neurological infections that has been well known since ancient ages. It is avertable deadly viral disease of Rhabdoviridae family, Genus Lyssavirus. The virus uses nerve cells for their multiplication and produces mutation in the nervous system. There is no treatment for rabies, but we can avoid this by taking preventive measures. Vaccination for dogs is also available. The purpose of this comprehensive overview is to summarize the rabies and its medical importance.

Introduction

Rabies is a disease transmitted to humans through infected animal bites (all mammals) mainly dogs (reservoirs of infection) pets (40%) and stray (60%).

Myths about Rabies in India:

- Some herbal extracts and concoctions will cure rabies.
- People also resort to witch crafts and religious practices.
- Washing of wounds can cause hydrophobia.
- Dietary changes can cure, that is, shift from vegetarianism to non-vegetarianism or vice-versa; stopping consumption of white things, etc.
- A single dose vaccine will prevent rabies.
- Vaccines are more effective if taken in empty stomach.
- One should avoid bathing or eating meat or eggs during vaccination.
- Gems and stones have magical properties against rabies.

Avoid:

- To watch dog for 10 days (practically not feasible) is risky and treatment should be initiated as early as possible.
- Keeping vaccine in freezer. If accidentally kept it should not be used.
- Cauterization of the wound.
- Suturing and bandaging the wound because it may inoculate the virus deeply in to the wound.
- Debridement of the wound too much as this may cause problem with wound closure and appearance.
- Storage of vaccine at room temperature.
- Exposure to the Sun light, heat, or dust (vaccine should be stored at +2–8°C)
- Mixing of IMR and ID schedule.
- Using IG and rabies vaccine in same syringe and at same anatomical sites (it should never be practiced).
- Vaccine should be diluted with the diluent provided.

Clinical Features

See **Table 1**.

Prophylaxis and Treatment

Questions to be Asked/to Start PET?

The animal which bit you was pet (immunized or non immunized) or stray.

TABLE 1 Clinical features

Human beings	*Animals*
• Hydrophobia is fear from water and difficulty in swallowing liquid, typically unique to human beings. There are violent jerky contractions of the diaphragm and accessory muscles of respiration start working • Prodromal stage (2–10 days) • Local pain, fever, with an inclination to vomit • Skin is sensitive to temperature, air currents • Neuroloical stage (2–7 days): Aphasia, incoordination, paresis, paralysis, change in mental status, hyperactivity • Late stage—Hypotension, coma, DIC, cardiac arrhythmia, cardiac arrest, fatality	• Rabid dogs are able to drink liquid, swim (no hydrophobia) • If a rabid dog is not able to drink water, it is because of the paralysis of jaw muscles and not due to hydrophobia • Inability to drink is because of paralysis of jaw muscles • Attacks without provocation and lacks direction, remains isolated and refuses to eat/drink, with excess salivation

Was the bite provoked or unprovoked?

Did you clean/wash the wound gently/thoroughly? (This helps wash away the virus.)

Decision to Initiate PET?

Should be taken well in time, as delay may increase the risk for developing clinical rabies. PET is nearly 100% effective when used appropriately. Factors that should be taken into consideration when deciding whether to initial PEG include:

- The epidemiological likelihood of the implicated animal being rabid.
- The category of exposure (I-III)
- The clinical features of animal.

Diagnosis

Availability of the Animal for Observation and Lab Testing

During life, the diagnosis is usually made on clinical grounds but rapid immunofluorescent techniques can detect antigen in corneal impression smears or skin biopsies.

But for most cases in developing countries, the vaccination status of the implicated animal alone should not be considered when deciding whether to give or withhold prophylaxis.

Examination of CSF often reveals mild mononuclear-cell pleocytosis with a mildly elevated protein level. The presence of rabies virus-specific neutralizing antibodies in CSF suggests rabies encephalitis, regardless of immunization status.

Detection of rabies virus RNA by RT-PCR is highly sensitive and specific. This technique can detect virus in fresh saliva samples, skin biopsy specimens, CSF, and brain tissues.

Direct Fluorescent Antibody Testing with rabies virus antibodies conjugated to fluorescent dyes is highly sensitive and specific. The test can be performed quickly and applied to skin biopsy and brain tissue samples. In skin biopsy samples, virus antigen may be detected in cutaneous nerves at the base of hair follicles

Golden rule: It may be safest to assume that the animal that bits you has rabies and treatment includes—

- Local
- Rabies shots

  Fast acting shot (Rabies immunoglobulin)

  -A series of rabies vaccines.

Local Treatment (Wound Toilet)

Wash the saliva containing rabies virus and clean the wound with soap/detergent (soaps are viricidal) and flush the wound under running water for at least 15 minutes. After cleaning, anti-microbial agents, disinfectant, sanitizer can be applied.

Rabies Immunoglobins

The protective antibody takes 7–14 days to develop after initial dose of vaccine; hence, RIG should be started as soon as possible because it provides activity against rabies virus by providing passive immunity, beginning immediately after administration and lasts for about 7–10 days during which period active immunity to rabies develops and protects the individual.

Severe multiple bites on head, neck, face hands, and genitalia in particular have a short incubation period of only 4 days. Thus, these individuals are vulnerable to rabies despite the timely and full course of any modern rabies vaccine and proper wound care. In these individuals only RIGs are lifesaving, as their timely and proper administration neutralizes the virus in the wounds and prevents its progression into CNS. RIG provides protection, which begins immediately after administration and lasts for about 7–10 days, during which period active immunity to rabies develops and protects the individual.

Often, this failure of modern cellular vaccines in most cases has been because RIG was not use in high risk category III cases

There are two types of RIGs:

- ERIG (Equine Rabies Immunoglobulion):
  - It is heterologous in origin
  - Produced from hyper immunized horses
  - Economical as compared to HRIG; hence, more affordable
  - The currently manufactured ERIG are highly purified with least adverse effects. Most of the ERIG available are F(ab')2 fragment free from reactogenic Fc fragment
  - Dose is 40 iu/kg body weight up to a maximum of 3,000 iu (given after sensitivity test)
- HRIG (Human Rabies Immunoglobulin):
  - Homologus in origin
  - Longer half-life when compared to ERIG; hence, given in half the dose of ERIG
  - Does not require prior skin testing

  HRIG are imported, expensive, and scarce.
- Dose is 20 iu/kg body weight up to a maximum of 1,500 iu.

RIGs should be given as a single dose and should not be repeated.

Vaccines

Human rabies vaccines are made from inactivated or attenuated rabies virus and have gone through successive improvements since the time of Pasteur. The first rabies vaccine was developed by Pasteur, which was nerve tissue based and virus was inactivated by drying, but this vaccine had a risk of activation of the virus and allergic reaction to the presence of nerve tissue or myelin. Myelin-free vaccine prepared from neonatal mouse brains were introduced by Fuenzalide et al.

Subsequently purified duck embryo vaccine (PDEC) was developed, which was highly immunogenic rabies vaccine that can be used safely and effectively at low doses, both for primary immunization and for treatment after exposure. Subsequently, more second generation rabies vaccine were developed like human diploid cell vaccine (HDCV), vero cell, purified chick embryo cell (PCEC). PCEC vaccine with PM (Pit men-moore) strain.

Advantages:

- It is more advantageous than many other cell line based rabies vaccines.
- It is more readily scalable to large scale commercial vaccine production.
- The vaccine produced by the present process has a very large yield, efficacy safety as well as the process is much cost-effective than many of the other processes known for the preparation of rabies vaccine.
- It has unique stabilizing agents, which make the vaccine more stable even at accelerated temperature.
- This method provides vaccine with high yield, greater potency, and immunogenicity, which make the vaccine cost-effective and unique.

All modern anti-rabies vaccines are freely interchangeable. The safest vaccine, free of complications, is human diploid cell stream vaccine.

Vaccines can be given:

- In pregnant woman
- In lactating woman
- Along with other vaccine (EPI, i.e., expanded program on immunization) vaccines
- To a child with chicken pox or measles
- To HIV +ve or AIDS patients
- To patient with jaundice
- To patients who are on antimalarials or steroids or taking immunosuppressive drugs. Generally, vaccine should be avoided with these drugs but if cannot be avoided then vaccine on day 0 may be doubled and given at two sites
- With a higher potency

Indications for doubling the first dose (0 dose) of rabies vaccines:

- Patients who seek treatment after a delay of 48 hours or even months after having been bitten should be dealt in the same manner as it expose occurred recently.

- Patients with very high risks exposures on extensive bites.
- Immunodeficient patients, or those on immunosuppression drugs, e.g., antimalarials, anticancer drugs, etc.
- Severely malnourished patients.
- Patients with underlying chronic disease like cirrhosis of liver.
- Patients where RIG is indicated but unavailable.

Discussion: Rabies is one of the oldest diseases known in recorded medical history. It is caused by a bullet shaped RNA rhabdovirus that is a member of the rhabdoviridae family, genus lyssavirus. Generally, rabies is transmitted by saliva from infected animal bites but may also be transmitted by scratches, secretions that contaminate mucous membranes, aerosolized virus that enters the respiratory tract and corneal transplants.

Rabies is a neglected disease of poor and vulnerable population whose deaths are rarely reported. It occurs mainly remote rural communities where measures to prevent dog to human transmission have not been implemented. Under reporting of rabies also prevents mobilizations of resources from the international community for the elimination of human dog mediated rabies.

Prevention of Rabies

This consists of:

- Elimination of stray dogs
- Registration and licensing of dogs
- Immunization of dogs and pets

Since dogs are the major reservoir of rabies transmission in India **(Table 2)**, there population must be controlled. Way back in 1985, the dog population was estimated to be 80 million as per census by agriculture ministry. It appears this population might have grown substantially.

For killing of dogs strychnine had been in use for long time, its use is not advocated these days because drugs being very hazardous and in humane. Saturated solution of magnesium sulfate administered IV is the ideal and recommended method for killing dogs. After destroying the dogs, the concass should be hygienically disposed off. But this is not allowed.

The dog destruction used to be one of the pivotal activities at the primary health center in India. Sanitary inspectors used to destroy dogs in rural areas after obtaining the requisition from village panchayats. Now this has been stopped. Human way of dog destruction is in practice in municipal areas. No solution seems to be in hand to destroy stray dogs in rural areas, the menace continues to grow. Similarly, monkey menace has been additional burden in urban areas, besides dogs.

Municipal authorities hold the responsibility of dog catching licensing and dog destruction by humane way to prevent cruelty against animals.

Sterilization of dogs and monkeys has been attempt to reduce their population.

TABLE 2 Reservoir animals

Frequently	*Sometimes*	*Occasionally*	*Not reported*
Dogs Cats	Monkeys, Horses, Sheep, Cow, Buffaloes, Donkeys, Pigs	Camels, Elephants, Foxes, Mangoose, Jackals, Bears	Bats, Rodents, Birds

Pre-exposure Immunization in Animals

Pre-exposure immunization of pet animals against rabies is recommended.

Single dose: The vaccine is prepared as 20% suspension of brain from sheep infected with modified rabies virus. The virus in the brain suspension is inactivated phenol or B-propiolactone (BPL). It's only used for pre-exposure immunization.

Veterinary Antirabies Vaccine Multiple Dose

This vaccine is also prepared from sheep brain infected with modified rabies virus. The virus in the vaccine is killed with phenol or BPL. The vaccine is given in multiple doses and can be used for both pre- and post-exposure immunization of dogs, cats, and other domestic animals. This vaccine confers higher degree of protection than conferred with single dose vaccine.

Epidemiological cycles:

- *Urban:* As many as 99% of human cases in India are due to bites by urban rabid animals, which maintain a cycle amongst themselves. DOG→DOG→Other animals, and man being an accidental victim and dead end of infection.
- *Sylvatic:* Cycle propagates itself within wild animals who sometimes transmit the infection to urban

animals as well as man. Bat rabies has not been conclusively reported from this country. No courier state has been convincingly demonstrated in dogs and in all practical purposes it is taken as non-existent.

Mode of transmission:

- Licks on damaged skin and mucous membrane or scratch
- Directly from the bite by Rabid animals
- Handling saliva of rapid animals or patient
- Organ transplantation particularly by corneal graft etc.
- Unboiled milk of Rabid infected cow
- Urine, tears, nasal secretions, and sweat
- Aerosol contamination
- Mechanical transmission

After local multiplication at the wound site, the virus enters the nerves and travels at the rate of 3 mm/hours to the dorsal root of ganglion, then reaches the anterior horn cells of the spinal cord and brain, developing rabies encephalitis, and inevitable deaths.

Incubation period: On an average 20–90 days, but 4 days to 8 years have been reported.

Pathology

- Minimal pathologic changes
- The brain is edematous and congested on gross appearance
- Histopathologically:
  - Perivascular cuffing and gliosis
  - Minimal neuronal damage (necrosis)
  - Presence of Negri bodies is pathognomonic

Conclusion

- A much feared disease known to man since ancient times is rabies.
- A deadly disease, but also a 100% preventable disease.
- Taking right steps at right time can reduce exposure to infection and prevent rabies.
- When in doubt about the degree of exposure to rabies risk, it is safer to over treat that to under treat.
- Criterion for "protection" after immunization—is that the rabies virus neutralizing antibody (RVNA) titer of ≥0.5 iu/mL of serum in the vaccinated person which is considered protective.
- Person receiving/completed anti-rabies immunization either pre-exposure or post-exposure can donate blood, but the recipient does not benefit from the transfer of rabies neutralizing antibodies due to hemodilution.
- Health education of public on prevention and control of rabies and management of bites and their response to bite at local level is crucial to save lives. This should be through primary health-care infrastructure besides mass media as also formal and non-formal education channels.
- In developing countries, where human rabies globulin may not be obtainable, 0.1 mL of vaccine may be given intradermally into eight sites on day 1, with single boosters on days 7 and 28.

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CHAPTER

178 Biomarkers for Diagnosis and Prognosis of Severe Malaria

Manoj Kumar Mohapatra

Abstract

Biomarkers are different cellular, biochemical, or molecular products, which are measured in different biological samples to assess the diagnosis and prognosis of malaria.

Introduction

Malaria is an intricate parasitic disease caused by intraerythrocytic parasite of the genus Plasmodia. Five species, *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale,* and *Plasmodium knowlesi,* are responsible for human malaria. Almost all deaths due to malaria are caused by falciparum malaria, and, despite all efforts, still it persists as a disease of high mortality. Improper diagnosis and development of drug resistance are two factors that make the disease difficult to control.[1]

For a long time, detection of the parasite in peripheral blood smear has been considered as the gold standard of diagnosis but with a lot of limitations. Further, definite indicators of bad prognosis factors are necessary for prognosis of patients of severe malaria. Therefore, there is necessity of detecting different biomarkers for diagnosis and prognosis of malaria.

Biomarkers

Biomarkers may be defined as different cellular, biochemical, or molecular alterations, which can be measured in different biological samples to assess the diagnosis, prognosis, or therapeutic responses of a disease. There is no suitable classification of biomarkers. However, Frank and Hargreaves have attempted to classify the biomarkers into the following three types:[2]

- *Type 0:* Measures of natural history of the disease and correlate with clinical outcome.
- *Type 1:* Determines the biological effect of therapeutic intervention.
- *Type 2:* Characteristic or variable that reflects how a patient feels/functions/survives, i.e., a clinical end point.

Biomarkers for Malaria

In malaria, host and parasite interaction is of paramount importance. Therefore, biomarkers related to the parasite may be used for diagnosis and from the host may be utilized for prognosis. When parasite enters the human body, parasitic proteins trigger the host immune systems, which are associated with malarial pathogenesis and severity. The molecules released during pathogenesis can be used as diagnostic biomarkers. *P. falciparum* severe infection has diverse effect on multiple systems causing multiorgan failure. Molecules released during complications like cardiac dysfunction, circulatory dysfunction, kidney dysfunction, and alteration of cell signaling can be used as prognostic biomarkers or biomarkers of severity.[3]

Criteria for an ideal biomarker: An ideal biomarker should be:

- Less costly
- Easy to detect and evaluate
- Can be used in low-resource settings
- It can be used at the point of care
- It should have the power to distinguish different forms of the disease like symptomatic versus asymptomatic or uncomplicated versus severe malaria
- It should provide better prognosis
- It can guide treatment

Biomarkers used for diagnosis are HRP II (Histidine rich protein II), Parasite Lactate dehydrogenase, Hemozoin, Aldolase, Haptoglobin.[4]

Biomarkers used for severity of disease are vascular dysfunction (angiopoetin-Tie-2 system), RBC membrane dysfunction (gamma GT), serum uric acid, eGFR, Procalcitonin, lipase, cardiac markers (PPARG coactivator 1 alpha, CPK-MB), Apoptosis markers (DAPK1; death associated protein kinase-1), hypoxia and cerebral malaria (HRP II, IFN-gamma, Lymphotoxin-alpha, chemokine CXCL10), neurological dysfunction (ApoE, apolipoprotein).

Biomarkers to assess protective immunity are antibodies to ICAM-1 binding *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1) and to glycosylphosphatidylinositol (GPI).[5]

Diagnostic Biomarkers

Histidine Rich Protein

P. falciparum synthesizes a unique set of soluble HRPs during the asexual erythrocytic development. There are three types of HRP, namely HRP I, II, and III in the order of discovery.[4]

HRP-I is also known as knob-associated protein. It produces knob like protrusions on the cell surface of parasitized RBC that helps in cytoadherence of infected erythrocytes to venular endothelium. HRP-II helps in heme binding and heme detoxification by hemozoin formation. It is exclusively found in *P. falciparum*. HRP-III, also known as small histidine alanine rich protein (SHARP) was found to have polymorphisms in gene repeats and shares homology with HRP-II.

Amongst these HRPs, HRP-II was found to be transported from parasite through the host cell cytoplasm to the circulation and can be detected in urine of infected patients. Its release in abundance makes it an important parasite antigen for diagnosis of malaria.

Parasite Lactate Dehydrogenase (pLDH)

Normally, the requirement of glucose for the metabolism of RBC is modest. But after the invasion, plasmodium consumes an excess amount of glucose for its growth and metabolism. The extra glucose has been taken from the blood by the parasite and metabolized by anaerobic glycolysis and glucose is converted to lactic acid and excreted to circulation. The final enzyme of this glycolytic pathway is lactate dehydrogenase, and hence is over expressed and can be used for diagnosis purpose.[5]

Hemozoin

The parasite infects the RBCs and digests hemoglobin resulting in release of amino acids and toxic-free heme (ferriprotoporphyrin IX), which is polymerized to hemozoin. It helps the parasite to survive from the heme toxicity. It plays a role as a visible marker in identifying parasites; therefore, popularly termed as malaria pigment.[3]

Other Biomarkers

Apart from these, Aldolase and Glutamate dehydrogenase are two enzymes, which can be used for diagnosis purpose.

Haptoglobin

Haptoglobin (Hp) is an α2 glycoprotein that binds rapidly to free hemoglobin (Hb). After rupture of parasitized RBC and hemolysis of non-parasitized RBC, free Hb binds to Hp forming a complex which is rapidly cleared by the mononuclear phagocytic system, resulting in a state of hypohaptoglobinemia, which can be used as a clinical and epidemiological biomarker of falciparum malaria.[6]

Biomarkers of Severity and Prognosis

In addition to the diagnostic performance, biomarkers have been identified for the prognosis of severe malaria. Endothelial cell activation is crucial in pathogenesis of *P. falciparum* malaria. Activation of endothelial cells causes release of procoagulant and inflammatory proteins like tissue factor, Ang-2 (angiopoetin-2), I-CAM, and E-selectin.

Ang-1 and Ang-2 are ligands of the Tie-2 receptor which is expressed on endothelial cells. Ang-1 is constitutively produced and excreted into blood by pericytes and

smooth muscle cells and also stored in platelets. It binds to Tie-2 receptor, thereby acting as agonist resulting in anti-apoptotic and anti-inflammatory status of endothelial cell. Ang-2 is produced in endothelial cell and prestored in Weibel Palade Bodies (WPB) together with vWBF. Upon endothelial activation, there is exocytosis of WPB, Ang-2 released and replace Ang-1-Tie-2 interaction. This interaction stimulates inflammatory response. Further studies based on this pathogenesis showed that decreased Ang-1 and increased Ang-2/Ang-1 ration are robust biomarkers to distinguish uncomplicated malaria from cerebral malaria. However, they do not correlate with parasitemia.[7]

PCT is a prohormone of calcitonin containing 116 amino acids with a molecular weight of 13 kDA. Under physiological conditions, calcitonin is produced and secreted from C-cells of thyroid gland after intracellular proteolysis to circulation with plasma half-life of a few minutes. Therefore, under normal condition PCT level is low (<0.5 ng/mL). The origin of PCT in infection is thought to be extrathyroidal and the predominance of PCT without increase in calcitonin indicates the presence of a constitutive pathway within the cell that bypasses the enzymatic conversion of PCT to calcitonin.[8]

High negative predictive value of S.PCT may be helpful for a rapid exclusion of critical malaria on admission. When S.PCT was ≤2 ng/mL the patients can be managed in the general ward or domiciliary treatment may be given; with 2–10 ng/mL the patients can be managed in the general ward with special attention or in high dependency unit (HDU) and can be shifted to ICU when necessary; and if more than 10 ng/mL the patients should be shifted to ICU for management.[9] Different biochemical investigations that determine dysfunction of different organ systems can be used as biomarkers of severity.

Elevated level of gamma glutamyl transferase (GGT) was observed when there is increased RBC membrane damage contributed by oxidative stress. Markers of liver dysfunction like serum LDH and total bilirubin is significantly elevated in severe malaria. Serum lipase, a pancreatic enzyme which has been associated with acute pancreatitis, a rare complication of *P. falciparum* can be used as a biomarker.[10] Cardiac biomarkers like PPARG coactivator 1 alpha and CPK-MB are significant cardiac biomarkers indicating of severe malaria and can be used as biomarkers.[11]

DAPK1 (death associated protein kinase 1) is known as a mediator of apoptosis and autophagy. When there is an extracellular signal trigger, DAPK1 is phosphorylated, which increases its catalytic activity and causes cellular death mediated by p53 pathway. When there is an increased parasite burden, there is inhibition of DAPK1 and p53, a strategy of parasite survival during metabolic stress. Therefore, decrease in apoptotic markers DAPK1 and p53 signify severe malaria.

Apo-E is a major lipoprotein in brain and has been seen dominant in several neurological diseases. Hence, several studies have been carried out to assess its correlation with cerebral malaria as a neurological biomarker.[5]

Biomarkers of Protective Immunity

- *Antibodies to ICAM-1 binding PfEMP1-DBL beta:* Expression of diverse *P. falciparum* erythrocyte membrane protein-1 (PfEMP1) gene variants allows clonal antigenic variation and cytoadhesion to endothelium. Adhesion occurs via specialized PfEMP1 domains known as duffy binding like (DBL) and cysteine rich interdomain region (CIDR) and antibodies against them are significantly associated with protection against severe malaria. This class of DBL beta domain could be used as diagnostic antigens.[3]
- *IgG antibodies to synthetic GPI:* In malarial parasites, GPI is a glycolipid that is found both free and as an anchor sustaining many proteins on the parasite membrane including merozoites. In animal studies, it has been found that antibodies against GPI were able to delay mortality by *P. berghei*, by blocking toxic immune response. Further studies showed that GPI was found to be present across all stages of malarial parasite life cycles suggesting that antibodies against GPI could be able to prevent both erythrocytic and hepatic infection and block transmission of parasite from human to mosquito. These observations highlight that IgG to GPI can be potential biomarkers of immune status.[3]

Conclusion

Unlike other diseases biomarker research in malaria is slow. However, recently biomarker research on malarial pathogenicity has taken a leap as evidenced by discovery of HRP-II, pLDH, aldolase, hemozoin, angiopoietin, procalcitonin, etc. Further, it is now important to distinguish complicated and cerebral malaria as early as possible so that treatment can be implicated to reduce the mortality.

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CHAPTER

179 How Fatal Is *Plasmodium vivax*—To Be Understood and Its Management

Smita Gupta, Neeraj Kapoor, Ankit Grover

Abstract

Malaria caused by *Plasmodium vivax* is often a life threatening disease leading to significant mortality in our society. Though severe malaria has been attributed to *Plasmodium falciparum*; however, mortalities and complications associated with vivax malaria cannot be overlooked. The ability of *vivax* to remain dormant in the form hypnozoites causing relapse and increasing complications by cytoadherence and rosette formation further adds to the disease burden. Chloroquine resistance is an emerging challenge in the management of patients with vivax malaria. Complications like hemolysis, cerebral malaria, ATN, and acute respiratory distress syndrome are also now attributed to *Plasmodium vivax* malaria.

Introduction

Malaria is a life threatening protozoal disease caused by Plasmodium parasite, which is transmitted to humans by bite of an infected female Anopheles mosquito. Of the five parasite species that cause malaria, two of them, *Plasmodium falciparum* and *Plasmodium vivax*, pose the greatest threat. World Malaria Report 2019 states that nearly half the population of the world was at risk of exposure to malaria in 2018.[1] An estimated 228 million cases of malaria were there worldwide in 2018 in contrast to 231 million cases in 2017 of which around 405,000 deaths globally due to malaria. Currently, India accounts for 4% burden of malaria globally and 87% of the Southeast Asia.[2] Most vulnerable group includes children less than 5 years of age accounting for 67% of deaths due to malaria worldwide.[1] The most prevalent parasite in African region is *P. falciparum* (99.7%), whereas *P. vivax* remains as the prevalent parasite in America, accounting for 75% of all malarial cases.[1] In India, malaria is a major health problem with 0.88 million cases occurring per year. Severe Malaria (as per the WHO guidelines) accounts for approximately 400–1,000 deaths per year[3] and most of them are due to *P. falciparum*.

P. falciparum known to cause Severe Malaria has been contributing to maximum morbidity and mortality worldwide whereas infection by *P. vivax* is always thought to be a benign disease, classically causing mild symptoms. But recently it has been seen that the infection by *P. vivax* no longer results in a non-critical illness having so many case reports showing its association with severe life threatening complications. There are historical evidences too, showing its severity which come from reports on neurosyphilis therapies in early 1990s reporting 5–15% mortality rates in America and European treatment facilities using *P. vivax* for treatment of syphilis indicating that it always had a severe outcome.[4]

Plasmodium vivax: Epidemiology

The most widespread infections of all malarial parasites is P. Vivas which affects majority of the parts of subtropical & tropical areas of the world. Nearly 2.5 billion people are affected by *P. vivax* infection in the world and 16 million clinical cases occur annually.[5,6] Highest burden is borne by Southeast Asian countries and South America out of which 53% of cases occur in South East Asia with India alone bearing around 47% of the total burden.[5,6] it has a wider

geographical variation and distribution due to its ability to stay dormant in liver cells and then cause relapses and its capability to survive in cold weather. As per the studies, it has been reported that many people in Africa are resistant to *P. vivax* infection due to absence of Chemokine Duffy antigen receptor on RBCs but this theory has been put to question by many reporting cases in Duffy negative patients also.[7,8]

In 2014, there were 2.14 million cases of *P. vivax* worldwide, 18% of them occurred in India alone.[9] In the recent past the number has been increasing accounting for nearly half of all the malarial cases. The incidence of *P. vivax* varies across India with ten states accounting for nearly 89% of total cases.[10] Out of these Jharkhand, MP, Odisha, UP, and Gujarat carry 64% of the total burden. It is becoming a problem mainly in urban settings of India probably due to construction work, migration, and ever growing slum areas, and resulting in peaks in morbidity and mortality. Within the Urban Malaria Scheme, 98% of all malaria cases were *P. vivax* in 2014.[10] Its transmission occurs throughout the year, but it peaks during rainy or post-rainy seasons.

Risk Factors and Pathophysiological Mechanisms Leading to Its Malignant Course

P. vivax infection now poses a great threat with multiple reports showing severe clinical presentations and deaths. A meta analysis[11] published in 2014 showed that *P. vivax* as a major cause of "Severe Malaria" and warranted a prompt and early detection of its clinical manifestation resulting in early initiation of therapy so that it could be life saving. Many risk factors have been discussed related to its severe course. Children below 5 years of age are at risk of developing critical illness and ultimately dying within 1 year of their initial presentation.[12] Genetic polymorphism varies and shows alpha and beta thalassemia patients having increased risk and Duffy negative and G6PD deficient patients having decreased risks of *P. vivax* infection.[13]

Relapse

The ability of *P. vivax* to persist as dormant stage as hypnozoites in liver initiates infection in the blood resulting in frequent relapses ranging from weeks to months and years.[14] The variation in time of relapse varies from one region to another and it is observed that in tropical countries the dormant period of relapse is usually 8–10 months.[15,16] The exact mechanism how hypnozoites initiate relapses is still unknown.

Increased Pyrogenicity

In contrast to *P. falciparum*, which is known to invade all stages of erythrocytes, and as a result parasitemia can exceed as high as 20–30%, *P. vivax* is known to invade the reticulocytes rather than the erythrocytes, resulting in lower parasite biomass and parasitemia, which rarely exceed 2–3% in blood even in severe infection. *P. vivax* in spite of having lower pyrogenic threshold has been observed to have higher endothelial activation, increased production of cytokines, and a proinflammatory response as compared to *P. falciparum*.[14] The main reason could be presence of higher levels of genomic content (GC) in vivax genome, and thus having higher contents of CpG motifs, which are recognized by receptor 9 leading to cell activation and inflammatory responses.[17-19] Toxins contributing to increased pyrogenicity of *P. vivax* have been found to be cholesterol or triglyceride fraction of plasma at the time of paroxysm of fever.[14] The imbalance between pro- and anti-inflammatory cytokines production is related to severe clinical conditions in *P. vivax*.[20]

Sequestration and Rosetting Phenomenon

The classical pathogenesis of severe *P. falciparum* infection leading to "Severe Malaria" shows sequestration of parasite in endothelial tissue causing microvascular obstruction, inflammation ultimately resulting in hypoxemic, and ischemic damage in organs. Similar studies are now documenting that there is binding of vivax infected RBC to endothelial cells via receptors like ICAM 1 but to a much lesser frequency than the *P. falciparum* infected RBCs.[21] They also seem to be attached to glycosaminoglycans like chondroitin sulfate and hydraulic acid.[22] Severity of *P. falciparum* is associated with the above phenomena, which is also seen in *P. vivax* but it shows a moderate level of cytoadherence to endothelial cells and ultimately resulting in inflammatory responses in organs like lungs. In fact this phenomenon of sequestration and adherence of infected RBCs and accumulation of malarial pigment deposits to the intervillous spaces of placenta has been associated with pregnancy induced malaria leading to

anemia and intrauterine growth retardation although it appears to be less severe.[14]

Apart to adhesion phenomenon, it is also known that vivax too has a tendency to form rosettes, which has been mentioned in literature more than 20 years ago,[23] although seen more frequently with falciparum. Rosettes in *P. vivax* are formed by interaction of infected RBCs containing trophozoites, schizonts, or gametocytes. The rosettes of *P. vivax* are stable even under high physiological shear stress and cause increased rigidity of infected RBCs thereby contributing to sequestration of *P. vivax* in the microvasculature.[24]

Chloroquine Resistance

The recommended drug in management of both *P. falciparum* and *P. vivax* is chloroquine, but now resistance has started developing to this drug especially in endemic areas. This is attributed to presence of polymorphism in chloroquine resistance genes pvcrt-0 and pvmdr-1 in South India.[25]

Clinical Manifestations and Complications

Fever is the main complaint of malaria and symptoms start to appear as soon as the blood stage infection starts with the invasion of RBCs by the merozoites. As the life cycle of *P. vivax* repeats every 42–56 hours, the paroxysm of febrile episodes occurs during similar intervals and classically the fever is termed as the tertian fever.[26] Fever is usually intermittent, may go as high as 40 degrees in non-immune individuals and children associated with chills and rigors followed by profuse sweating and weakness. Other non-specific clinical features include abdominal discomfort, malaise, fatigue, and muscle aches. In few patients, a prominent headache, altered sensorium, or irritability may be observed. Headache may be very severe but usually signs of meningeal irritation like neck stiffness and photophobia are absent.

In areas of high-relapse rate, anemia has been observed to be the most common finding in both children and adults. The most likely causes involved are cumulative losses of infected RBCs, lysis of uninfected RBCs, and defect in production of red cells.[27-30] It is said that for every one infected RBC in circulation, approximately 34 uninfected RBCs are removed and thereby leading to severe anemia. A higher inflammatory response, in the spleen leading to higher losses of RBC, seems to be its explanation in spite of low parasitemic index. Also its tendency to relapse usually at 3–4 weeks interval repeats the cycle before the hematological recovery takes place from previous infection. Inflammatory cytokines also result in dyserythropoiesis and bone marrow suppression.[31,32] Usually a palpable spleen is found several day after infection but many of the otherwise healthy individuals have been found to have a palpable spleen indicating repeated infections in an endemic area. Mild hepatomegaly may be observed in children. Mild jaundice may be seen in adults and usually resolves in 1–3 weeks indicating uncomplicated infection.

P. vivax also has pulmonary complications and the spectrum ranges from cough, acute breathlessness, pulmonary edema to ARDS, and death. A meta-analysis published in 2017 showed that out of 49 studies 59.1% case studies reported acute respiratory distress syndrome (ARDS), 20.4% respiratory distress, 4% respiratory failure, 2% lung injury, and 2% studies reported pulmonary edema.[33] They concluded that respiratory complications and ARDS occur in lower frequency in vivax than in falciparum, but mortality resembles that of falciparum. Female gender, presence of comorbidities, respiratory complications at time of hospital admission, and low-hemoglobin level were associated with deaths. Another meta-analysis was published in 2014[11] in which three studies showed higher incidence of ARDS among *P. vivax* as compared to *P. falciparum*.[34-36] The presence of lymphocytes, neutrophils along with phagocytosed pigments in the pulmonary vasculature is the main cause of direct damage to lung parenchyma, diffuse inflammation, and alveolar damage.[37]

Acute kidney injury (AKI) remains a major cause of morbidity and fatality with incidence ranging from 15% to 40% in numerous studies.[38,39] Mostly it is due to *P. falciparum*, but AKI has been reported in 12–20% *P. vivax* infection also, whether it is due to solely vivax or mixed infection is still debated. Mortality associated with *P. vivax* AKI is 10–15%, which is comparable with *P. falciparum*[39] and 10–20% may require renal replacement therapy. Kidney complication are mainly due to hemodynamic dysfunction and immune response and clinically they present as oligoanuria, severe metabolic acidosis, and hypercatabolic state.[40] A study conducted in 2017[41] discussing the clinic histologically profile on 30 patients showed fever in all cases, oliguria in 23%. Renal biopsy

performed among 6 patients revealed features of ATN in 4 patients, one had features of thrombotic microangiopathy, while one revealed acute cortical necrosis. Another study[42] conducted showed that a high index of suspicion for diagnosing thrombotic microangiopathy should be kept if patient has persistent anemia, thrombocytopenia, jaundice, and non-recovering renal failure, such patients usually respond to plasmapheresis. The inciting event may be the lesion in endothelium of renal microvasculature.

Cerebral malaria a complication of *P. falciparum*, characterized by diffuse meningoencephalitis, is seen to occur with *P. vivax* also.[43] The patient usually presents with signs and symptoms of acute febrile encephalopathy, seizures, and coma. Focal neurological deficits are unlikely. However, a case presenting with Status Epilepticus has been described.[43] Though the exact pathogenesis remains elusive, but similar pathogenesis of sequestration of infected erythrocytes have been described.[44] One pathogenesis regarding cerebral malaria is genetic variation resulting in variant interspersed repeats genes, the largest subtelomeric multigene super family found in *P. vivax*.[45,46]

So it is understood that features of Severe Malaria can also be seen in *P. vivax* infection as commonly found in *P. falciparum* leading to multiorgan involvement. A study conducted in 2019 among 150 patients showed Severe Malaria among 42% of cases (as per WHO criteria) with mortality of 1.33%.[47]

Management and Treatment

Main pillar in elimination of malaria is early diagnosis and treatment thereby reducing disease burden and preventing complications, and deaths. Malaria is a notifiable disease in India. For diagnosis, uses of light microscopy or immunochromatography-based rapid diagnostic tests (RDTs) are being used.[48] The gold standard for diagnosis is direct visualization of *P. vivax* parasites on Giemsa stained blood smears by light microscopy. It is a low cost with high sensitivity diagnostic test. Parasitemia is detected by thick smears and at least 200 fields should be examined well before concluding negative diagnoses. Thin smears are used to calculate the parasite density. The parasite density of *P. vivax* is lower in areas where mixed infections are common making the diagnosis more difficult.

Since the early 1990s RDTs have popularized as diagnostic tools as they can detect one or more plasmodium species and are time saving without the requirement of a skilled lab personnel.[26] This test has a high sensitivity at higher parasitic load and may give false negative at lower parasitic load. This test can be positive even 1 month after successful treatment. A new recently developed real time micro PCR based diagnostic device has been claimed to have high sensitivity and specificity.[48]

Treatment of *P. vivax*[3]

The objective of treating malaria caused by *P. vivax* is to cure both blood stage and liver stage infections thereby preventing recrudescence and relapse both, respectively. The ability of *P. vivax* to from hypnozoites possesses a great challenge in management of patients.

WHO Malaria Treatment Guidelines, 3rd edition,[3] suggest treatment of all suspected and confirmed uncomplicated malaria patients with chloroquine or Artemisinin Combination Therapy (ACT).

Chloroquine Sensitive Malaria[3]

Oral chloroquine at total dose of 25 mg/kg (initial dose of 10 mg/kg on first day followed by 10 mg/kg on second day and 5 mg/kg on third day) **(Box 1)**.

ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment, that is, all malaria infections can be treated with an ACT. The exception is artesunate + sulfadoxine pyrimethamine, where resistance significantly compromises its efficacy.

Chloroquine Resistant *P. vivax*[3]

ACTs containing piperaquine, mefloquine, or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas.

BOX 1 Treatment uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria

- In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae*, or *P. knowlesi* malaria with either an ACT (except pregnant women in their first trimester) or chloroquine.
  Strong recommendation, high-quality evidence
- In areas with chloroquine-susceptible infections, treat adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae*, or *P. knowlesi* malaria (except pregnant women in their first trimester) with an ACT.
  Strong recommendation, high-quality evidence

BOX 2 Preventing relapse in *P. vivax* or *P. ovale* malaria

- To prevent relapse, treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient and people with G6PD deficiency) with 14-day course of primaquine in all transmission settings.
  Strong recommendation, high-quality evidence
- In people with G6PD deficiency, consider preventing relapse by giving primaquine base at 0.75 mg base/kg bw once a week for 8 weeks, with close medical supervision for potential primaquine-induced adverse hematological effects.
  Strong recommendation, high-quality evidence

In pregnant or breastfeeding women, weekly chemoprophylaxis with chloroquine is recommended until delivery followed by completion of breast feeding. Treatment for future replases can then be decided on the basis of G6PD status **(Box 2)**.

Severe Malaria

All patients including adults, children, infants, pregnant women in all trimesters, and lactating women with Severe Malaria are to be treated with intramuscular or intravenous artesunate for at least 24 hours and until they are able to tolerate oral medication. Artesunate is prescribed at a dose of 2.4 mg/kg at 0, 12, 24, and 48 hours. Once a patient has received at least 24 hours of parenteral therapy and who can tolerate oral therapy, complete treatment with 3 days of an ACT should be advised. Intravenous quinine can be considered as an alternative agent at a loading dose of 20 mg/kg followed by 10 mg/kg in 8th hourly dosing only, if artesunate is not available.

Symptomatic management of ARDS, seizures, and AKI is to be done according to institutional protocols.

Conclusion

Managing patients with severe malaria should caution the mind of a clinician in view of *Plasmodium vivax* as a causative agent and potential drug resistance in the same. Patient may present with hemolysis, jaundice, acute renal failure, cerebral malaria, or acute respiratory distress syndrome. Use of artemesin-based therapy is the treatment of choice for severe and drug resistant malaria caused by *Plasmodium vivax*.

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CHAPTER

180 Emerging and Re-emerging Infectious Diseases in India—This Millennium

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Abstract

Majority of emerging and re-emerging diseases are zoonotic. Viral and parasitic infections are more common causative agents for emerging diseases than bacteria. Zoonotic diseases are more likely in our country due to our usual habit of keeping livestock in close proximity.

After the last influenza pandemic in 1918, the prevailing COVID-19 pandemic is almost over 1 year in existence. Whole world is now reeling with this emerging infectious disease along with various re-emerging diseases in between.

Introduction

Since antiquity human population have faced several epidemics of emerging & re-emerging infectious diseases with a significant death toll. Plague (in 14th century), smallpox (in 16th century) and Spanish flu (in 20th century)—were responsible for huge death to the tune of 200, 56, and 50 millions respectively.[1] With the advent of antimicrobials and effective vaccines in 20th century infectious diseases no longer remained the major threat for mortality, especially in developed countries.[2,3] But for last few decades a slew of newer infectious diseases (Avian Influenza, NIPAH, SARS, COVID-19) have emerged. Some of them have epidemic potentials with significant morbidity and mortality.[4]

Definitions

Emerging Disease

Infectious diseases are said to be EID when incidence of one Inf. disease has increased abnormally within the recent past or threatens to increase in the near future. Diseases that fall in this category are:

- *New disease*
- *Old disease with new feature:* Here new means in respect to new location or new population (prevalence in different age group), new feature (changed C/F or non-responsiveness to conventional therapy)

Re-emerging Infectious Disease

A past disease, which was once well controlled or eradicated, has shown its reappearance is considered to be re-emerging infectious disease.

Origin of Infectious Diseases

Majority of EIDs are zoonotic and over 30 new infections have emerged in last three decades globally and most common agents are viruses & prions (37%) followed by protozoa (26%).[5] Many of them have epidemic or pandemic potentials with high fatality rate and ~60% of them are zoonotic in origin, especially wildlife in origin.[5-7] *In India, zoonotic diseases are more likely as livestock usually stay in close proximity to human dwelling.*[8]

Infections from Animal to Man—How?

To get into the depth of origin of these EIDs we have to look back to our changed behavior. Human encroachment to animal habitat through deforestation and use of terrain for their personal living and farming has lead to increased interface with wild animals. This is considered to be an important or potential factor for jump of some microbes (with or without mutation) usually found in animal kingdom, to human population. Many of them have epidemic potential and spread is facilitated across countries by fast travelling and wild trafficking.

Important Diseases

Important emerging and re-emerging diseases in India in this millennium that deserve mentioning are:

Virus:
- NIPAH (2001)—West Bengal
- Chandipura (2003, 2004, 2007)—Andhra Pradesh, Gujarat, Maharashtra
- Chikungunya (2005)—Andhra Pradesh
- Influenza-H1N1 (2009)—Andhra Pradesh
- CCHF (2011)—Gujarat
- COVID-19/SARS-CoV2
- Zika Virus Disease

Bacteria:
- Diptheria (2001–2015)—Many states (Andhra Pradesh, Assam, Delhi, Gujarat, Karnataka, Nagaland, West Bengal, etc.)
- Plague (2002, 2004)—Himachal Pradesh, Uttarakhand
- MDR/XDR Tuberculosis

Protozoa:
- ACT resistant Falciparum Malaria

Abridged Information of the above Diseases are Put Forward Except Malaria and TB

Nipah Virus Disease

Nomenclature:
- Nipah virus (NiV) belongs to family Paramyxoviridae & Genus *Henipavirus*.
- Named according to its first discovery in Sungai Nipah village of Malaysia.
- It could be considered South Asian disease as all the outbreaks (more than ten) after 1999 have occurred in this region only.

Human affection: In various ways:
- More commonly found in male with history of high exposure to pigs.
- Food borne by consuming fresh date palm sap contaminated with saliva, urine of fruit bats, natural host of NiV, while they feed on it.
- Human to human transmission is possible if patient has respiratory symptoms.[9]

Clinical feature:
- Male predominant disease with M:F = 4.5:1.
- Presents with fever (97%), headache (65%) with altered sensorium and abnormal brainstem functions (50%).
- Dizziness, vomiting, hypotonia, areflexia, dysautonomia (hypertension, tachycardia, excessive sweating) may be present.[10]
- Siliguri (West Bengal) cases in 2001 showed additional feature of acute respiratory distress with tachypnea in half of the cases, making human to human transmission possible (unlike Malaysian outbreak) with high fatality of 62.5%.[11]
- NIPAH virus alert in Kerala was again found in 2018.

Management and prevention:
- Mainly supportive and barrier nursing methods are advocated.
- Ribavarin—tried but inconclusive in vivo trial.
- Monoclonal antibody targeting NiV G glycoprotein was found to be effective in ferret models.
- Vaccine—a subunit vaccine against *Hendra* virus (used in horses), a member of *Henipavirus*, offers a great potential for NiV through cross protection.[12]

Chandipura (CHP) Virus

- Named as per its first documented place of emergence, Chandipura, Nagpur of India in 1965 and possibly it is sandfly borne disease.
- In 2003, Chandipura AES (Acute Encephalitis Syndrome) outbroke in Children in Andhra Pradesh with high fatality (55%) but luckily residual neurological deficit was rare in recovered children.[13]
- After this two more focal outbreaks were observed in Gujarat (2004) and Maharashtra (2007).

Chikungunya

Chikungunya is a self limiting disease and prevalent in tropical and subtropical areas of Africa and Asia.

Chikungunya means "to be bent over" as per Swahili language of Tanzania (Africa) where from the very first case was reported.

Causative agent:

- Chikungunya virus (CHIKV) of arboviridae family of the genus *alphavirus*.
- Vector—day-biting infected Aedes Aegypti and Albopictus mosquito.
- Reservoir of infection—Non-human primates

Clinical features:

- High fever (102–05°F) with severe joint pain (patient becomes bent over) and skin rash.
- Usually follow acute self limiting course but around 10–15% of cases develop subacute (3 weeks to 3 months), or chronic Chikungunya.
- Chronic Chikungunya may present as RA or post-chikengunya-rheumatic muskuloskletal (pcRMSK) disorder.

After 1973, in 2006 re-emergence of chikungunya infection in India was found in epidemic form and affected 1.2 million Indians with high morbidity rate.[14] From 2006 to 2012 chikungunya was reported from 22 States and union territories.

Diagnostic test:

- IgM against CHIKV

Treatment:

- NSAID for 1 or 2 weeks will suffice in majority of patients.
- Chronic cases may need anti-rheumatic drugs like hydroxychloroquine or methotrexate.

Influenza Virus (H1N1)

Influenza virus is a respiratory virus and is of 4 types—A, B, C, and D.

Type A Influenza Viruses has produced several pandemics in humans and is nomenclatured depending on which one of 18 different *Hemagglutinins (HA)* & 11 different *Neuraminidases (NA)* is present as surface protein. It originates either as Avian or Swine.

Influenza A Virus caused the largest and the deadliest pandemics before the occurrence of COVID-19 and four Influenza A Virus pandemics since beginning of 20th century:

- Spanish Flu (1918)—due to H1N1 with 50 million death
- Asian Flu (1952)—due to H2N2
- Hong Kong Flu (1968)—due to H3N2
- Mexican Flu (2009)—due to H1N1 pdm09

The Mexican Flu (2009) pandemic got spread rapidly to over 214 countries worldwide including India. Globally total death toll was 18,449.[15]

A total of 1,54,259 Indians were tested for H1N1 pdm09 influenza till August 8, 2010, with 23.4% being positive including 1,833 reported deaths. Maharashtra and Gujarat were worst affected states.[16]

Treatment:

- Supportive therapy
- Neuraminidase inhibitors—Block virus release from infected cells. Used both for prophylaxis & therapy:
  - Oseltamivir—Oral
  - Zanamivir—IV
  - Peramivir—IV/IM
  - Laninamivir—Intranasal

  Formulations for use. Last two molecules are unavailable here.

Crimean-Congo Hemorrhagic Fever (CCHF)

Name was derived from the first two places of its occurrence—Crimea (in 1944) & Congo (in 1956) caused by single stranded RNA virus of Bunyaviridae family.

Virus continues its life by animal (livestock)-tick-animal cycle.

Human gets infection by:

- Infected tick bites
- Handling of infected animal tissues (Slaughter house workers, farmers, veterinarians)

Clinical feature:

- Incubation period 1–9 days.
- High index of clinical suspicion is needed. Presents with fever, myalgia, headache, lymphadenopathy, and bleeding manifestation (varying from petechial rash to internal mucosal bleeding).[17]
- Fatality rate ranges from 9% to 50%.

India saw the confirmed outbreak of CCHF in 2011 in Gujarat.[18] Total 42 cases were reported till 2013 with high death rate of 59.9%.

Important D/Ds:
DHF, leptospirosis, severe malaria, meningococcal infection, and other viral hemorrhagic fevers.

Diagnosis:
- RT-PCR—sensitive, specific
- Rapid test
- Antibody—antiviral IgG and IgM detection

Treatment:
- Supportive therapy
- Ribavirine—if instituted within 5 days possibly improves the prognosis

COVID-19/SARS-CoV2

Microbes in their quest to be ahead of human, they undergo some mutation to increase their capability of jumping to human from their animal source and human to human transmission as well to reach epidemic/pandemic potential. While this article is being written whole world is reeling under the threat of a zoonosis *COVID-19/SARS-CoV2—biggest threat in last 100 years.*

Corona Virus-related Diseases

Corona virus (CoV), a respiratory virus, normally causes diseases in mammals (including birds) like—camels, civets, bats, etc. This virus is transmitted to human through droplet/fomite & usually produces mild-to-moderate respiratory illness. But through mutation it has caused following diseases with high fatality rate:
- Severe Acute Respiratory Syndrome (SARS)—First noticed in 2002 in China, soon followed by worldwide spread with total reported 8,000 cases and 800 deaths. It was acquired from bat.[19]
- Middle East respiratory syndrome (MERS)—Acquired from dromedary camels (affected from bat). First noticed in 2012 in Saudi Arabia then spreading to other Arabian Peninsula and Republic of Korea. By 2016, over 1,700 cases detected with mortality of 35%.
- Novel Corona Virus Disease (COVID-19/SARS-CoV2)—This ongoing pandemic is being greatest threat of all infectious diseases in last hundred years. Discussed below briefly.

COVID-19/SARS-CoV2 Disease

In December 2019 in Wuhan, Hubei Province of China, an epidemic of respiratory illness with moderately high fatality of unknown etiology was noticed, later proved to be caused by *novel corona virus* (SARS-CoV-2/COVID-19) with human to human transmission.

Origin of Novel CoV Infection—Speculated to have originated *from bats, a natural carrier of CoV, but bats remain in hibernation during winter*. As low temperature prevails in December in China, so intermediate host was thought of. *The virus likely jumped to humans from pangolins (long snouted mammals often used in food and traditional Chinese medicine) along with possibly other multiple intermediate hosts.*

Burden of COVID-19 patients—Infection rate of COVID-19 per day is varying greatly from country to country. Many western countries are braced with 2nd wave of COVID.

Highest infection in a day in India till 20/12/2020 was found on 11/09/2020 and it was 97,570. Little short of 1 lakh/day. Gradually with some fluctuation it then came down to 26,624 on 19/12/2020. Total burden of COVID as on 20/12/2020 is shown in **Table 1**.

Vaccines update (till December, 2020)—Researchers throughout the world putting in great efforts round the clock to contain the devastating situation of COVID-19 pandemicity by finding an effective treatment and/or vaccine against SARS-CoV2. This has lead to an unprecedented public/private partnership to go through a fast tracked vaccine development process.

On August 11, 2020, Russia make COVID vaccine, Sputnik-V, is the world's first vaccine as per bulletin of Ministry of Health of Russian Federation. Russia has started Phase 3 and Phase 4 (administration to general people) trial simultaneously though experts has raised their concern for safety profile **(Table 2)**.

India too is progressing fast keeping pace with other countries. As per ICMR reporting on 20th August, 2020, two indigenously developed vaccine candidates—*Bharat Biotech's COVAXIN* (both intrademal & IM), *Zydus Cadilla's Zycov-D* have started human trial in India, so also *Oxford Astra-Zeneca's Covidsheild* with its Pune based

TABLE 1 Burden of COVID (on 20/12/2020)

Scenario	*Total COVID-19 cases*	*Recovered cases*	*Deceased*
Global	7,66,26,187	5,37,51,202	16,91,942
India	1,00,47,131	95,95,711	1,45,669

TABLE 2 Few more vaccines globally underway

Candidate	*Sponsor*	*Trial phase*	*Institution*
bacTRL-Spike	Symvivo	Pre-clinical	Symvivo Corporation
PittCoVacc	UPMC/University of Pittsburgh School of Medicine	Pre-clinical	University of Pittsburgh
Recombinant vaccine	Vaxart	Pre-clinical	Vaxart

manufacturing partner Serum Institute of India. *Oxford-AstraZeneca vaccine may be the first shot available for Indians by the end of 2020.*

AstraZeneca is likely to get regulatory approval from the UK's independent regulator by the end of this year for a rollout to begin in early 2021, according to the UK Oxford University/AstraZeneca vaccine company.

Trials of the Oxford vaccine show the following as per their claim:

- Stop *70% of people developing Covid symptoms*. Could increase protection up to 90%
- The data also shows a *strong immune response in older people*
- It is given in two doses
- Trials with more than 20,000 volunteers are still continuing

This may be one of the easiest vaccines to distribute, because it does not need to be stored at very cold temperature.

It is made from a weakened version of a common cold virus from chimpanzees that has been modified to not grow in humans.

WHO and most nations globally are willing to prioritize vaccine recipients as follows:

- Health-care workers (HCW)
- People >65 years of age
- People with comorbidities (like DM, Cancers, CVD, COPD)

Clinical feature:

- Incubation period—2–14 days
- Asymptomatic—some patients
- Majority shows features of fever (45.4%), headache (70.3%), dry cough (63.2%), sore throat (52.9%), asthenia (63.3%), and some developed dyspnea. Anosmia (70.2%) and altered taste sensation (49.8%) may be early symptoms in some patients.[20]
- Diarrhea may be the presenting feature of COVID-19 in ~20% of cases.

Silent Hypoxia in COVID

Silent hypoxia is a danger sign of COVID-19 infection. It means person's oxygen level in blood cells and tissue may drop due to COVID-related diffuse pneumonia without any initial warning in the form of cough, dyspnea, tachypnea, etc. until patient develops ARDS.

So arterial O_2 saturation (SpO_2) detection at regular intervals is a must for detection of silent hypoxia and to initiate supportive therapy at earliest possibility.

Treatment

No full-poof definitive but supportive therapy available at present.

Aggressive isolation measures aimed at reducing transmission in the community is our best weapon.

The followings had been tried with mixed results:

- *Hydroxychloroquine (HCQ):* Antimalarial with in-vitro activity against SARS-CoV-2 and may have immunomodulating properties. WHO recommends for prophylaxis but not for therapy (directive on 25/05/2020).
- *Azithromycin:* Shows anti-SARS-CoV-2 activity in vitro.
- *Anti-influenza agent (Favipiravir, Oseltamivir) and broad-spectrum antiviral (Remdesivir), anti-HIV agent (Lopinavir/Rtonavir):* Showing varying degree of activity against corona viruses in vitro.
- *Convalescent plasma:* Tried in severe or immediately life-threatening COVID-19 infections with favorable result in some studies.
- *HFNO (High flow nasal oxygen):* HFNO in awake prone position is considered to be win-win position to avoid invasive ventilator in some patients of declining SpO_2.
- *Other therapies:* Anticoagulant (LMWH), Anti IL6 receptor inhibitor (Tocilizumab), Invasive Ventilator, ECMO (extra-corporeal membrane oxygenation) are other therapeutic options in some specific patients.

Case fatality: Differs in different countries. In India, till August 2020 overall mortality was ~1.56.

Mortality increases significantly in:
- Patients >65 years
- Patients with comorbidities (DM, renal failure, COPD, on chemotherapy, etc.)
- Patients needing ventilatory support

Zika Virus

Zika virus disease is caused by the Flavivirus, the same family of virus causing dengue. Several Zika virus outbreaks were found in both North & South America since 2015, but it has emerged in India just with only three (3) confirmed cases in 2017—as per report of Ministry of Health & Family Welfare, Govt. of India. All these three cases were reported from Bapunagar, Gujarat.

- *Transmission:*
  - Mainly by bite of infected Aedes mosquito.
  - Sexual activity and blood transfusion can sometimes lead to this disease transmission.[21]
- *Clinical features:* Majority (80%) are asymptomatic, 20% of cases have low grade fever, myalgia, rash, and sore throat.
- Concern lies if pregnant women contract this disease in first trimester, which may lead to microcephaly and brain abnormalities of infant.[22]

Diphtheria

We all know that exotoxin-producing *Corynebacterium diphtheria is the causative agent. Its incidence has reduced to a great extent globally* due to successful implementation of childhood vaccination. *From 1 million* before 1980s to 1 lakh in 1980 and reduced to 4.5 thousand in 2015. Diphtheria is a rare disease in developed countries but global burden contributed mainly by sub-Saharan Africa, India, and Indonesia.[23]

In 15 years tenure (during 2001–2015) almost half of the global diphtheria cases were from India, and CBHI (Central Bureau of Health Intelligence) India reported 41,672 cases of Diphtheria in 10 years (2005–2014) with mortality of 2.2% cases.

Diphtheria is now considered EID as it shifts toward higher median age than its earlier preference for under five children. It could be related to lack of 100% coverage of three doses of diphtheria vaccination (80% coverage) and expected low coverage of booster dose after 10 years. This may lead to waning immunity against diphtheria among school-going children and adults.[24] Some Indian study showed higher prevalence among muslim children and it was about 38% in Delhi as stated in a study.[24]

Plague

We doctors now bear a wrong impression that plague is almost nonexistent in India and not getting proper emphasis in medical undergraduate and postgraduate teaching. So doctors are not properly aware of its consideration in differential diagnoses.

Plague infection in India continues to exist as enzootic in wild rodents and epizootic spread of plague from wild to commensal rodents facilitate human transmission. Thus, it leads to re-emergence/outbreaks of plague in India in 2002 (Shimla, HP) and 2004 (Uttarakhand) of this millennium.[25,26]

Causative Agent and Transmission in Humans

Plague is a *zoonoses* (wild rodents) and caused by Gram-negative bacilli, *Yersinia pestis*, spreading between rodents through their fleas.

Ways of transmission to man:
- By bite of infected fleas
- Coming in contact with infected tissues of rodent
- Human to human transmission through droplets in pneumonic plague

Conclusion

This has been proved beyond doubt that significant percentage of infectious diseases are zoonotic in origin. In last three decades thirty (30) emerging infectious diseases detected globally, majority of them are viral in origin and approximately 60% of them are zoonotic especially wildlife in origin. In India zoonotic diseases are more likely as here domestic/pet animals are kept in close proximity to their residence.

Through awareness and/or legislation if we can make human contact with animals (domestic/wild) scientifically modified or restricted (in some situations) emerging and re-emerging diseases could be avoided globally to a great extent.

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Section 13

Section Editor: **BB Rewari**

Human Immunodeficiency Virus

CHAPTER

181 Human Immunodeficiency Virus-Tuberculosis Coinfection: Challenges

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Abstract

Human immunodeficiency virus (HIV)-tuberculosis (TB) coinfection is a growing concern, both nationally and Internationally. TB-related complications accounts for >25% of deaths in people living with HIV (PLHIV). Delay in diagnosis of HIV-TB coinfection could lead to emergence of MDR/XDR TB. Manifestations depend on the stage of disease and can have varied presentation. There has been significant progress made in both diagnosis and treatment of the condition. Knowledge of drug interactions, overlapping drug toxicities, as well as timing of initiation of ART following ATT administration is important. Proper ART and ATT therapy selection and dose adjustment are imperative.

Introduction

Human immunodeficiency virus (HIV)-tuberculosis (TB) coinfection is global health problem, and continues to pose challenges. World Health Organization (WHO) in 2018 estimated that, almost 8,62,000 people living with HIV (PLHIV) were coinfected with TB worldwide.[1] TB is one of the leading causes of death, among patients with HIV, and accounts for almost one-third of the deaths.[1] PLHIV are 19 times more likely to develop tuberculosis, than those without HIV. A vast majority of death (84%) due to HIV-TB coinfection were reported from Africa. Delay in diagnosis of HIV-TB coinfection can lead to emergence of MDR/XDR TB. TB continues to be a top killer among infectious diseases, with WHO report estimating that about 1.5 million people died of tuberculosis alone in 2018, including the 2,51,000 people with HIV-TB coinfection. The worldwide incidence[1] for TB for 2018 was estimated to be 10 million, amongst which only 7 million have access to antituberculosis therapy (ATT) (R1), and about 0.5 million people developed drug resistant TB. The prevalence for HIV[1] at the end of 2018 was 37.9 million, amongst which 23.3 million (62%) patients received antiretroviral treatment (ART), and 0.77 million died from HIV-related illnesses. The number of patients receiving ART increased to 24.5 million, by June 2019. TB is among the most common illnesses, among PLHIV, and is fatal, if undertreated/untreated. So early detection of TB and prompt linkage to ATT and ART can prevent or delay these deaths.

Presentation and Diagnosis of HIV

The clinical manifestation depends upon staging of HIV disease, and presence of opportunistic infections (OIs). Presentation can range from being asymptomatic, to experiencing fever, headache, rash, or sore throat. As the immune system gradually weakens, patients may develop cough, diarrhea, weight loss, or generalized lymphadenopathy. If treatment is delayed, patients can develop severe illness like tuberculosis, cryptococcal meningitis, bacterial pneumonia, pneumocystis jiroveci pneumonia, kaposi's sarcoma, and lymphoma.

Diagnosis of HIV infection: Diagnosis of HIV infection is based on following tests:

- HIV-ELISA (Enzyme-linked immunosorbent assay)—It is 50% sensitive after 22 days of HIV infection and 95% positive within 6 weeks. Sensitivity is 99.9%.
- Western Blot Test—It is confirmatory test for HIV. It is highly specific test and is based on antibody to core protein (p24) and envelope glycoprotein (gp41).
- HIV Rapid Antibody Test—It provides result within 16–20 minutes, easy to perform and is a screening test.
- Absolute CD4 Lymphocyte Count—It is predictor of HIV progression, so risk of progression to AIDS, OI, or malignancy is high with CD4 < 200 cell/μL.
- CD4 Lymphocyte Percentage—It is more reliable than CD4 Count. If less than 14%, risk of progression to AIDS to OI or malignancy is high in absence of treatment.
- HIV Viral Load—It indicates the amount of active replication of HIV, indicating disease progression and response to antiretroviral drugs.
- P24 Antigen—It indicates replication and is positive even before seroconversion.

Antiretroviral Therapy

Usually three drugs from two different groups of ARV drugs are given **(Tables 1 and 2)**.

Presentation and Diagnosis Tuberculosis

Tuberculosis is caused by infection with mycobacterium tuberculosis. The infection may be active TB or latent tuberculosis infection (LTBI). Active TB may be pulmonary TB or extra pulmonary TB. LTBI is presence of mycobacterium tuberculosis organism without symptoms or radiographic evidence of TB disease.

Diagnosis of TB in HIV-infected Persons

Screening of TB should be done using clinical algorithm, that is, cough, fever, weight loss, or night sweats and should be evaluated for TB.

- *Radiological findings:* It may show diffuse micronodular infiltrations, as in miliary tuberculosis, or show

TABLE 1 NACO (National AIDS Control Organization) recommended first-line ART regimen

ART regimen	*Recommended*
Tenofovir + Lamivudine + Efavirenz	First-line ART regimen for all ARV naïve PLHIV patients with HIV-1 infection, age >10 years and body weight >30 kg
Abacavir + Lamivudine + Efavirenz	First-line ARV regimen for all patient with abnormal serum creatinine. All adults and adolescents with body weight <30 kg
Tenofovir + Lamivudine + Lopinavir/ritonavir	First-line ART regimen for all women with single dose NVP exposure in past pregnancy, all confirmed HIV-2 or HIV-1 and HIV-2 coinfection
Zidovudine + Lamivudine + Nevirapine Zidovudine + Lamivudine + Efavirenz	All patients who are on either of these first-line regimens initiated earlier, need to be continued on same regimen unless failing

TABLE 2 WHO 2018 recommended first-line antiretroviral therapy regimen

Population	*Preferred*	*Alternatives*	*Special situations*
Adult men and adolescent boys	TDL	TLE600 TLE400	AZT + 3TC + EFV600 TDF + 3TC (or FTC) + PI/r
Pregnant (>8 weeks) and breast feeding women and adolescent girls			
Women and adolescent girls with effective contraceptive or not of childbearing potential			
Women and adolescent girls of childbearing potential who want to become pregnant and have no effective contraception	TLE600	TLE400 TDF + 3TC (or FTC) + PI/r	AZT + 3TC + EFV600 TDF + 3TC (or FTC) + RAL

TDL = TDF + 3TC + DTG, TLE = TDF + 3TC (or FTC) + EFV
TDF, Tenofovir; 3TC, Lamivudine; DTG, Dolutegravir; FTC, Emtricitabine; EFV, Efavirenz; PI/r, Protease inhibitors/ritonavir; AZT, Zidovudine; RAL, Raltegravir

pleural effusion, pericardial effusion, or tuberculous pulmonary lesions.

- *Sputum smear microscopy:* It is easy to perform and is inexpensive. There is direct microscopic examination of sputum for AFB (acid fast bacilli) after Ziehl-Neelsen staining.
- *Sputum culture:* Culture of sputum or other samples is the corner stone in definitive diagnosis of tuberculosis. Culture can be done in egg-based solid medium such as Lowenstein-Jensen or Agar based Middlebrook medium. These are sensitive but slow as it may take 6–8 weeks of incubation. It may also be cultured in liquid medium detecting growth of mycobacteria in 1–2 weeks time using carbon dioxide production or O_2 consumption with radiometric sensors = BACTEC 460, florescent sensors = BACTEC MGIT 960, calorimetric sensors = MB/BacT system, pressure sensors = ESP culture system, or Redox Reagent, such as Alamar blue.
- *Molecular assays:* Xpert MTB/RIF is diagnostic method of choice in HIV positive people. Its sensitivity in positive smear patient is 98.2% and in patients with sputum smear negative is 68%. It is more than 99% specific. It is done by nucleic acid amplification method (NAAT, real time polymerase chain reaction = RT-PCR). It detects mycobacterium tuberculosis quickly (<2 hours). In TB/HIV coinfection, its sensitivity is 79%. Some of the modified versions of NAAT are:
  - LAMP—Loop Mediated Isothermal Amplification.
  - FISH—Fluorescence In Situ Hybridization.
  - LPAs—Line Probe Assays. LPA is more than 75% sensitive and 100% specific. It detects MTB.
  - Gene Xpert/RIF—It is cartridge-based nucleic acid amplification assay, is TB specific, and detects RIF resistance with 99.1% sensitivity and exclude resistance by 100% specificity.[2,3]
- *Serological tests:*
  - Antibody detections—There is negative recommendations by WHO.
  - Antigen detection by ELISA-based assay—LAM—Lipoarabinomannan assay in urine is better in HIV infected than HIV uninfected HIV patients.
- *Other tests:* IGRA—Interferon gamma release assay. This is useful in diagnosing latent TB.
- *Quantiferon:* TB Gold Test—It is in vitro test for detecting latent TB.

TABLE 3 Antituberculous treatment schedule

Type of TB case	*Treatment regimen*
New: A TB patient who has never had treatment with anti TB drugs or has taken it for <1 month	2H7R7Z7E7 + 4H7R7E7
Previously treated: A TB patient who has received 1 month or more of any TB drugs in the past	2H7R7Z7E7S7 + 1H7R7Z7E7 + 5H7R7E7

E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide

Treatment of TB

All PLHIV diagnosed with TB should be started with antituberculous treatment **(Table 3)**.

Challenges in HIV-TB Coinfection

In management of HIV-TB coinfection, the main challenges are:

- Timing of initiation of antiretroviral treatment.
- Immune reconstitution inflammatory syndrome (IRIS).
- Drug interaction in patient on antiretroviral therapy.
- Overlapping drug toxicity.

Timing of Initiation of Antiretroviral Treatment

A number of trials have shown that providing early ART to HIV-TB coinfected persons during antituberculosis treatment reduces mortality.[4] It is now recommended by Health and Human Services and Infections Disease Society of America, that ART should be started 2 weeks after initiation of antituberculosis treatment in most patients, with CD4 count less than 50 cells/mm^3. For those with CD4 count more than 50 cells/mm^3 ART should be started after 2–8 weeks time. It is reasonable to give ATT for 6 months duration; however, some guidelines favor 9 months rifamycin based therapy.

Immune Reconstitution Inflammatory Syndrome

It is an inflammatory reaction, following the initiation of effective ART, due to improvement in immune system of HIV patient, leading to paradoxical worsening of symptoms and signs, of untreated or partially treated OIs

or neoplasm (paradoxical IRIS) and undiagnosed cases (unmasking IRIS). Signs and symptom may appear 2–12 weeks after initiation of ART, and is most commonly seen, when ART is started with CD4 count less than 50/mm^3, and close to diagnosis of OI. IRIS occurs in 10% of all cases put on ART, and 25% of those who have CD4 lymphocyte count less than 50/mm^3. It manifests as fever, increase in size of lymph glands, and pulmonary infiltrates. Severe cases may be fatal. It is treated by antimicrobials for OI, corticosteroids, and continuation of ART.[5]

Drug Interactions in Patients on Antiretroviral Therapy

Rifampicin induces Cytochrome P450, and leads to increased metabolism of HIV drugs, resulting in its decreased concentration in serum, to subtherapeutic levels, that may lead to HIV treatment failure and antiretroviral drug resistance.

- *Rifampicin and NNRTIs:* Drug interaction between rifampicin and NNRTIs are important, because first line ART includes NRTIs with NNRTIs like Efavirenz or Nevirapine. Multiple cohort studies and randomized controlled trial have shown that standard adult dose of efavirenz (600 mg/day) with two NRTIs is well tolerated and highly efficacious in achieving complete viral suppression along with rifampicin-based antituberculous treatment.[6,7] Efavirenz should not be used in first trimester of pregnancy, those intolerant to efavirenz or NNRTIs, resistant strains of HIV, or children less than 3 years of age.
- *Rifampicin and Nevirapine:* Rifampicin reduces serum concentration of nevirapine by 20–55%.[8] In India in a randomized trial nevirapine 200 mg/day for 2 weeks than 200 mg/bd or efavirenz 600 mg/day with rifampicin based ATT, those on nevirapine showed more virological failure and severe toxicity.[9] So efavirenz is more effective, and less toxic than nevirapine for HIV-TB coinfection.
- *Rifampicin and Protease inhibitors:* It has been found that when protease inhibitor based ART is given with rifampicin in HIV-TB coinfected persons, concentration of protease inhibitor may be diminished by more than 90%.[10] Studies have shown adequate serum concentration of PI can be achieved by super boosting (standard those of PI + higher dose of ritonavir), or doubling the dose (doubling dose of both PI and ritonavir), that is, 400 mg/100 mg twice daily to 800 mg/200 mg twice daily (double dose), along with rifampicin 600 mg/day, but there is possibility of increased risk hepatotoxicity with the regimen.
- *Rifampicin and Triple nucleos(t)ide:* Because of lack of evaluation nucleosides or nucleotides alone are not recommended for treatment of HIV-TB coinfection.
- *Rifampicin and Integrase inhibitors:* Raltegravir when used with rifampicin, it is recommended to double the dose of raltegravir to 800 mg twice daily, because concentration of raltagravir is reduced by almost 55%. Dose of the dolutegravir should also be doubled, that is, 50 mg bd when used with rifampicin.
- *Rifampicin and CCR5 receptor antagonists:* Increased dose of maraviroc is recommended when used with rifampicin.

TABLE 4 Drug interactions between ATT and ART

ATT drugs	*ART drugs*	*Drug interaction*	*Action to be taken*
Rifampicin	NRTIs	No	Given in usual dose
	NNRTIs	Yes	Aviod nevirapine. Use efavirenz in usual dose
	Booted PI	Yes	Replace rifampicin with rifabutin (150 mg od)
	Integrase inhibitors	Yes	Double dose of integrase inhibitor Dolutegravir 50 mg bd Raltegravir 800 mg bd

NACO guideline: NRTIs, nucleos(t)ide reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor

TABLE 5 Overlapping adverse reactions of ATT and ART

ATT	*ART*	*Adverse reactions*
RIF/INH/PZA	NEV/EFV	Rashes
PZA/ETB	ZDV/TDF/PIs/DTG	GIT intolerance
RIF/PZA	TDF/EFV/PIs	Hepatitis
INH/RIF/LZD	ZDV	Anemia
INH/CYS	EFV/DTG	CNS toxicity
STM/KANA/Capreomycin	TDF	Renal dysfunction

NACO: CYS, cycloserine; DTG, dolutegravir; ETB, ethambutol; INH, isoniazid; LZD, linezolid; PZA, pyrazinamide; RIF, rifampicin

- *Rifabutin and Protease inhibitors:* Rifabutin has less effect in comparison to rifampicin on metabolism of drugs mediated by cytochrome P450 3a enzyme.[11] Rifabutin 150 mg daily (instead of 300 mg/day) is recommended when used with ritonavir boosted lopinavir (as ritonavir also influences CYP3a metabolizing enzyme, so increases concentration of rifabutin leading to rifabutin toxicity-uveitis).
- Rifampicin, if used with nevirapine, causes concentration of nevirapine to reduce, so rifabutin should be preferred instead of rifampicin.
- Efavirenz reduces the concentration of rifabutin, so rifampicin should be preferred ATT with efavirenz.

Latent TB Treatment

LTBI should be treated in cases of HIV coinfection. INH 300 mg daily for 9 months or Rifampicin 600 mg/day for 4 months, as per recommendations. No dose adjustment of ART is needed when INH is used **(Tables 4 and 5)**.

ATT and antiretrovirals produce several overlapping toxicities, so treating clinicians should monitor for these overlapping adverse reactions.

Conclusion

HIV-TB coinfection is a curable but potentially lethal combination. Timely diagnosis and early institution of treatment in HIV-TB coinfection reduces morbidity and mortality. Both HIV and TB have the potential to exacerbate and worsen each other. ATT in proper dose along with ART is corner stone of the treatment. HIV-TB coinfection poses many challenges because of management of both diseases, and is complicated by drug interactions between ATT and ART, risk of IRIS, and overlapping drug toxicity. So ATT should be started immediately and ART should be initiated as soon as the ATT is tolerated (2–8 weeks). Proper selection and dose adjustment of both antiretroviral drugs and antituberculous drugs for HIV-TB coinfected patients are important components of patient management.

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CHAPTER

182 Advanced HIV Disease: Prioritizing the Most Vulnerable among PLHIV

S Anuradha

Abstract

Although the mortality among PLHIV has shown a significant reduction with effective ART, the decline in the number of deaths has plateaued during the past few years. This is due to the persistent burden of HIV associated mortality and morbidity in a significant section of PLHIV who still present to health-care systems with "advanced HIV disease (AHD)." It has been estimated recently that nearly 30–40% PLHIV initiating ART in resource limited countries have CD4 cell count <200 cells/mm and almost 20% have CD4 <100 cells/mm. The risk of death among PLHIV with AHD is high. This risk increases with declining CD4 cell counts, particularly with CD4 <100 cells/mm. AHD also contributes to increased health-care expenditure. Hence, it is important to identify PLHIV with advanced disease early and deliver a specialized package of interventions that will prevent the morbidity and mortality.

Introduction

It is estimated that 37.9 million people globally had Human Immunodeficiency Virus (HIV) infection in 2018 and new HIV infections had decreased to 1.7 million. Out of these, 24.5 million people living with HIV (PLHIV) received Antiretroviral Treatment (ART). In India, there are 2.1 million PLHIV of which 88,000 are newly infected and 1.18 million are receiving ART (56% coverage).

The number of PLHIV dying annually from AIDS-related causes has diminished by 48% in 2018 from 2003.[1] This decline in mortality is chiefly due to increased access to ART and early initiation of ART according to the World Health Organization (WHO) 2016 guidelines on "universal use of ART," recommending "life-long ART to all children, adolescents and adults including all pregnant and breast feeding women living with HIV regardless of CD4 count or clinical stage." However, the decline in the number of deaths has plateaued during the past few years. This is due to the persistent burden of HIV associated mortality and morbidity in a significant section of PLHIV who still present to health-care systems with "advanced HIV disease (AHD)."

Advanced HIV Disease

After the WHO recommended "universal ART for all PLHIV irrespective of clinical or immune status," national programs of most countries have implemented it. Earlier initiation of ART, along with enhanced availability of HIV testing, has resulted in a betterment in overall condition at ART initiation,[2] as evidenced by an increase in the average CD4 cell count globally at the commencement of treatment.[3]

Notwithstanding this improvement, nearly half of PLHIV present with AHD to health-care systems. The WHO has developed a consensus definition for PLHIV with advanced disease at entry to the health system and those patients who are "stable on ART."[4]

According to WHO guidelines for management of AHD, July 2017,[5] advanced HIV disease is defined as—

- "having a CD4 cell count less than 200 cells/mm^3 *or*
- A WHO clinical stage 3 or 4 event
- Any child younger than age 5 years with HIV is considered to have advanced HIV disease"

The risk of death among PLHIV with AHD is high. This risk increases with declining CD4 cell counts, particularly with CD4 <100 cells/mm^3 [6-8] AHD also contributes to increased health care expenditure.[9]

Erstwhile the distinct definition of AHD, there was lack of clarity and confusion regarding the designation of the term. The term "late presenters" was used often. The patients with CD4 count <350 cells/mm^3 at presentation or those with an AIDSdefining illness (irrespective of CD4 count) were considered to be late presenters of HIV, as per the European Late Presenter Consensus definition.[10] Varying cut offs of CD4 counts <200/mm^3 or <100 /mm^3 have been used to classify PLHIV presenting late. The WHO definition has helped evolve a uniform standard definition that makes analysis and comparisons easier.

Prevalence of AHD and Risk Factors Associated with It

It has been estimated recently that nearly 30–40% PLHIV initiating ART in resource limited countries have CD4 cell count <200 cells/mm^3 and almost 20% have CD4 <100 cells/mm^3.[11,12] In some reports almost half of all PLHIV have AHD.[13]

The International epidemiology Databases to Evaluate AIDS (IeDEA), along with Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) examined the CD4 cell counts of PLHIV at start of ART globally.[11] This evaluation included nearly 1 million PLHIV across North America, South America, Asia-Pacific, Sub-Saharan Africa, and Europe. Countries were classified as per the World Bank classification in 2015 as low income countries (LICs), lower middle income countries (LMICs), upper middle income countries (UMICs), and high income countries (HICs). *Overall, the median CD4 count at presentation improved across the globe*: from 78 cells/mm^3 in 2002 to 287 cells/mm^3 in 2015 in LICs, from 99 cells/mm^3 to 234 cells/mm^3 in LMICs, from 71 cells/mm^3 to 311 cells/mm^3 in UMICs, and from 161 cells/mm^3 to 327 cells/mm^3 in HICs. Although the median CD4 cell count increased significantly across all groups of countries, it continued to remain below 350. The increases in LICs and UMICs were more than that in LMICs or HICs. This increase was more noticeable in women compared to men, except in the HICs.

The proportion of people starting ART with AHD in Africa is about 55%, varying from 31% in Swaziland to almost 77% in Senegal. A study from four high burden countries in Sub-Saharan Africa Cameroon, Mozambique, Uganda, and Zimbabwe demonstrated that the fraction of PLHIV presenting with AHD persisted to be steady: 19.4% in 2012 to 16.1% in 2016. It ranged from 14.5% within Uganda to 29.8% in Cameroon.

A nationwide longitudinal cohort in the Netherlands by Eline LM et al., revealed that among the HIV patients registered into care between 1996 and 2014, 53% presented late and 35% had advanced HIV disease. Among late presenters and advanced disease, the median CD4 was 150 cells/mm^3 and 80 cells/mm^3 respectively. Late presentation was more commonly associated with being a heterosexual male (OR-1.59), injecting drug use (OR 2.0), age ≥50 years, region of origin, and location of HIV diagnosis.[14]

A cross sectional study from South-Western China by Xi Hu et al, including 46000 newly diagnosed PLHIV from 2012-2016 demonstrated 70% PLHIV were late presenters while 45.1% presented with advanced HIV disease. Higher prevalence of AHD was found among male gender, heterosexuals, older age-group, lower education, and divorced/widowed persons.[15]

Data on the precise prevalence of AHD is lacking from India. A single center study from Delhi has reported that 83.7% of PLHIV were late presenters while 33% of PLHIV had AHD with 9.5% having CD4 cell count below 50 cells/mm^3 at presentation. The median CD4 cell count was determined to be 242 cells/mm^3.[16]

This emphasizes that late presentation among PLHIV remains a major challenge all over the world.

Impact of AHD on Mortality and Morbidity

PLHIV who have AHD are prone to greater risk of mortality and morbidity due to multiple factors such as lower CD4 response after ART, increased risk of OIs and their complications, polypharmacy, non-adherence, and suboptimal virological suppression.

Morbidity and mortality are even higher in initial 3 months particularly in first 4–8 weeks. In a meta-analysis

by Alana T. Brennan et al. to determine early mortality in lower- and middle-income countries of Sub-Saharan Africa, Asia, and Caribbean it was revealed that early mortality was 6% (5.5–6.3%). When mortality estimate was calculated assuming that PLHIV who were lost to follow-up had died, the overall estimate increased to 10%.[17]

A study from Uganda and Zimbabwe by Walker AS et al. to assess mortality during first year of ART demonstrated that 5.4% PLHIV died, with half of the deaths reported in the initial 3 months. Mortality risk was highest between 30–50 days and, it reduced rapidly thereafter till about day 180. Further, it continued to decline slowly over time. One-year mortality in PLHIV was: 9.4% in CD4 <50 cells/mm^3, 4.5% in CD4 between 50–99 cells/mm^3 and 2.9% in CD4 >100 cells/mm^3.[8]

Tuberculosis, severe bacterial infections, chronic diarrhea, cryptococcal meningitis, cerebral toxoplasmosis, *Pneumocystis jiroveci* pneumonia, and anemia were the chief causes of mortality in adult PLHIV with AHD. Among children, tuberculosis, severe bacterial infections, pneumonia, diarrheal diseases, malnutrition, and wasting are the leading causes of death.[8,18,19]

A landmark study, REALITY, was conducted across Zimbabwe, Uganda, Malawi, and Kenya in ART naïve PLHIV with CD4 <100 cells/mm^3. It was found that mortality rates were highest during first 4 weeks of starting ART, decreasing through week 8 and substantially dropping further through 24 and 48 weeks. The leading causes of death were opportunistic infections: tuberculosis cryptococcal meningitis, severe bacterial infections, and immune reconstitution inflammatory syndrome (IRIS). This study also highlighted that patients with the greatest risk of dying had a high burden of symptoms, weight loss, lower CD4 count, low albumin and hemoglobin levels.[20]

Another crucial observation was that loss to follow-up is more likely among those with AHD. This increases the risk of mortality in these patients and adds to the threat of transmission of HIV.

With such life-threatening events and adverse outcomes, patients with advanced disease remain the most vulnerable among the PLHIV. It is imperative that these patients be brought into the health-care systems early. It is also crucial to initiate ART at the earliest in these patients, even on the same day as presentation. This will prevent missed opportunities for initiating treatment.

It is due to these concerns that the WHO recognized that the people with AHD are a specially vulnerable group who need a specific and specialized package of interventions for them.

Package of Interventions for PLHIV with AHD

In July 2017, the WHO released comprehensive guidelines for the management of AHD and rapid initiation of ART. The guidelines provide suggestions for a public-health-approach for managing PLHIV with AHD including timing of ART initiation.[5]

The "package of interventions" recommended include the:

- Co-trimoxazole prophylaxis,
- Tuberculosis preventive treatment,
- Use of Xpert MTB/RIF for tuberculosis diagnosis among symptomatic PLHIV,
- Using the lateral flow lipoarabinomannan (LF-LAM) antigen test for people with symptoms suggesting TB with CD4 count ≤100 cells/mm^3 or who are seriously ill,
- Cryptococcal antigen screening in all with CD4 cell count ≤100 and pre-emptive antifungal treatment for those with positive blood cryptococcal antigen.[2]

This is summarized in **Table 1**.

Two large randomized trials instituting packaged interventions among PLHIV presenting with AHD were done. The first one named REMSTART, was conducted in Zambia and the United Republic of Tanzania, and compared ART-naive PLHIV with CD4 count <200 cells/mm^3 receiving a specialized package of care versus standard care. ART initiation was done around 2 weeks (delayed beyond 2 weeks only in those with TB). A 28% reduction in mortality and a trend toward better adherence was observed in the intervention group compared to the group receiving standard care at 6 months.[21]

In the second trial, REALITY, PLHIV with CD4 <100 cells/mm^3 were enrolled from Kenya, Malawi, Uganda, and Zimbabwe. Study subjects were randomized to receive either the standard care (as per existing respective national guidelines) or an enhanced prophylaxis package of 12 weeks of fluconazole (100 mg once daily), 12 weeks fixed-dose combination of co-trimoxazole (800 + 160 mg) + isoniazid (300 mg) + pyridoxine (25 mg), 5 days of 500 mg of azithromycin once daily and albendazole (400 mg single dose). ART was started simultaneously with all drugs. In the enhanced prophylaxis package arm, there was a

TABLE 1 Diagnosis and prophylaxis components of package of care interventions for advanced HIV disease (WHO)[5]

Areas for the package	*Intervention*	*CD4 cell count*	*Adults and adolescents*	*Children*
Screening and diagnosis	Sputum Xpert MTB/RIF as first test for TB diagnosis in symptomatic patients	Any	Yes	Yes
	Urine LF-LAM* for TB diagnosis in patients with symptoms and signs of TB	≤100 cells/mm^3 Or at any CD4 cell count value if seriously ill	Yes	Yes**
	Cryptococcal antigen (CrAg) screening***	≤100 cells/mm^3 ****	Yes	No
		≤200 cells/mm^3****	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis	≤350 cells/mm^3 or WHO clinical stage 3 or 4 event. Any CD4 cell count value in settings with high prevalence of malaria and/or severe bacterial infections	Yes	Yes
	TB preventive treatment[§#]	Any	Yes	Yes
	Fluconazole pre-emptive therapy for CrAg-positive patients without evidence of meningitis	≤200 cells/mm^3****	Yes	Not applicable (Screening not advised)
ART initiation	Rapid ART initiation	Any	Yes	Yes
	Defer ART initiation if clinical signs and symptoms are suggestive of TB or cryptococcal meningitis	Any	Yes	Yes
Adapted adherence support	Tailored counseling to ensure optimal adherence to advance disease care package, including home visits if feasible	<200 cells/mm^3	Yes	Yes

*Urine LF-LAM: lateral flow urine lipoarabinomannan assay.
**Limited data for children.
**CrAg screening and pre-emptive therapy is strongly recommended at CD4 <100 cells/mm^3 and conditionally recommended at CD4 <200 cells/mm^3.
****When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 cell count <100 cells/mm^3 (strong recommendation; moderate-certainty evidence) and may be considered at a higher CD4 cell count threshold of < 200 cells/mm^3 (conditional recommendation; moderate-certainty evidence).
[§]Co-trimoxazole, isoniazid, and pyridoxine are now available as a fixed-dose combination tablet.
[#] For children <12 months of age, only those with a history of TB contact should receive TB preventive treatment, if the evaluation shows no active TB disease.

reduction in mortality by 27% over 24 weeks. Mortality due cryptococcus infections significantly decreased (1.5% to 0.4%), and mortality due undetermined causes decreased from 6.0% to 3.8%. The incidence of OI also reduced: TB by 28%, cryptococcal meningitis 62%, and admissions to hospitals by 17%. Majority of deaths occurred within the initial 3 weeks of the study, emphasizing the need for early prophylaxis among PLHIV with AHD.[22]

Both these large studies in patients with advanced HIV disease have demonstrated the benefits of delivering a specialized and specific package of interventions to this extremely vulnerable subset of PLHIV.

Conclusion

The world has committed toward ending AIDS as a significant public health problem by 2030. However, without rapid escalation of services, the HIV epidemic will outrun the global response. To prevent this, The UNAIDS Fast-Track strategy sets out 90-90-90 targets for prevention and treatment. This includes, reducing new annual HIV infections to fewer than 500,000 by 2020 and to fewer than 200,000 by 2030, and AIDS related deaths by 90% by 2030, in comparison to 2010 levels.

Hence, it is necessary to identify PLHIV with advanced disease and deliver a package of interventions consisting of screening, prophylaxis and treatment of OIs, early ART initiation and enhanced adherence support. This will mitigate the high, early mortality seen in advanced HIV disease and also reduce the AIDS-related mortality rate overall. At the same time this will reduce the health-care costs and reduce community transmission. It requires an effort and commitment on part of programs and governments to develop strategies for advanced HIV care in their own country's context. The National AIDS Control Organization of the Govt. of India is also developing a specialized package of interventions to be delivered to this population. These are the most vulnerable among the PLHIV. Additional and special support to this population will have far reaching implications for the country and the world.

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CHAPTER

183 Antiretroviral Therapy in 2020

BB Rewari, Priyanka Ojha

Abstract

ART has changed the outlook of HIV from a virtual death sentence to a chronic manageable disease. The current guidelines are to provide ART initiation to all those infected with HIV regardless of their CD count of WHO clinical stage. The standard of care is a triple drug combination (Tenofovir +Lamivudine+ Dolutegravir) in a single pill once daily and is a lifelong therapy. Adherence to therapy is most crucial for good outcomes of therapy and to reduce chances of resistance, hence patient counseling is an important component of HIV care. Availability of high-quality generic drugs helped increase the coverage of ART significantly, thereby reducing the chances of transmission from those with HIV. Besides ART, antiretroviral drugs are also used for post exposure prophylaxis (PEP) after accidental exposure and pre-exposure prophylaxis (PrEP) for those at high risk of HIV.

Introduction

Antiretroviral therapy (ART) is seen as a panacea for People Living with HIV (PLHIV) and has helped save millions of lives in addition to improving quality of life. In addition, this has saved many countries from catastrophic economic consequences of the disease.

Zidovudine, being used for some malignancies, was the first drug shown to be effective against HIV in 1985. Soon it was felt that virus developed resistance quickly and drug becomes ineffective in less than a year with Zidovudine monotherapy. By 1995, many studies had demonstrated the clinical benefits of using a two-drug combination of Zidovudine or Stavudine in combination with Lamivudine. The year 1996 was a landmark in ART journey when results of using a triple drug combination using protease inhibitors were revealed at the International AIDS Society (IAS) conference in Vancouver. These drugs over the years have transformed lives of millions of people and have changed outlook of HIV from that of a virtual death sentence to a chronic manageable condition. The **Figure 1** shows the development of various antiretroviral (ARV) drugs over last three decades.

Besides treating those with HIV, ARV drugs are also used for preventing mother to child transmission of HIV (PMTCT), for preventing acquiring HIV infection in case of accidental exposure to the virus (post-exposure prophylaxis, PEP) and for preventing HIV infection in HIV negative individuals with substantial risk of being infected (pre-exposure prophylaxis, PrEP).

What are Options Available for ART

Highly Active Antiretroviral Therapy (HAART) or simply ART is a combination of three ARV drugs from different groups in a fixed dose combination (FDC). The “one pill a day” therapy has potential for good adherence as ART is a lifelong therapy. Production of generic formulations of these drugs have helped reduced its costs from USD 10,000 to less than USD 80 now making it affordable for most people. In addition, roll out of free ART program in countries have helped increase coverage of ART resulting

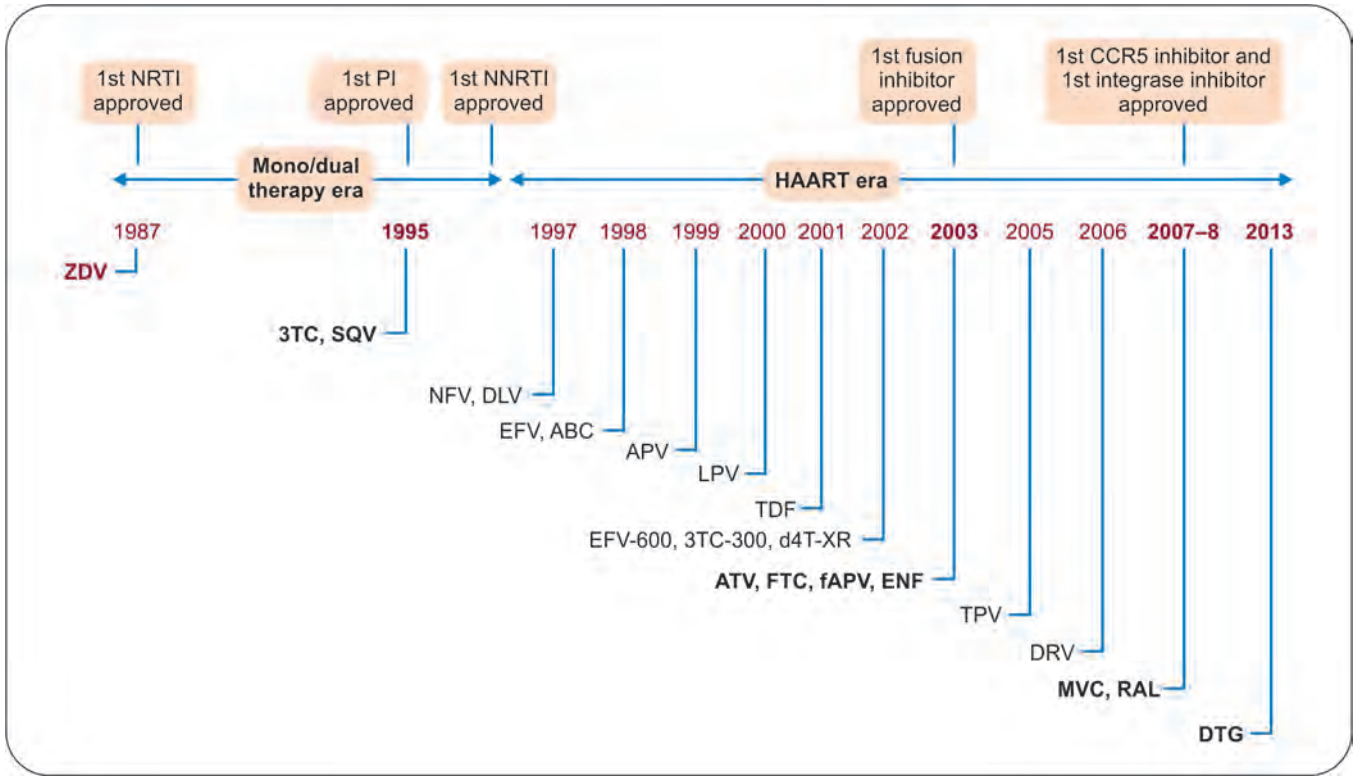

Fig. 1: Evolution of ARV therapy

in individual patient benefits, as well as, prevention of transmission of HIV due to reduction in viral load. Presently available ARV drugs cannot cure HIV as the virus remains dormant in resting states in some cells like spleen, brain, bone marrow, etc. It starts replicating again if the ART is stopped. Hence, ART is a lifelong therapy.

The ARV drugs broadly act at various steps in life cycle of virus either by blocking enzymes (reverse transcriptase, protease, integrase) needed for replication or by blocking entry of HIV into CD4 cells (Fusion inhibitors) or by blocking maturation of virions and their budding out from CD4 cells. Based on the site of action, these drugs are broadly divided into six classes **(Table 1)**. There are over 26 drugs/combinations. The drugs commonly used in India are listed in the following table.

The combinations of antiretroviral drugs inhibit the replication of HIV leading to slowing of disease progression, while reduced CD4 cell destruction leads to better immunity and fewer opportunistic infections. Over the years, the drugs have been evolving toward better efficacy, fewer toxicities, better pharmacokinetics, fewer drug-drug interactions, and lesser chances of resistance. This has led to optimization of ART, and WHO has released updated ART guidelines in July 2019.

When to Start ART is No Longer a Question or Discussion Point

In the early days when HAART was just being introduced, it was considered that a "hit hard, hit early" would be adopted. However, evidence that emerged in those years questioned the advantages of early HAART. Till about 3 years ago, treatment for HIV infected person was based largely on the CD4 count levels and clinical stage of the infection. The CD4 count cut-off point for ART initiation was less than 200 cells/cmm in 2004 and later moved to less than 350 cells/cmm in 2010. The cut-off was advanced to less than 500 cells/cmm in 2013 while in 2016, the recommendation came to TREAT ALL, regardless of clinical stage or CD4 count. The basis for these changes has been evolving evidence from various randomized clinical trials (RCTs) and large observational cohorts

TABLE 1 Classes of ARV drugs currently in use in India

Category	*Drugs*	
Nucleoside reverse transcriptase inhibitors (NsRTIs)	Zidovudine (AZT/ZDV)	Lamivudine (3TC)
	Abacavir (ABC)	Emtricitabine (FTC)
Nucleotide reverse transcriptase inhibitors (NtRTIs)	Tenofovir (TDF)	
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine (NVP)*	Efavirenz (EFV)
Protease inhibitors (PIs)	Lopinavir (LPV)	Ritonavir(RTV)
	Atazanavir (ATV)	Darunavir (DRV)
Integrase Inhibitors	Raltegravir (RGV)	Dolutegravir (DTG)
CCR5 entry inhibitor	Maraviroc**	

*Being phased out
**Used sometimes in private sector

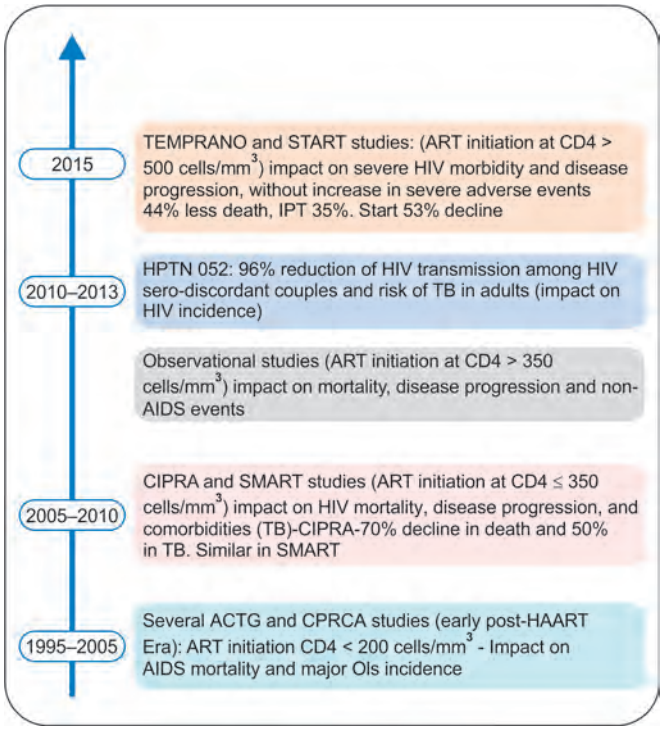

Fig. 2: Overview and timelines of "when to start ART" studies

which have revealed that with earlier ART initiation, there was a significant delay in progression to AIDS and reduction in incidence of TB. These studies are briefly summarized in **Figure 2**.

Hence, the current recommendation (since 2016) is to initiate ART for all those who present with HIV infection regardless of CD4 count or WHO clinical staging.

What is Latest WHO Recommendations on which Drugs to Start in ART

As described earlier, ART comprises of using at least three drugs from two different groups of ARV drugs in a combination, preferably in single pill, to improve adherence to therapy. The most commonly used combination is using two drugs from NRTI and one from NNRTI. So far most developing countries have been following a combination of Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + Efavirenz (EFV 600 mg) in a single pill, as standard of care. In 2018 ART update, WHO recommended use of Dolutegravir (DTG) in the first-line ART based on evidence that with DTG:

- Viral suppression is faster than with EFV (Avg. 4 weeks for DTG vs. 12 weeks for EFV),
- DTG has fewer side effects,
- Fewer drug-drug interaction, and
- Patients on DTG have a higher threshold for developing resistance.

The SINGLE study compared the efficacy and safety of DTG as compared to current standard of care (Tenofovir plus Lamivudine plus efavirenz). A total of 833 participants who had an HIV-1 RNA level of >1,000 copies/mL were chosen and randomly assigned to DTG-ABC-3TC group or EFV-TDF-FTC group. The key findings from study revealed that at week 48, the proportion of participants with an HIV-1 RNA level of <50 copies/mL was significantly higher in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (88% vs. 81%, P=0.003). It was also seen that DTG-ABC-3TC group had a shorter median time to viral suppression

than EFV-TDF-FTC group (28 vs. 84 days, P<0.001), as well as greater increases in CD4+ T-cell count (267 vs. 208/cubic mL, P<0.001). The proportion of participants who discontinued therapy owing to adverse events was lower in the DTG-ABC-3TC group than in the EFV-TDF-FTC group (2% vs. 10%).

The results from some other studies like FLAMINGO, SPRING2, and SAILING showed that DTG achieves viral suppression much faster than EFV (Avg. 4 weeks for DTG vs. 12 weeks for EFV). There are very few discontinuations on DTG regimen due to drug toxicity (<2%), less than with DRV/r and EFV. Main clinical adverse events seen are rash (2% vs. 13%) and neuropsychiatric events (including dizziness). These were significantly more with common with EFV (5% vs. 35%), while insomnia was reported more frequent in DTG (13% vs. 7%) (SINGLE study). DTG has a strong resistance barrier. No known treatment-emergent resistance were seen across trials. This was a very significant finding as it is well known that EFV has a very week genetic barrier to resistance.

Accordingly, the WHO guidelines on what to start were updated in 2018 to include DTG as preferred first-line drug along with Tenofovir and Lamivudine. However, an ongoing observational Tsepamo study in Botswana identified a signal of potential safety risk for developing neural tube defects among infants born to women who were taking DTG at conception. Interim analysis identified four neural tube defects out of 426 women taking DTG at the time of conception, for a rate of 0.9% (0.37–2.4%). So, 2018 guidelines specified that women and adolescents of child bearing potential who wants to become pregnant and have no effective contraception should not use DTG and continue to be provided an Efavirenz based regimen.

As new evidences from Tsepamo study became available it showed that the risk NTDs associated with use of DTG at the time of conception is less than originally signaled. The updated prevalence in the study has declined from 0.94% to 0.30%. The difference remains statistically significant compared to EFV, but the overall risk remains low. This new data presented in IAS 2020 (abstract #11299) includes 39,200 births surveyed from March 2019 to April 2020. Neural tube defects were identified in 0.19% of infants born to women on Dolutegravir at the time of conception and in 0.04% of infants born to women who started taking Dolutegravir during pregnancy. The risk-benefit models suggest that the benefits of DTG for women of childbearing potential (WCP) newly initiating ART are likely to outweigh the risks. According to WHO, the benefits of DTG outweigh the risks. Women of child-bearing age or potential should be provided informed choice about the benefits and risks for the use of DTG. DTG has been found to be in breast milk of women on DTG, resulting in significant plasma concentration in infants, and thus a potential important tool to reduce the mother-to-child transmission of HIV infection.

The ART guidelines released by WHO in July 2019 recommend that a *Fixed Dose Combination (FDC) of Tenofovir, Lamivudine (or Emtricitabine)* and *Dolutegravir (TLD)* should the *preferred first-line regimen* for all adults including women and upgraded the recommendation from "conditional" to a "strong" recommendation. It also recommended to adopt a woman-centered approach to health care should be taken that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women's autonomy in decision-making and provide information and options to enable women to make informed choices.

Tables 2 and 3 summarize the WHO 2019 ART guidelines.

In line with these guidelines, National AIDS Control Organization has also revised its ART guidelines on 17th September, 2020, and TLD based regimen is now the preferred regimen for ART initiation in new patients, DTG is also preferred for second-line ART for those failing on NNRTI and also to be used for PEP.

Initiating and Monitoring ART

Before starting ART, a full examination of person should be done to rule out any active opportunistic infection. He should undergo basic investigations like complete hemogram, routine biochemistry, CD4 count, and viral load (if available) as per guidelines. ART should not be started in the presence of an active OI. In general, OIs should be treated or stabilized before commencing ART. A proper counseling of person needs to be done highlighting the need for high levels of adherence to therapy and person must understand it is a lifelong therapy. A nutritional assessment and required supplementation are essential part of the counseling. A caregiver should be identified for each person to provide adequate support. Caregivers must be counseled and trained to support treatment adherence, follow-up visits, and shared decision-making.

TABLE 2 WHO ART initiation guidelines (July 2019)

2019 WHO guidance: preferred and alternative 1L regimens for adults and adolescents		
Preferred 1L regimen	***Alternative 1L regimen***	***Special circumstances***
TDF + 3TC (or FTC) + DTG[a]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b] AZT + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG[a] ABC + 3TC + DTG[a]

a. Effective contraception should be offered to adult women and adolescent girls of childbearing age or potential. DTG can be prescribed for adult women and adolescent girls of childbearing age or potential who wish to become pregnant or who are not otherwise using or accessing consistent and effective contraception if they have been fully informed of the potential increase in the risk of neural tube defects (at conception and until the end of the first trimester). If women identify pregnancy after the first trimester, DTG should be initiated or continued for the duration of the pregnancy.
b. bEFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher. DTG-based ART is preferred, and if DTG is unavailable, a boosted PI-based regimen should be used. The choice of PI/r depends on programmatic characteristics.
c. NRTI backbone to be changed to unused NRTI (lamivudine can be retained as any resistance to it will make virus less fit).

TABLE 3 WHO ART guidelines for those with failure to first-line ART (July 2019)

Population	***First-line regimens***	***Preferred second-line regimens***	***Alternate second-line regimens***
Adults (≥30 kg)	2 NRTIs* + DTG	2 NRTIs* + ATV/r or LPV/r	• 1–2 NRTIs* + **DRV/r** • 1–2 NRTIs* + **DTG**
	2 NRTIs* + EFV	2 NRTIs* + **DTG**	

Topic	2002	2003	2006	2010	2013	2016	2018-2019
Earlier initiation when to start	CD4 ≤ 200	CD4 ≤ 200	CD4 ≤ 200 – Consider 350 – CD4 ≤ 350 for TB	CD4 ≤ 350 – Regardless CD4 for TB and HBV	CD4 ≤ 500 – Regardless CD4 for TB, HBV PW and SDC – CD4 ≤ 350 as proprity	Towards treatment initiation at any CD4 cell count or clinical stages	Towards treatment initiation at any CD4 cell count or clinical stages
Simpler treatment 1st Line ART	8 options – AZT preferred	4 options – AZT preferred	4 options – AZT or TDF preferred – d4T dose reduction	6 options and FDCs – AZT or TDF preferred – d4T phase out	1 preferred option and FDCs – TDF and EFV preferred across all pops	Continue with FDC and phased introduction of new options (DTG, EFV_{400})	Two NRTI+DTG as preferred first line ART for all adults and women (with informed choice to women of childbearing age
Less toxic, more robust regimens 2nd Line ART	Boosted and non-boosted PIs	Boosted PIs – IDV/r LPV/r, SQV/r	Boosted PI – ATV/r, DRV/r, FPV/r LPV/r, SQV/r	Boosted PI – Heat stable FDC: ATV/r, LPV/r	Boosted PIs – Heat stable FDC: ATV/r, LPV/r	Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)	Add more heat stable PI options (DRV/r) and new strategies (NRTI sparing regimens)
3rd Line ART	None	None	None	DRV/r, RAL, ETV	DRV/r, RAL, ETV	Encourage HIV DR to guide	Encourage HIV DR to guide
Viral load Better and simpler monitoring	No	No (Desirable)	No (Tertiary centers)	Yes (Phase in approach)	Yes (preferred for monitoring, use of PoC, DBS)	Support for scale up of VL using all technologies	VL ot 6 months, 12 months and then every 12 months

Fig. 3: Evolution of ART guidelines 2002–2020

Once a patient has been started on ART, patient needs to be monitored for signs of improvement due to ART as well as any new symptoms/signs which may indicate a side effect of a drug. It is recommended that in the initial phase of ART, patient needs to be monitored more frequently, preferably once in 2 weeks for initial 4–6 weeks, and then can be evaluated monthly.

The signs of improvement are weight gain, feeling of wellbeing, better appetite, better sleep, improvement in nutritional status, hemoglobin, etc., but more specifically increase in CD4 count and decrease in viral load at 6 months after ART initiation. Ideally the viral load should become undetectable 6 months after ART initiation. Once it becomes undetectable the viral load can be done annually and CD4 count monitoring can be stopped. It is also important to monitor lab parameters like Hb, renal functions periodically while on ART.

Conclusion

ART has been evolving rapidly toward earlier initiation with more robust and less toxic regimen. The **Figure 3** summarizes this evolution of guidelines till now.

It will continue to evolve as more evidences become available on long-term safety and efficacy of drugs. Recently US FDA has approved a two-drug therapy using only Dolutegravir and Lamivudine and many new drugs are under trial including once a month injectable option. Simultaneously lot of research is ongoing on finding a cure for HIV. Vaccine trials have been partially successful, but the best vaccine available is prevention and for those infected early diagnosis and linkage to treatment remains crucial.

In India, ART is available free of cost through 543 government-run ART centers across the country, wherein 14 lakh PLHIV are currently receiving free ART. There are additionally an estimated 1 lakh patients being treated in private sector. Being a lifelong therapy, adherence and affordability are two key issues. Hence, it is important for clinicians to carefully consider these factors before ART initiation to ensure good outcomes in long-term.

Suggested Readings

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CHAPTER

184 90-90-90: Are These Mere Numbers?

Sajith Kumar R

Abstract

With many new classes of drugs and molecules and changes in strategies, HIV-AIDS has become a chronic manageable infection. Various international and national agencies have adopted mechanisms to ensure that these are translated to reach the affected people. 90-90-90 target, which was supposed to be achieved by 2020 has been delayed due to the effect of Covid on health scenario. However, it's not just the numbers only, but also various benefits to the society that matters. The outlook toward persons living with HIV has changed, but lot more needs to be done to ensure access, adherence, and persistence. Uniform practices will lead to them becoming undetectable as far as viral suppression is concerned and untransmittable for the rest of the society.

Introduction

HIV/AIDS has been with human kind for many decades now. From 1981 to 2020, the management of HIV infected persons has taken many turns. Introduction of Antiretroviral Therapy has radically changed the quality of life for all. However, there are wide variations among populations in different continents. UNAIDS launched the Fast Track strategy in 2014 aimed at enabling all HIV infected persons for a long-term survival. The motto of 90-90-90 aimed at reducing the deaths by 90% by 2030 is being actively chased in all countries. This not only means a reduction in the numbers getting listed and in the number of survivors but also improvements in the quality of life among the surviving population. The decrease in the number and severity of opportunistic infections, ability to lead a normal life, and decreased quantum of infective persons in the world are other benefits of this strategy. This will also lead to significant reduction in hospitalizations and near normal socioeconomic status for the infected. While many countries have reached this target, many others are lagging behind and the gaps are getting reduced fast.

Antiretroviral Therapy

The list of drugs effective against human immunodeficiency that began with azidothymidine (AZT, zidovudine) is expanding fast. With the advent of the drugs that act on various phases of HIV replication, viz. fusion inhibitors, reverse transcriptase inhibitors, integration inhibitors, protease inhibitors, coreceptor antagonists, etc. it has become clear that viral load can be controlled. This will enable the person to lead a longer, symptom-free survival with reduced chance for opportunistic infections, malignancies. The most important prerequisites for this advantage to be transferred to the infected persons involve the triad of early detection, quick initiation, and strict adherence with regular monitoring. A detailed description of Antiretroviral Therapy is beyond the scope of this article.

The 90-90-90 Strategy

The Millennium Development Goals were established following the Millennium Summit of the United Nations in 2000, following the adoption of the United Nations Millennium Declaration. MDG 6 was to combat HIV/AIDS, malaria, and other diseases. The year 2015 was the target at that time. In 2015, they were replaced by 17 Sustainable Development Goals. Specific targets were described to be achieved by 2030.

SDG 3 (to ensure healthy lives and promote well being for all at all ages) contains the two targets:

Target 3.3: End AIDS as a public health threat by 2030.

Target 3.8: Achieve universal health coverage, access to quality health-care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all.

In addition, the following statements also are important for HIV related activities.

SDG 4: Quality education, including targets on comprehensive sexual and reproductive health (SRH) education and life skills.

SDG 5: Gender equality, including targets on sexual and reproductive health and rights (SRHR) and the elimination of violence, harmful gender norms, and practices.

SDG 10: Reduced inequalities, including targets on protection against discrimination, and the empowerment of people to claim their rights and enhance access to HIV services.

SDG 16: Peace, justice, and strong institutions, including reduced violence against key populations and people living with HIV.[4]

In 2014, UNAIDS announced the Fast Track strategy aimed at stepping up the responses in HIV prevention, control, and care particularly in low- and middle-income countries (LMIC). This was aimed at meeting the SDC-3 target to "end AIDS by 2030." This strategy aims to catch up with the expanding infected pool by providing care including antiretroviral therapy to reducing new HIV infections and AIDS related deaths by 90% in relation to the 2010 values. The targets include reduction of new HIV infections to fewer than 500,000 per year by the year 2020 and to 200,000 or less by the year 2030—equivalent to ending AIDS as threat to public health. Once this is achieved by the treatment cascade upgradation, HIV transmission will be reduced, HIV infection may not affect the health of a person and deaths from HIV-related issues will be minimum. This is also supported by the WHO recommendation for starting ART in all HIV infected persons at all CD4 counts.

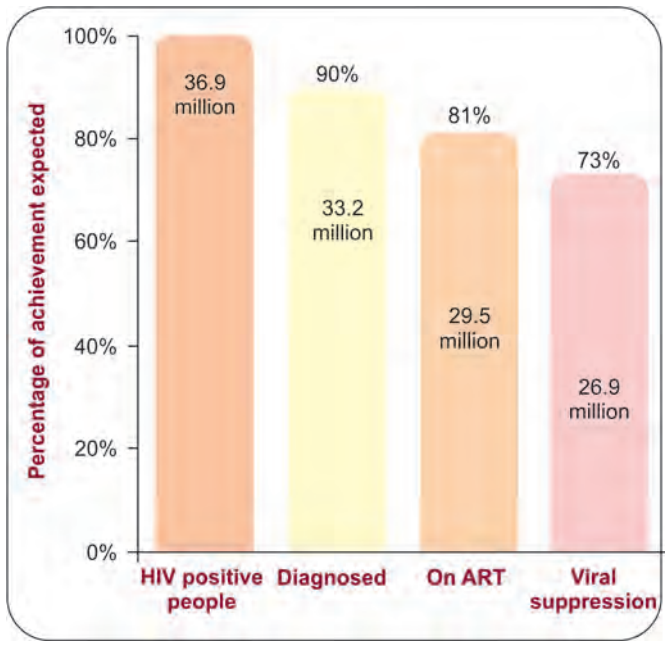

Fig. 1: The proposal as it was made in 2014

The 90-90-90 targets include aims to reach the following targets.[1,2]

- 90% of infected persons being identified,
- 90% of identified (infected) persons being started on antiretroviral therapy, and
- 90% of persons on ART achieving sufficient viral suppression **(Fig. 1)**.

UNAIDS has put forth the idea of five pillars for this project. It is actually a people centerd, rights-based approach. These include:

- Reduce new infections among women and girls to under 100,000 (current rates are approximately 700,000 per year globally),
- Ensure that 90% of people at risk of HIV can access preventive services,
- Make 20 billion condoms available annually in LMIC,
- Provide 25 million more with voluntary male medical circumcision, and
- Provide PreP (pre-Exposure Prophylaxis to 3 million people who have high risk behavior likely to lead to infection with HIV).

The fast track strategy also envisaged certain targets set for 2020, which includes:[3]

- Less than 500,000 people newly infected with HIV (75% reduction from 2010),
- Less than 500,000 people dying from AIDS-related illnesses, and
- Elimination of HIV related discrimination.

There was also a commitment to ensure that 30 million people will access antiretroviral therapy by 2020.

What has Happened?

There has been a marked scale up of antiretroviral therapy with over 28 million people on ART as of 2020, bringing the percentage from 25% in 2010 to 67% in 2019. The incidence: prevalence ratio is a metric that measures both the survival patterns and new infections. The global value for this was 7% in 2010 and has dipped to 4.4% in 2019. There were geographic variations. The ratio fell from 7% to 3.5% in Africa, while it was 3% in North America and Central Europe. Among individual countries, 25 have the value at 3%.

According to UNAIDS Global update 2020, among approximately 38 million infected persons all over the world, 81% knew their HIV serostatus, 67% were on antiretroviral drugs, and around 59% had undetectable viral loads. This is achieved by starting ART in approximately 25.4 million persons. This equates to 81-82-88% in comparison to the 90-90-90 figures.

The UNAIDS data as of 2019 is summarized in **Figures 2 and 3**.

Indian Scenario

India is one among the 193 countries participating in the 90-90-90 strategic plan. With over 2.1 million infected population, India has the third highest burden of HIV after South Africa and Nigeria. The National Health Policy (2017) and the HIV/AIDS Act (2017) explicitly states the commitment toward this. As stated therein "every person who is in the care or custody of the State shall have the right to HIV prevention, counseling, testing, and treatment services." This ensures that all including women and children, prisoners, and all irrespective of caste, creed, gender and beliefs, sexual, or otherwise will have equal access to counseling, diagnostic, and treatment services. NACO has released data, according to which 79.4% of the 21.40 lakh PLHIV in India know their status; 82.3% are on ART; 74% (among those tested) virally suppressed **(Fig. 4)**. The viral load testing is now available in ART centers across the country and the treatment cascade is being implemented effectively.[5]

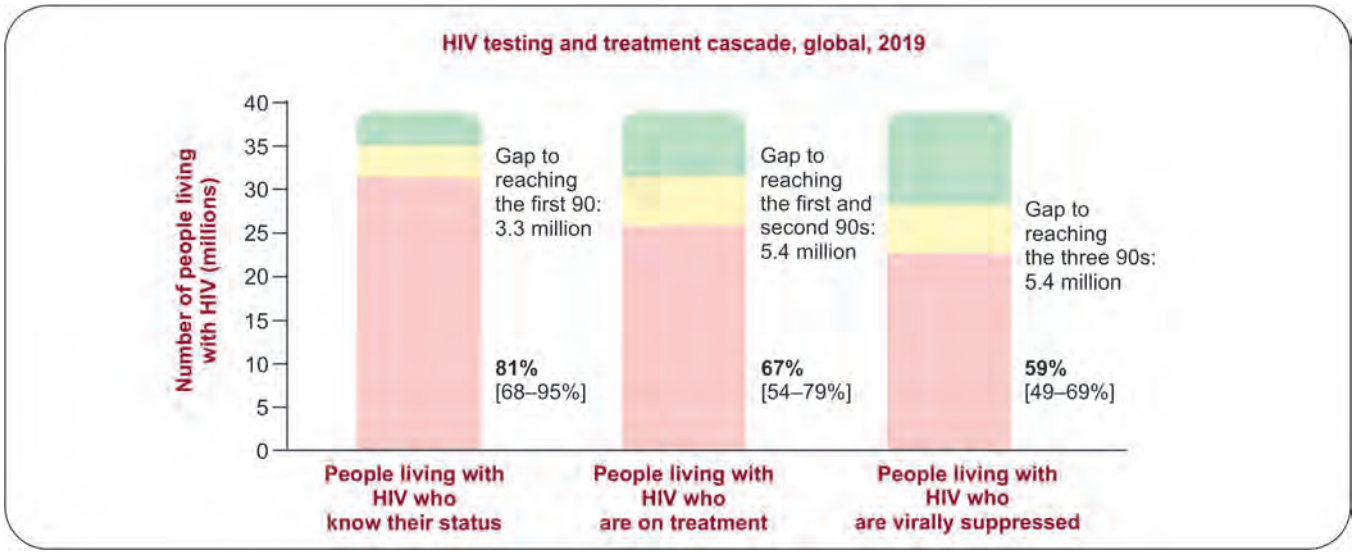

Fig. 2: HIV testing and treatment cascade, global, 2019

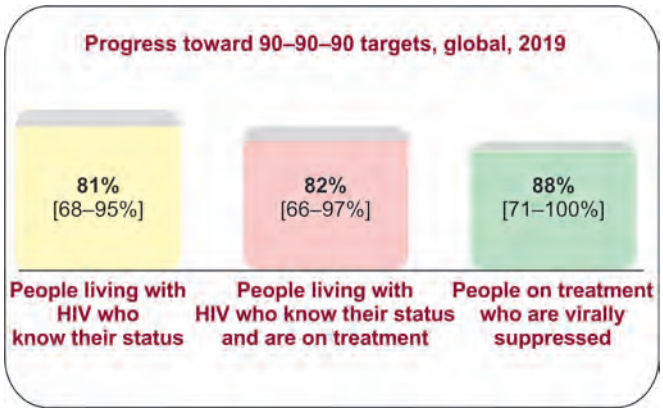

Fig. 3: HIV 90-90-90 status, global, 2019

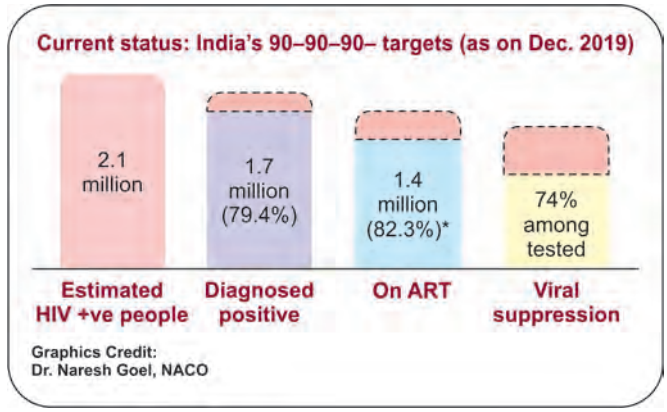

Fig. 4: 90-90-90 achievement status of India

Beyond Numbers

What the 90-90-90 strategy can achieve with full achievement of all targets is that 81% (90% of 90) of those infected will be put on treatment and 73% (90% of 81) of all infected is likely to be virally suppressed. This does not mean that 27% of infected persons are not going to be benefitted.

- Many studies have demonstrated the benefits of early detection in case of HIV infection. Test All strategy adopted by World Health Organization in 2016 has led to the following changes:
  - Supportive HIV testing policies have been accepted by most countries, an increase from 6 to 77 between 2015 and 2019. Self testing is promoted in 38 countries, as compared to 14 in 2017.
- Early and quick initiation of ART is producing wonders in the field of HIV care:
  - 60% of LMIC have started treating all infected persons regardless of CD4 count.
  - Lifelong ART for pregnant women is now standard practice in almost all countries.
  - 80% of countries have introduced treat all for children.
  - 72% countries have adopted single tablet regimen (TLE) as first line.
  - Dolutegravir (DTG) at lower price as a fixed combination drug is available in approximately 60% of LMIC.
- The cut off for start of therapy with antiretroviral drugs has been going up from the CD4 count of 200 cells/cmm to 350, 500, and has reached any CD4 count now. Starting ART early prevents the occurrence of opportunistic infections and malignancies and delays death. New data and analysis reveal the reduction in risk of developing non-AIDS events as well. This occurs regardless of age, sex, race, baseline CD4 cell counts, geographic region, or economic status. This benefit has been definitely shown to outweigh any difficulty with ART including toxicities, adverse outcomes, etc...
- Quick initiation immediately after diagnosis is another area that helps the achievement of 90-90-90 targets. Rapid initiation of ART is defined as starting therapy within 7 days of diagnosis. This has to be based on person's willingness and readiness. As early as 2017, same day initiation of ART was practiced in South Africa. This envisages the initiation of ART on the same day as diagnosis. This is reported to improve the outcomes faster but has been occasionally alleged to be associated with reduced rate of retentions.
- The quest for achieving the 90-90-90 targets has also led to more widespread availability and accessibility to viral load testing facilities. All over the world, this is now accepted as the standard monitoring tool during follow-up visits.
- The impact of the above measures on transmission need not be over emphasized. The equation "Undetectable = Untransmissible" is now widely accepted. This means that if a person takes ART and is virally suppressed (as envisaged in the 90-90-90 strategy), his undetectable Viral load is likely to be associated with a significantly less number of transmissions as well. This becomes a strong weapon for HIV prevention activities as well. Treatment as prevention thus becomes a reality.[6]

- The inclusion of lifelong treatment for women will also lead to less number of women with high viral loads and almost complete elimination of vertical transmission, offering lower incidence of HIV infection among newborns as well.
- HIV treatment saves money: Many modeling exercises show the cost effectiveness of ART as a cost-effective tool in the long run. Investments in HIV treatment scale-up lead to economic benefits at least double that of prevented medical expenses, as well as that in care of orphans and productivity in labor. The initial increase in cost attributed to cost of infrastructure, logistics, drugs, testing laboratories, etc. is expected to pay in the long run to reduce total cost of decreased morbidity and survival.

Conclusion

It is evident from the discussion above that the 90-90-90 strategy put forth by UNAIDS and embraced by all countries including LMIC is making changes not only in the counts but also in various aspects related to prevention, diagnosis, treatment, monitoring, and survival, thus ensuring better life to the HIV infected and to the upcoming susceptible generation.

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CHAPTER

185 Keeping Parent-to-Child Transmission Zero for a Decade—Trichur Experience

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Abstract

Knowledge about the efficacy of ARV drugs in preventing parent-to-child transmission (PPTCT) helped developed countries to achieve very low mother to child transmission rate. Due to various reasons, this remained unachievable in developing countries like India. PPTCT programme in India started in 2003 with Single dose Nevirapine schedule remained suboptimal till the adoption of Option B+ in 2014.

The Southern state of Kerala with health indicators comparable with the developed countries was always been an HIV low prevalent state. A model ART care facility was initiated in Govt.Mediacl College, Thrissur with the objective of providing comprehensive HIV health care incorporated to the existing public health system. Comprehensive PPTCT care by a dedicated "Team" was introduced as part of this package addressing various aspects of PPTCT, adjusted to existing the social mileu. This model proved quite successful and lead to near Zero transmission of HIV from mother to child in the last decade. Subsequently this model was adopted to other part of the state.

Introduction

Human immunodeficiency virus (HIV) continues to be a significant public health challenge world over. The fight against this pandemic started soon after the identification of the virus in 1982. With the knowledge that antiretroviral (ARV) drugs are useful in preventing mother-to-child transmission of HIV and that this is probably the only mode of transmission that can be prevented, Prevention of Parent/Mother-to-child transmission (PMTCT/PPTCT) became the major HIV prevention strategy aiming at reducing new infections, morbidity, and mortality. Currently, the transmission of infection from mother to child is eminently preventable.

A series of interventions were tried to achieve PPTCT at various levels. This include reduction of infection in the general community especially women of reproductive age group, avoidance of unplanned pregnancies, prevention of transmission from mother to child, post-exposure prophylaxis to the child and planning infant feeding options. PPTCT became a reality in the West in the mid-1990s with the introduction of zidovudine in pregnant women. However, it took decades for PPTCT to become competent in reducing the transmission in a significant proportion, mainly due to various hurdles in implementing PPTCT programs in the developing world, and because of the lack of adequate health-care delivery and public health infrastructure. Kerala a state known for high health indices and female literacy and equitable health care facilities remained an exception keeping both HIV prevalence and mother-to-child transmission to a minimum.

History of PPTCT

Global Scenario

ACTG 076 trial marked the beginning of a new era in PPTCT with zidovudine being recognized as the first

TABLE 1 Summary of Zidovudine Trials for prevention of mother-to-child transmission of HIV

Study	*Arm*	*Antepartum*	*ARV intrapartum*	*Neonatal*	*% Transmission*
PACTG	A	ZDV at >14 weeks	ZDV	ZDV for 6 weeks	7.6
076	B	Placebo	Placebo	Placebo	22.6
PHPT-1	SS	ZDV at >35 weeks	ZDV	ZDV for 3 days	10.5
	LL	ZDV at 28 weeks	ZDV	ZDV for 6 weeks	6.5
	LS	ZDV at 28 weeks	ZDV	ZDV for 3 days	4.7
	SL	ZDV at 35 weeks	ZDV	ZDV for 6 weeks	8.6

Adapted from: World Health Organization. Anti-retroviral therapy for treating pregnant women and preventing HIV infection in infants; recommendations for a public health approach - 2010 revision. Geneva, Switzerland: WHO Press; 2010[10]

effective drug in preventing mother-to-child transmission and the USA Public Health Service recommending its use in August 1994.[1] According to the ACTG 076 regimen, HIV-infected pregnant women were recommended zidovudine, from the14 weeks of gestation until delivery, followed by peripartum zidovudine infusion. Newborns were given 6 weeks of zidovudine together with replacement feeding. The treatment regimen reduced the risk of HIV transmission by approximately two-thirds.

Since then, many clinical trials have been undertaken to find out the most effective and affordable antiretroviral therapy (ART) regimen to prevent mother-to-child transmission. This search began with various modifications of ACTG 076 recommendation, like shortening zidovudine use to 8 weeks in the antenatal period.[2,3] Various trials with zidovudine for prevention of mother-to-child transmission of HIV are summarized in **Table 1**. The effectiveness of the "long-short" course (from 28 weeks in pregnancy for the mother and the upto 3 days for the baby) and the "short-long" course (from 35 weeks in pregnancy for the mother and upto 6 weeks for the baby) did not differ from that of the "long-long" course.[4]

Subsequently, PETRA Trials proved that starting zidovudine plus lamivudine at 36 weeks of gestation, followed by oral intrapartum dosing and 7 days' postpartum dosing of mothers and infants also can significantly reduce MTCT. Two-drug and three-drug regimens were tried subsequently for antenatal mothers, which too proved to be effective in reducing HIV transmission significantly.[4] The HIVNET012 trials conducted in Uganda, which confirmed the efficacy of the single-dose nevirapine regime in preventing vertical transmission of HIV was plagued by controversies soon after the release of its results in 2004.[5-7] But gradually this regimen became well accepted primarily because of the simplicity in implementation. **Table 2** summarizes the various treatment regimens proposed for PPTCT before the current three-drug regimen.

In June 2011, the Joint United Nations Program on HIV/AIDS (UNAIDS) introduced the *Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive*, which aimed at a 90% reduction in new childhood HIV infections and a 50% reduction in HIV-related maternal deaths by 2015.[8]

The WHO recommended two approaches for PMTCT prophylaxis. "Option A" recommended zidovudine monotherapy in the antenatal period, single-dose nevirapine during labor and a week-long tail of zidovudine and lamivudine in the postpartum period. HIV exposed infant was given daily nevirapine until the cessation of breastfeeding. An alternate option, "Option B" differed from option A in that, all pregnant women, even if not eligible for ART were advised three-drug combination ARV in the antenatal period, which was continued till the cessation of breastfeeding. Infants have advised zidovudine/nevirapine prophylaxis for the first 6 weeks of life.[9] A third option B+ that recommended triple ART for all HIV infected pregnant women irrespective of the clinical or immunological stage was also included in this update

With the recommendation for the initiation of ART at any CD4 cell count in the 2014 updated guidelines, the PMTCT Guidelines Committee also adopted the WHO option B+, so that all pregnant women would continue triple-drug therapy after delivery in the same way as all other adults.[9]

PMTCT guidelines committee of our country adopted the Option B+ in 2014 so that all pregnant and breast feeding women would be initiated on Triple ART irrespective of the stage , which would be continued lifelong.[9]

TABLE 2 Summary of various treatment regimens proposed for PPTCT before three-drug regimen

1994	*1998*		*1999*		*2000*	*2002*	*2004*
ACTG 076Trial 65% reduction of transmission	1998Thai Bangkok AP/IP AZT Trial 50% reduction	Cote d'Ivoire AZT Trial 37% reduction	PETRA AZT/3TC 50% red with long arm 38% reduction with short arm PETRA AZT/3TC 50% red with long arm 38% reduction with short arm	Two dose IP/PP NVP (HIV NET 12) 47% reduction breastfeeding	Thai long vs. short AZT4% transmission (Non breast feed)	Cote d'Ivoire AZT and IP/PP Nev 6.2% transmission	PHPT AZT + Nev <2% transmission

Infant feeding recommendations given by WHO in 2006 and later in 2010 promoted 6 months exclusive breastfeeding followed by complementary feeding with the gradual cessation of breastfeeding by 12 months when nutritionally adequate and safe alternate nutrition is established, along with ARV prophylaxis to mother and infant.[10] In 2016, infant feeding guidelines were updated, with the recommendation to continue breastfeeding to 24 months like general population along with the continuation of ART.

Indian Scenario

NACO launched India's first PPTCT program in May 2003 with the recommendation to administer single-dose NVP 200 mg regimen to all seropositive mothers not receiving highly active combination anti-retroviral therapy (HAART) at the onset of labor, and this was followed by one dose of 2 mg/kg nevirapine administered to all babies within 72 hours of delivery.[11] This was continued till 2014 after which there was a significant change in the scene with the adoption of Option B+.

Challenges in Implementation of PPTCT in India

PPTCT is not just provision for ART. It is a comprehensive care package involving various steps.

These steps include (but are not limited to) women agreeing to HIV testing, receiving their results, undergoing ART eligibility screening, initiating treatment or prophylaxis, and adhering to the prescribed regimen.[11] Infants must adhere to anti-retroviral prophylaxis regimens and undergo appropriately timed HIV testing.[12] Attrition at each point should be identified and corrected. But the implementation of PPTCT services in developing countries is not often practical due to various factors, which include:[12-16]

- Large HIV positive population
- Problems in testing
- Issues related to confidentiality, stigma, and discrimination
- Non-availability of maternal and child health services
- Low education status of mothers
- Non-availability of medicine
- Non-availability of health-care delivery system
- Lack of political commitment
- Difficulty to prioritise PPTCT among other health care services

Kerala Scenario

Kerala, a small southern state, has always maintained a coveted position in health and social development, often comparable with the developed world. Kerala has always remained a low-HIV prevalent state, and this low prevalence was no accident.[17] Kerala's health indicators are almost comparable to Western Europe, with equitable health-care facilities, very high female literacy and empowerment, and low HIV prevalence. This helped Kerala to adopt a different model of PPTCT practice silently. Various social factors like high-literacy rates, women empowerment, better socioeconomic status, good public health and MCH services, good health-care seeking attitudes, the involvement of public health in HIV prevention services, availability and accessibility to state-run ART clinics across the state, commitment from government and health-care workers in implementing the program helped the state in evolving its model.

The Trichur Experience

The Thrissur model HIV Care facility (TMHCF) evolved as a comprehensive HIV care facility in 2002. This facility was recognized as one of the models that helped the evolution of the national ART program.[18,19]

The basic principle of this model was that it is possible to provide comprehensive HIV care by making use of existing infrastructure and human resources in the public health system of India.[20] This model also suggested that provision of health care to PLHIVs at the existing health care systems would reduce the stigma and discrimination tremendously thereby improving the health care seeking attitude of the patients. These were the guiding principle for the care of pregnant women as part of comprehensive HIV care from the inception of HIV care facility in 2002. We also believed, it was possible to provide better PPTCT services in Kerala if we make use of the strengths of its health care system and the society comprehensively. One of the authors (K Ajithkumar) was instrumental in providing the zidovudine prophylaxis probably for first time in India immediately after the report of ACTG 076 was published in 1994 while he was part of HIV team at CMC Vellore. The first pregnant lady who approached this facility received ACTG 076 protocol, and this became the standard practice in the institution. The success of this approach led to the referral of many more pregnant HIV infected women from different parts of the state.

As more and more patients were approaching the center for PPTCT, the center evolved a team of health-care workers and devised its protocol for PPTCT services. The protocol thus evolved included:

- Testing and confirmation of HIV status of every pregnant lady and the partner
- Counselling of the PLWA and family addressing the confidentiality of individuals involved
- Helping the patient for disclosure to the immediate caregiver
- Offering lifelong care
- Counselling of the pregnant lady and the family by obstetrician and pediatrician and involving them in the team as early in the pregnancy as possible
- Planning feeding options early in the pregnancy
- Ensuring regular antenatal care and near 100% institutional delivery
- Initiating ART as early as possible in pregnancy
- Lower section cesarean section as the mode of delivery
- Supporting the couple/family in facing social and financial issues, including stigma and discrimination
- Linkage with PLWHA networks and other ART care centers for follow-up
- Linkage with other services like NGOs, CBOs, etc.
- Training of health-care workers in PPTCT
- Supporting private health-care providers in providing PPTCT services

All these components continue even now with appropriate modifications.

In the early days of TMHCF, there was no India specific guideline for PPTCT. So we evolved our own protocol and incorporated modified ACTG 076 protocol as part of this package. As intravenous zidovudine was not readily available, we continued oral zidovudine peripartum also. When the evidence on two drugs PPTCT became available, we shifted to it for a brief period.

Thus over the time with the evolving evidence, drug regimens for prophylaxis changed from zidovudine monotherapy through zidovudine + lamivudine and eventually to zidovudine + lamivudine + efavirenz. The time of initiation of ARV prophylaxis also changed accordingly. By 2010 every pregnant lady was receiving triple regimen as early as feasible.

Each HIV positive pregnant woman was counselled by the HIV team, pediatrician, and the gynecologist. An individualized treatment plan was charted for each patient considering their socioeconomic and health status and followed up by the counsellor. We followed planned elective cesarean section as mode of delivery. If the pregnant lady was not able to deliver in our hospital, her local gynecologist and pediatrician were contacted by our HIV team, and a suitable plan for the management of pregnancy was formulated. As far as possible, they were encouraged to bring the child to our institution for follow up, especially for nutritional evaluation and early infant diagnosis at the sixth week. Each mother-baby pair was followed up till at least the child reached 18 months and tested negative. Those women who were not registered in our center, but were referred late in pregnancy or in active labor and those who moved back to their primary care centers after delivery were also monitored.

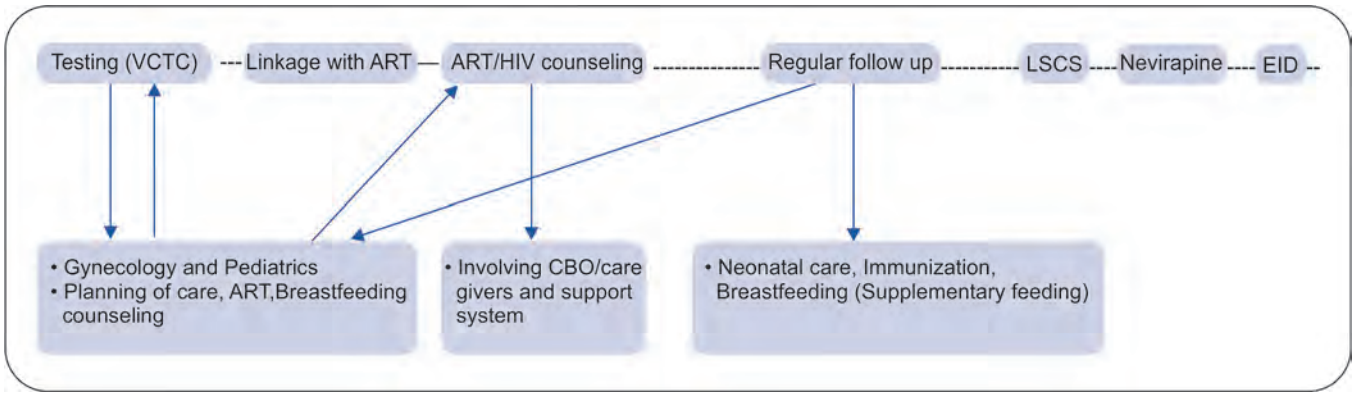
Mode of delivery: Planned LSCS was the option from the early 2000s in our institution. Vaginal delivery was resorted to only if the pregnant lady reaches the institution in advanced labor.

Flowchart 1 shows the flow of patients in PPTCT at TMHCF.

Infant feeding: We counselled not just the pregnant lady but the whole family regarding feeding options. The practical difficulties in avoiding breastfeeding, including the social stigma and confidentiality issues were acknowledged, and tailor-made plans were implemented for each family. Majority of our mothers opted exclusive replacement feeding initially, and these children were followed up regularly to make sure the children have not affected adversely by avoiding breastfeeds. Recently the infant feeding option has shifted more to breast feeding with more women getting diagnosed and initiated on ART early or prior to pregnancy, allowing well controlled disease states. The parents and families (especially in-laws) were regularly counselled and supported. The PPTCT was never a standalone service. It was synchronized and integrated with general MCH care and HIV care. So regular follow-up of mother and child was integrated with immunization services, pediatric/neonatal care, ART, etc. The strong relationship built between the pediatrician and the ART team continued until the child reaches adulthood irrespective of HIV status.

We made sure the social norms were followed by the pregnant ladies and families so that stigma and discrimination could be avoided.

Flowchart 1: Flow of patients attending PPTCT services in Thissur model HIV care



This model was helpful for both patients and gynecologists, as almost all deliveries were planned. This model addressed the medical and nonmedical problems faced by these women comprehensively and ensured adequate compliance and follow-up.

The success of Trichur team sent messages all around the state, and most ART teams followed this model across the state. This lead to the declaration of zero transmission of HIV from mother-to-child transmission in Kerala by Hon. Health Minister in 2010. Few mothers, who were lost to follow-up were all referred late in pregnancy or in labor. Till now, to best of our knowledge, only one baby, whose mother discontinued ART due to reduced tolerance and psychiatric illness, has become HIV infected.

Conclusion

Vertical Transmission of HIV is an eminently preventable infection. Like any other disease, the medical factors are equally or more critical in implementing a successful strategy. Though possible in principle, very few developing countries could reach zero PPTCT of HIV so far. The latest strategy of integrating PPTCT with HIV care and providing lifelong ART to every HIV infected individual will help in preventing mother-to-child transmission as well in the coming years.

The Govt. Medical College, Thrissur, could achieve a near-zero mother-to-child transmission rate from early 2000 itself solely due to the comprehensive, individualized HIV care by a dedicated team of health-care workers, integrating HIV care with the routine MCH services addressing the medical and psychosocioeconomic aspects of HIV infection simultaneously and not due to any significant upscaling of infrastructure. Because of this, Trichur model is one that can be adapted in most health-care settings in developing countries.

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CHAPTER

186 My 30 Years Experience in HIV Medicine

Alaka Deshpande

Abstract

HIV arrived in India 5 years after the western world. There experience guided our policies. The illiteracy, poverty, population, and inadequate health infrastructure were the imposing problems. The prompt response with awareness programs, cost free testing, management of OIs did help the patients. But the game changer was free access to cARVs. It lessened the morbidity and increased the longevity. However, the newer challenges emerge from time to time.

Introduction

Alma Ata declaration of Health for All by 2000 AD was made in 1980. It was in reference to conquering the known microbes and controlling infectious diseases in the Southern hemisphere.

The Clinicians even at that time were well aware that the newer challenges will be posed by resistant microbes including bacteria, fungi, and newly emerging viruses.

Over last four decades we are experiencing various viral epidemics and as a paradox almost all of them are emerging from the Southern hemisphere.

June 1981, exactly 6 months after Alma Ata declaration, a new disease entity was reported in MMWR which baffled the medical world. Young people were dying of Opportunistic infections without any evidence of known immune suppression. However, the investigations revealed cell-mediated immune-deficiency. Clinical spectrum evolved slowly, modes of transmission became known and the etiological virus was identified.

Indian Scenario

India was in second wave countries as HIV reached India in 1986 when Prof Jacob John could procure an ELISA kit and tested few samples of CSW in Chennai and detected positivity in two of them. This heralded the arrival of HIV in India. People were ignorant about it and few who read about it boasted about our culture and prophecised that it would never come in India. But, Govt. of India promptly responded and ICMR started the serosurveillance. Due to limited resources the universal safety precautions were almost non-existent. Glass syringes were boiled and reused. By 1990, we started getting clinical cases. The HIV phobia was so much that the private sector doctors were turning away the pts. And the Govt. hospitals had to bear the brunt. Even in our tertiary care Govt. hospital, I had to first impart training to our resident doctors and all the paramedics for safety precautions. Second, I started a dedicated HIV OPD in view of keeping patients' confidentiality, avoiding discrimination and giving enough time for counseling of the patients. Gradually, the attendance in the OPD went on increasing. Many of the cases presented in critical condition and succumbed within 24 hours. Autopsy of these cases was necessary. My pathology colleague accepted the challenge and we could carry out 150 autopsies of AIDS cases. Autopsies were good learning lessons.

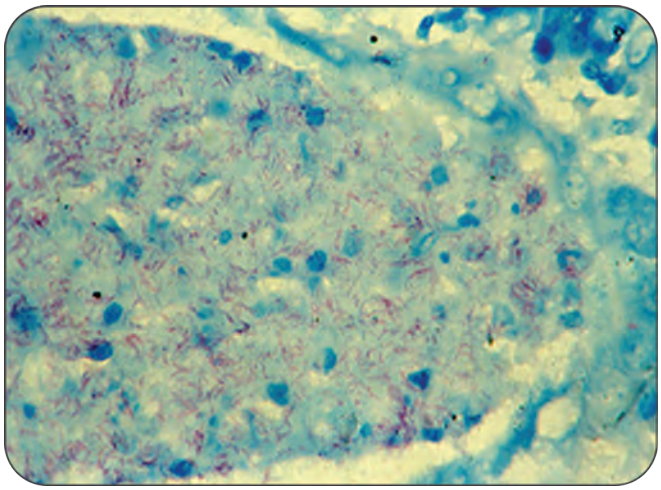

Fig. 1: Kidney teeming with mycobacteria

We could establish mycobacteriosis-organs teeming with mycobacteria **(Fig. 1)** in absence of clinical or gross pathological evidence on autopsies.

We noticed multiple pathologies in one single patient endorsing severe immunodeficiency. Sixty-seven percent showed tuberculosis along with other OIs.

All these OIs were newly seen by us; hence, we had to develop appropriate tests to diagnose them. It was a time consuming process as these OIs were not seen earlier because 1994–1995 neither long-term steroid used nor an ambitious organ transplant program was in place. Slowly we evolved.

It was necessary to share our experience of lack of preparedness for infrastructure to manage increasing number of HIV cases and how we could surmount the difficulties. A proper training had to be imparted for medical fraternity in the country. National AIDS Control Organization (NACO) was set up by Govt. of India. Under the aegis of WHO, NACO, CMAI (NGO) with support from Norad, we 21 Professors conducted training workshops in the country. It was a great experience. This was in 1992–1993.

In 1981, this new disease entity was identified as a mysterious dreadful disease. With revelation of deficiency of cell mediated immunity (CMI) presenting with various OIs (Syndrome—cluster of symptoms) the disease got its first name as Acquired Immunodeficiency Syndrome (AIDS). Now we know it as retroviral disease. It spread rapidly all over the world causing a serious pandemic without any treatment. The natural history was unfolding. Medical research finally identified the causative organism—the first human retrovirus which was called as Human Immunodeficiency Virus (HIV). After the discovery of HIV, the laboratory diagnostic tests were developed.

The serodiagnosis was based on detection of anti-HIV antibodies by ELISA technique. A positive test needed confirmation by Western Blot test, which was immunoblotting multiple antibodies. The test was cumbersome, expensive, and time consuming. Further facilitation came by using the same principle of detecting multiple antibodies using three different antigens to detect three different antibodies using technically different three tests S, R, and E—simple, rapid, and elisa.

These tests are indirect tests which detect antiviral antibodies indicating exposure to the virus. It had its window period. Science was evolving as the pandemic was spreading relentlessly. The direct tests detecting virus itself qualitatively by DNA PCR and quantitatively by RT-PCR to measure viral load developed over the time period each having its own indications.

CD4 counts were used to assess the severity of immune deficiency.

This disease no longer remained only a medical problem. It encompassed all the aspects of human life. Just to give a small example—I would recall that NACO held a special meeting of experts regarding issue of a death certificate. The discrimination was to the extent of refusing cremation/burial of a patient whose death certificate mentioned AIDS as the cause of death.

The story of evolution of HIV will remind the readers of prevailing situations with various RNA virus epidemics in last decade or so.

Clinical Spectrum

Clinical spectrum varied depending on the severity of immune deficiency. Over three decades, I have seen almost all the OIs in our patients. However, predominant was tuberculosis. It occurred minimum 2–3 times in a patient. Depending on the severity of immune deficiency the TB presentation differed. In early immunodeficiency it was like any non-HIV TB, with moderate immunodeficiency it was extrapulmonary or disseminated TB and severe deficiency (CD4 <50) it was mycobacteriosis. Multiple OIs were seen simultaneously in the stage of AIDS.

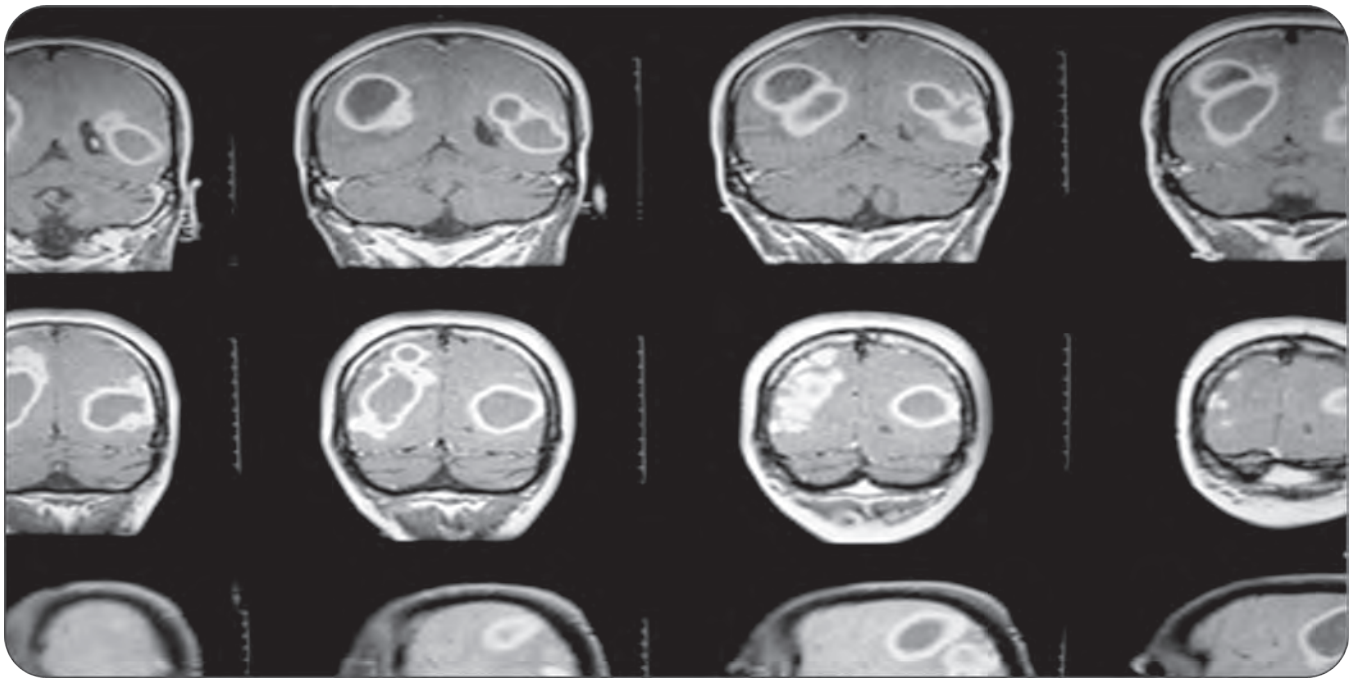

Fig. 2: Nocardial abscesses in brain

TABLE 1 Etiology of fungal meningitis

Cryptococcus neoformans	21
*Rhodotorula mucilaginosa**	28
Candida albicans	03
Trichosporon	02
Ascospores	01
Geotrichum	02
Aspergillus	03
Normal	17

*Largest series of Rhodotorula from aseptic CSF compartment.

It was intriguing for me to see patients with cryptococcal meningitis treated with inj Amphotericin responding by negative test for crypto antigen. And within a week patient clinically deteriorated and showed presence of fungus in CSF on India ink preparation. So we carried out fungal culture of CSF in these cases and were surprised to note that the etiology of fungal meningitis was as shown in **Table 1**. Fungal culture positive in 75.6% of cases.

Four cases of dementia of six months duration were subjected to neuro-imaging **(Fig. 2)**.

The aspiration from these lesions demonstrated AFBs, but the culture grew Nocardia. I had a large series of various lymphomas associated with HIV. Just to cite one of them **(Fig. 3)**, with huge hepatomegaly, ptosis, with infiltration of extraocular muscles and CD4 110 cells only.

In the decade of 1991, despite all efforts of community awareness and expanding centers for HIV care, the patients used to report to the hospital very late. Antiretroviral therapy was not available; hence, the life span was limited, and morbidity and mortality were high.

During these years, some of our concepts had to be re-examined and appropriate measures had to be taken.

One such misconception was that if either of the spouses is positive the other will also be HIV infected.

We used to do couple counseling extensively so as to protect either of them from OIs and STDs. Couples were counseled regarding barrier protection with condom. But our study showed that about 25% were strictly abstinent. About 40–50% were using condom occasionally and the remaining expressed their inability to follow the protection due to hutment, poverty, fear of getting identified in a joint family, etc.

The intriguing fact was that 40% of our couples having 3–4 kids were discordant. Later on I had undertaken a

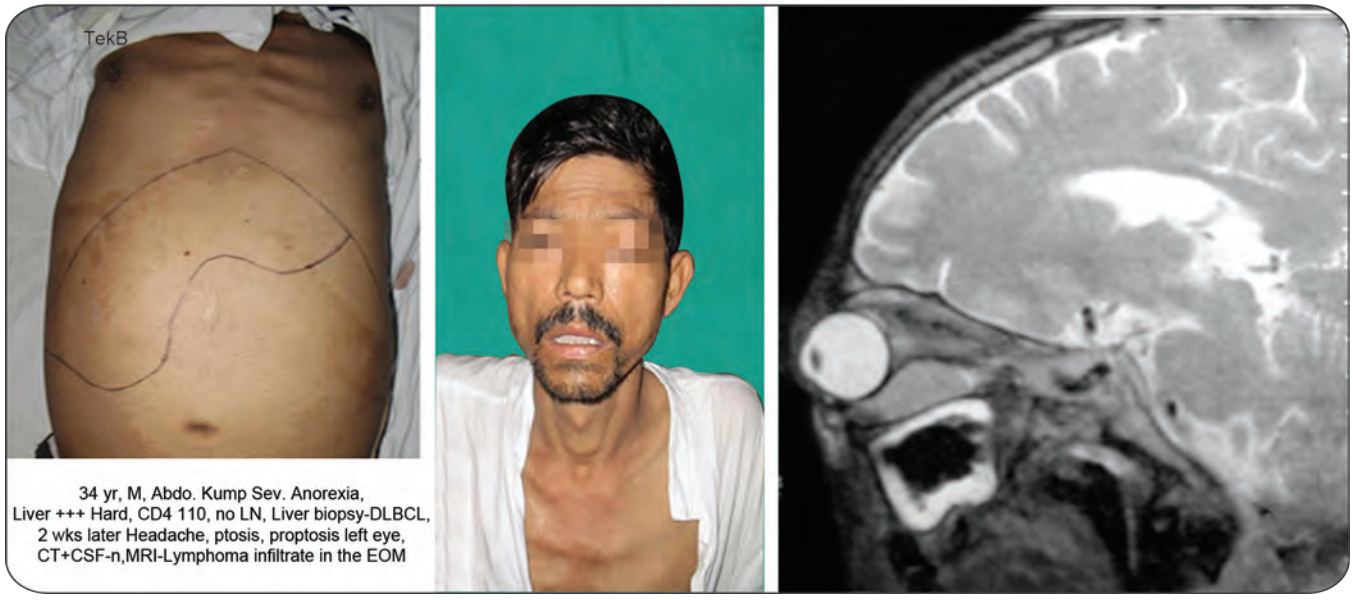

Fig. 3: A case of large diffuse B-cell lymphoma

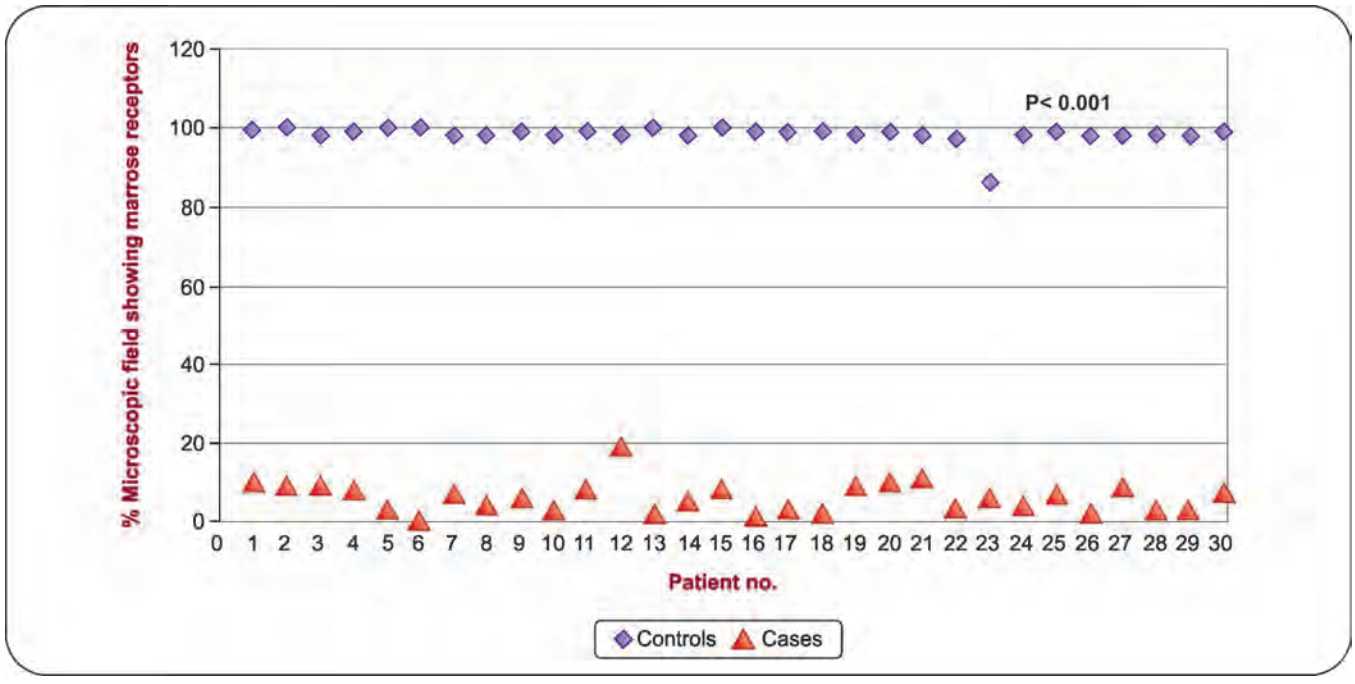

Fig. 4: Mannose receptors in vaginal epithelium

study of mannose receptors **(Fig. 4)** in vaginal epithelium of discordant couples.

The seronegative wives had mannose receptors but the seropositve wives were deficient in these receptors.

Antiretroviral Treatment

Azidothymidine (AZT): The first antiretroviral drug was discovered in 1987, had expedited approval of US FDA. HIV had just arrived in our country in 1986 so there was

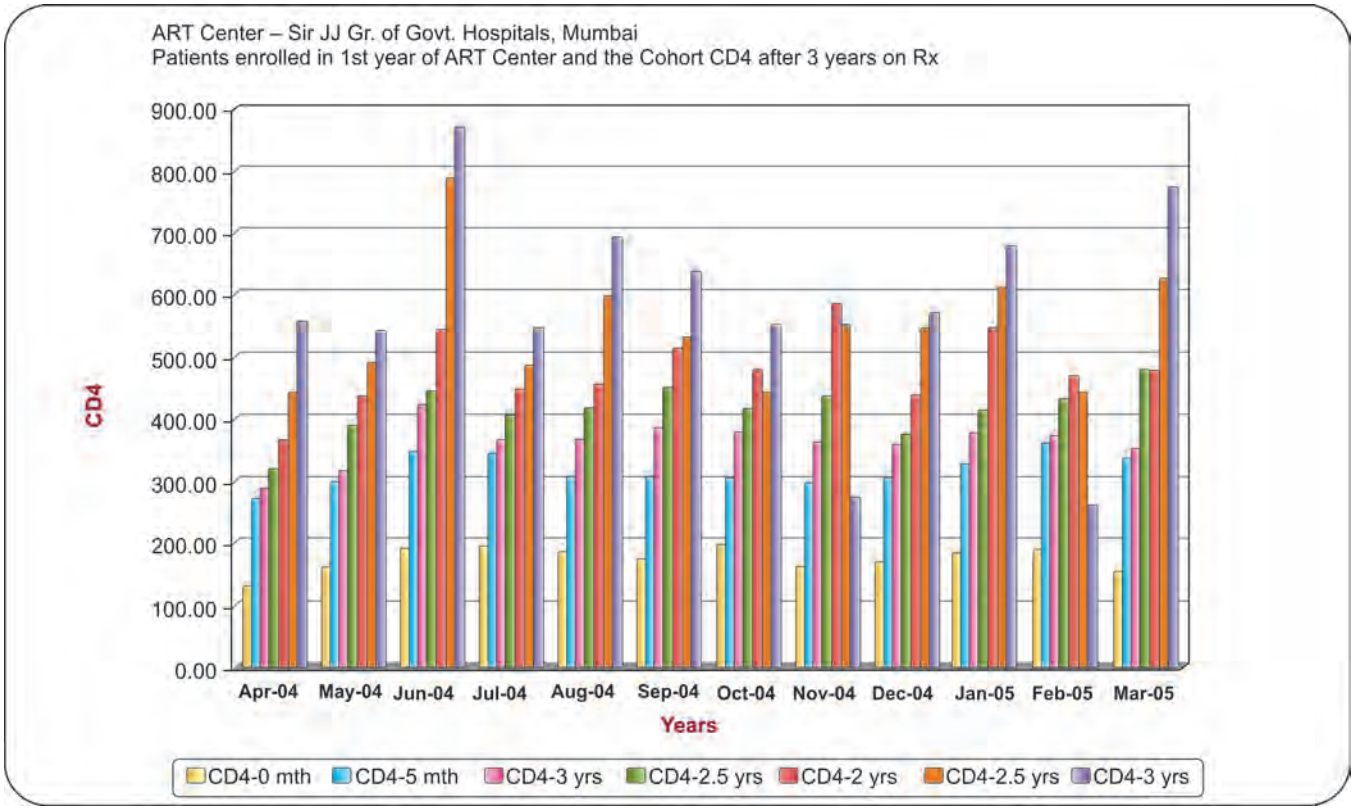

Fig. 5: CD4 rise after ART

no question of its use then. But in western world AZT being the only hope; it was used inadvertently and like penicillin within few months serious side effects and AZT resistance became apparent. Over next 3–4 years combination therapy became successful to control the viral load. Combination antiretroviral (cARV) therapy was not affordable to 95% of HIV infected people living in the developing world.

NACO was giving free therapy for OIs but treating OIs without ARVs was like amputating a diabetic gangrene without treating DM. Fortunately in 2000, the Special Session of United Nations General Assembly (UNGASS) upheld health as a basic human right and providing access to free ARVs became the responsibility of the Federal Govt. WHO launched an ambitious program of treating 3 million HIV patients by 2005.

Western world had ARV experience since 1987. With experience the guidelines were modified from time to time. There are American (DHHS), British (BHIVA), IAS (European) guidelines but as they have unlimited access to ARVs the guidelines have individualistic approach. But our National guidelines are based mainly on WHO guidelines.

A community oriented therapy program needs uniform guidelines, based on the efficacy of drugs, availability of resources including finance, apart from other factors like distribution, storage, etc. Indian National Guidelines were developed by Technical Experts of the country under the NACO initiative.

Govt. of India launched the free ART program in March 2004, the launch started from my institute having the largest number of HIV patients in J J Group of Govt. Hospitals, Mumbai.

It was a game changer. The first combination that was used for maximum number of patients was STAV + LAM + NVP being the lowest cost yet effective combination. The rise in CD4 was significant as shown in **Figure 5**. As the immunity improved the OIs almost disappeared, great improvement was seen in morbidity and mortality.

But as said earlier within a short time, a large number of side effects of cARV were seen. The most obvious was lipodystrophy **(Fig. 6)** which disfigured patients who

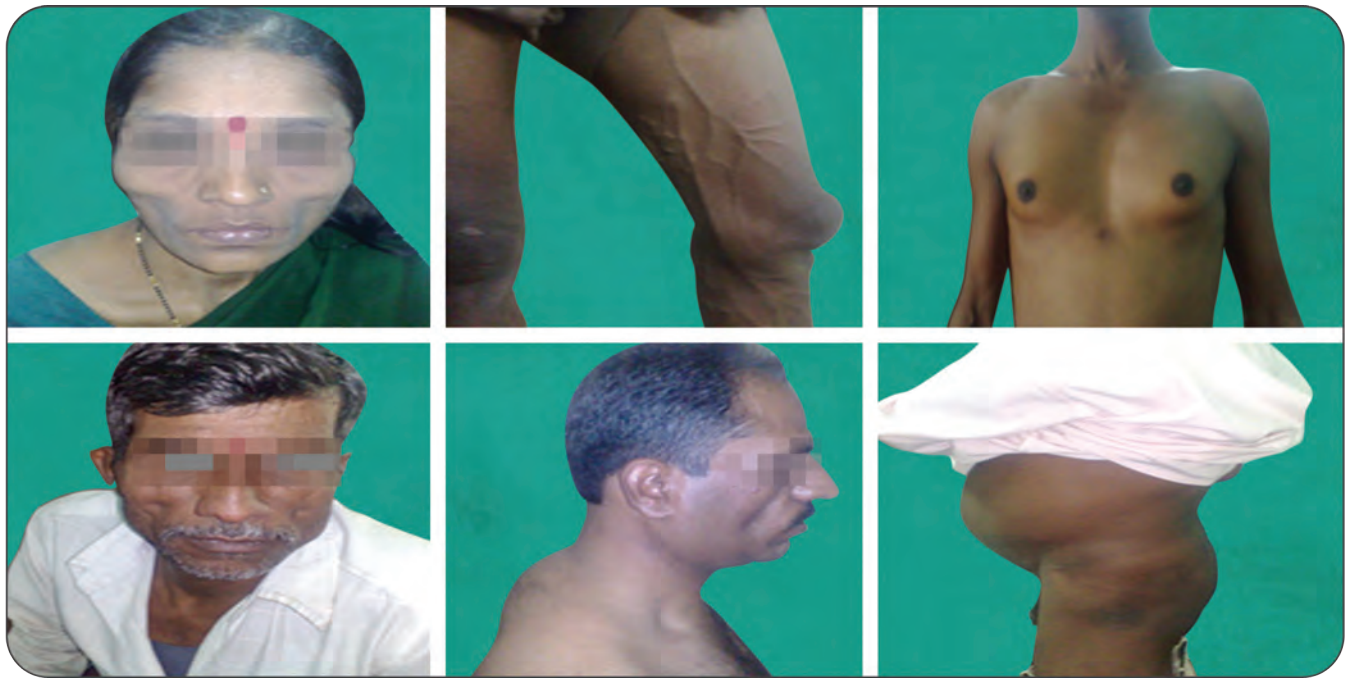

Fig. 6: Lipodystrophy

started looking sick although the disease status was improving. They feared being identified and discriminated.

The ARV toxicity profile to the first-line ART in my experience is shown in **Table 2**.

Patients' therapy compliance was a challenging issue. Ignorance, working pattern, inherent forgetfulness, and in few cases their alcohol addiction were major obstacles in compliance. In addition, Mumbai being the financial capital of India, a large number of the patients were migrant laborers. It was a major factor for their risk behavior and also a major factor for non-compliance because 3 months in a year they used to go back to their native place for farming. As a result the drug resistance was developing.

From 2004 to 2008, ART centers were being established all over the country. Apart from uniform therapy guidelines, the doctors had to be trained in this new arena.

Although a network of ART centers was being developed large number of the patients refused to attend the nearby centers for the fear of being identified. The social implications of the disease made the management difficult.

In 2008, first-line drug therapy was showing evidence of therapy failure mostly due to development of drug resistance. It was necessary to change the ARVs; therefore, second-line ART was initiated from 2008. The major change was introduction of tenofovir (TDF) and in few cases ritonavir boosted protease inhibitors.

TABLE 2 ARV toxicity

AZT marrow suppression	8%	Pancreatitis	2%
Lipoatrophy	34%	Lipodystrophy	5%
Toxic neuropathy	10%	Hyperlactatemia	2%
Hepatotoxicity	3%	Drug rash	6%

In first 6 months after TDF, I had 17 cases of TDF induced nephropathy. Nephropathy was not anticipated with less than 6 months exposure to TDF. Three years later a study on TDF nephropathy showed long-term exposure to STV use prior to TDF was the culprit.

For the first time NACO started estimation of viral load in selected first-line failure cases who did not show expected rise in CD4.

In this exercise I detected quite a few cases of immuno-virological discordance. These patients had low CD4 and undetectable viral load. I thought of a possibility of HIV-2 infection which so far was not identified in the country.

It was not possible in a Govt. set up at that time so I tied up with a private set up which had newly introduced HIV-2 Western Blot. I could detect 167 cases of HIV-2 which till then were receiving NNRTI in vain. After these results, diagnostic tests to differentiate between HIV-1 and HIV-2 were introduced and therapy was appropriately amended. Many newer drugs have been added to the armamentarium.

Despite offer of cost-free CD4, free viral load and free therapy, still we keep getting patients with OIs. It clearly indicates therapy failure due to non-compliant patient.

My recent data analysis showed that 31.3% of cases on ART were receiving cARV for past more than 15 years. The ART initiation criteria then was CD4 <200 cells. It can be deduced that these cases acquired the infection 8–10 years prior to initiation of ART. In earlier years, in absence of ARVs, patients were succumbing to AIDS within few days to weeks. But longevity increased so well after ART that people who acquired the infection in the age group of 25–35 years are now in their fourth and fifth decade. Quite a large number of them have crossed 60 years of age. And now apart from retroviral disease 18% of the cases are suffering from non-communicable diseases like hypertension, diabetes mellitus. It adds to the complexity of management.

In our earlier counseling in order to build up the hope and dispel their anxiety, patients were informed that soon there will be a breakthrough to wipe out the virus. We also hoped for anti-HIV vaccine but the virus is far more tricky than expected. We succeeded in controlling the viral load but could not get rid of it. The recent development of long acting injectables offers hope for improved compliance and long-term viral suppression.

HIV vaccine remained elusive over three decades. There is no breakthrough as yet because of multiple portals of entry, multiple groups and subgroups of HIV and constant mutation.

Avoidance of human risk behavior is the mainstay of prevention but it is the most challenging task, almost impossible. Safer sex practices, targeted interventions, PrEP, all have limitations and are related to human behavior. Finally, the only hope is to control human reservoir by Test and Treat!

HIV is a forerunner of all the new viruses, which emerged in last decade. For example, SARS, Chikungunya Nipah, H1N1, H5N1, Zika, Ebola they all, like HIV, are single stranded RNA viruses. No vaccine against any of these RNA viruses has so far been developed. Although HIV warned us about universal precautions, we have miserably failed in developing necessary infrastructure and safe culture! It is evident from the recent pandemic of SARS-CoV-2.

There is a long way to go!!

Conclusion

Knowledge about various aspects grew as the epidemic evolved. Though ART is a game changer, presently the main challenges are compliance of the patients and emergence of drug resistance. After all it is not possible to change the human behavior.

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CHAPTER

187 HIV and HBV Coinfection—Double Trouble

PK Agrawal

Abstract

Management of HIV/AIDS has undergone a revolution in recent years. Introduction of HAART lead to dramatic decrease in mortality associated with opportunistic infection that complicates advanced HIV infection. Incidence of chronic hepatitis has declined tremendously after introduction of vaccination of infants for Hepatitis B. But there is increased prevalence of HIV-HBV coinfection because both share common modes of transmission. HIV-HBV coinfection shows more rapid progression to end stage liver disease and liver fibrosis. Agents selected for the treatment of HIV-HBV coinfection should be active against both viruses.

Introduction

In recent years the management of HIV/AIDS has undergone a revolution. There was a rapid and dramatic decrease in mortality associated with opportunistic infection that complicate advanced HIV infection after the introduction of HAART. Since the emergence of vaccination of infants for Hepatitis B, the incidence of chronic hepatitis has declined tremendously. But as both Hepatitis B & HIV share common modes of transmission, there is increased prevalence of HIV-HBV coinfection. Hepatitis B infection is more frequent and more severe in HIV patients. The progression to cirrhosis and end stage liver disease is more rapid than in those not HIV infected. Coinfection of HIV may cause reactivation of Hepatitis B in HBsAG antibodies patient, especially in immunocompromised people. One of the most frequent causes of non-AIDS related death in HIV patients is liver disease caused by Hepatitis B.

Epidemiology

Since transmission routes of Hepatitis B and HIV are more or less similar (e.g., sexual contact, mother to child transmission at birth, parental (blood to blood), and through other infected bodily fluids. So there is high frequency of confection of HIV with hepatitis B. Worldwide nearly 10% of HIV infected population also infected with Hepatitis B. It is expected to be higher approximately 20% in Southeast Asia, 5% in North America and Western Europe. Higher rate of coinfection of HBV and HIV has been observed in MSM (men having sex with men) than heterosexuals or injecting drug users. Prevalence of HBsAg (2–14%) has been observed in HIV infected Indian population. Another studies indicated approximately 22% and 30% showing quite high frequency. These variations in study most probably due to small sample size data multicentre studies and unavailability of multirisk group data. Thus, in India, overall epidemiological trend remains obscure. According to NACO in 2017 National Adult (15–49 years), HIV prevalence in India is estimated at 0.22%. Total number of PLHIV is estimated at 21.40 lakhs. India is estimated to have 87.58 thousand new HIV infection in 2017. According to Journal of Clinical & Translational Hepatology (2017) it is estimated that about 200 crore of worldwide population have been exposed to the Hepatitis B Virus (HBV) of whom 350 million harbor

it chronically. India falls in the intermediate endemicity zone (prevalence of 2–7%, with average of 4%) with disease burden of about 50 million. Out of 36.7 million PLHIV globally, 2.7 million people also had HBV infection.

Pathogenesis

Hepatitis B is an immune mediated infection. Interaction of the virus and the host immune system leads to liver injury progressing to cirrhosis and hepatocellular carcinoma. HIV weakens the immune system by infecting and destroying CD4+ T Cells which leads to immunodeficiency. HIV attached to the CD4+ protein on the surface of these and other cells to gain entry. HBV is more or less 100 times more infectious than HIV. The risk of chronic Hepatitis B is greater in cases of HBV/HIV coinfection. It is demonstrated that in coinfection of HIV with HBV mortality due to liver disease is 19 times that of HBV infection alone and eight times more than in person with HIV infection alone. Mortality increase in individuals with CD4+ T-Cell counts. After initiation of highly active antiretroviral therapy (HAART), there is immune reconstitution leading to more liver damage. There are higher HBV DNA levels, lower serum ALT, more liver fibrosis, and more risk of end stage liver disease in the patient with HIV-HBV coinfection. Although healthy adults who are infected with HBV has less than 10% chance to develop into chronic hepatitis B, when an HIV positive adult is infected, the risk is up to 25%. CD4 restoration is less than satisfactory in response to HAART in these patients.

Treatment

For the treatment of HIV-HBV coinfection, agents selected should be active against both viruses. First goal of the clinician is to select the patient whether to treat for HIV alone, for HBV alone or for both the viruses. For patients having HIV or HIV with HBV the treatment endpoints remains the same although loss of HBeAg or HBsAg as well seroconversion to anti-HBeAg and anti-HBs is not common. The treatment must include agents active against both viruses in HIV-HBV coinfection. Not doing so will lead to emergence of HIV strains that are resistance to NRTI (nucleoside reverse transcriptase inhibitor). The recommendations from the recent the USA & Europe guidelines advocate the use of two anti-HBV drugs as part of HAART in HBV-HIV coinfection. The aim of this combination therapy is to decrease the development of resistance even though very little data exists on either mono- or coinfected patients with such therapy. The preferred treatment for dual HBV/HIV coinfection is the combination of tenofovir and lamivudine (emtricitabine). Removal of HBV therapy or change in HIV therapy for virologic failure may lead to rebound hepatitis. Hence, on changing ART always consider HIV therapy with activity against HBV. Latest studies suggest that despite faster decline of antigen level on addition of pegylated interferon for the treatment of HBV active ART in HBeAg positive coinfected person, HBeAg, or HBsAg clearance did not increased. Tenofovir alafenamide (TAF) is now available with comparable efficacy to Tenofovir but with reduced toxicity. Others—New antiviral agents like HBV entry inhibitors are currently in development. Even after HBsAg seroconversion, cessation of HBV active NRTI is safe or not remains unknown.

Vaccination

Vaccination against Hepatitis A and B should be given to all HIV patients who are not immune. In HIV positive patients the immunogenicity to HBV vaccination is decreased that is reflected by lower antibody titers, gradual waning immunity and seroconversion rates of 18–65%. Response to vaccination is poor in HIV patients especially in those with lower CD4 counts. These individuals poorly maintain the antibody titers after vaccination. May consider increase dose (double the dose of HBV vaccine) for adequate response. One month after completion of vaccine schedule anti-HBS titers should be checked. Patients with anti-HBS titer less than 10 IU/mL, a second vaccine cycle is recommended. Improved response may expect with higher CD4 counts and undetectable plasma HIV RNA on doubling the HBV vaccine dose.

Conclusion

The liver is frequently affected in patients with HIV. HIV/HBV coinfection shows more rapid progression to end stage liver disease and liver fibrosis. Since both HIV and HBV share common modes of transmission so the incidence is high with coinfection. Liver disease considered to be one of the leading causes of death in patients with HIV in post HAART era. Agents selected, for the treatment of HIV-HBV coinfection, should be active against both viruses. For better outcome in HIV-HBV coinfected patients there is increase need of close working relationships between primary care providers, infectious disease specialists, and hepatologists.

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CHAPTER

188 Aging and HIV Infection: The Shape of Things to Come

Jaya Chakravarty, Aakash Rai

Abstract

The life expectancy of the PLHIV (People Living with HIV) has increased significantly because of increased availability of ART and "treat all" strategy, leading to increased proportion of patients with HIV are living longer. The challenges faced by aging PLHIV can be either associated with HIV related pathology (increased risk for chronic conditions), complications due to HIV treatment and age related pathology (cardiovascular diseases, diabetes, etc.).

Often older individuals are detected late as clinicians do not think that they are at risk for HIV infection. Early detection of HIV and prompt start of ART in older PLHIV should be done to decrease mortality. Aging PLHIV are at increased risk of malignancies. The risk of anal canal, colon, prostate, lung, hepatic, and oral cavity malignancies are increased in PLHIV as compared with age-matched general population, especially after 50 years of age. Screening for these malignancies should be done for early detection and effective management.

Long-term use of ART there is an increased risk of metabolic syndrome in the form of increase in centripetal fat, raised triglyceride & cholesterol levels, raised blood pressure and insulin resistance which are all risk factors for cardiovascular disease. Focus should be on drugs with excellent efficacy and minimal drug interaction and side effects when considering any ART for aging PLHIV. As this population is at increased risk for cardiovascular disease, counseling for lifestyle modifications like smoking cessation, regular exercise, and healthy diet would also decrease mortality and morbidity.

Introduction

With easy availability of antiretroviral therapy (ART), Treat All strategy by WHO, the life expectancy of the People Living with HIV (PLHIV) has increased significantly leading to increased proportion of patients with HIV a living longer. PLHIV are known to experience age-related comorbidities at relatively younger ages when compared with the general population. Thus many publications on HIV define older as ≥50 years of age. The challenges faced by these aging PLHIV are due to the disease itself, accelerated aging, and therapy-related toxicities and long-term side effects.

Burden of Disease

Approximately, there were 5.7 million individuals ≥50 years were living with HIV infection by the end of 2016 and it is estimated that by 2020, 21% of PLHIV will be in this older age group. Moreover, there were approximately 110,000 new infections occurring in persons of this age group in 2016.[1] This could be an underestimation as older individuals are frequently not perceived by their clinicians as being at risk for HIV infection and, consequently, are less likely to be tested for HIV compared with younger adults.[2,3]

In a study of 8,255 older adults who accessed HIV care in England, Wales, and Northern Ireland.[4] Almost half of older adults had CD4 cell count less than 200 cells/μL at the time of diagnosis. They were 14 times more likely to die within a year of diagnosis compared with older adults who were diagnosed at young age. Most studies have demonstrated that, despite successful ART and viral suppression, immune recovery is less robust with increasing age, highlighting the importance of early diagnosis and treatment.[5]

System-wise Non-AIDS Morbidity

The manifestations in older PLHIV could be due to HIV-related pathology, treatment-related complications, and age-associated pathology **(Table 1)**. Other manifestations that occur earlier or more commonly in this subset are bone-related pathologies like osteoporosis and fractures, neuropsychiatric manifestations, malignancies, and renal failure.[6]

Immune activation: HIV infection is a major source of inflammation in both treated and untreated individuals. ART that suppresses the viral load reduces these inflammatory markers but does not make it normal. This immune activation causes accelerated aging of T cells (immunosenescence) meaning that a PLHIV is physiologically older than his actual age. This causes increased incidence of age-associated conditions including cardiovascular, bone, metabolic, and neurocognitive diseases, which are generally seen at a later age in non HIV patients.[6-8]

Malignancies: PLHIV are at increased risk of malignancies.[9] The AIDS defining malignancies like Kaposi sarcoma, Non-Hodgkin lymphoma (NHL), and invasive cervical carcinoma are gradually decreasing. With increase survival of PLHIV, the incidences of non-AIDS-defining cancers are increasing. The risk of anal canal, colon, prostate, lung, hepatic, and oral cavity malignancies were excessively raised in PLHIV as compared with age-matched general population, especially after 50 years of age **(Fig. 1)**.[10]

This increased incidence of malignancy among PLHIV may be due to immunosuppression, direct effects of the HIV virus itself, coinfection with other oncogenic viruses, environmental factors, and possibly the use of antiretroviral drugs. Malignancies occur at an earlier age, have higher tumor grade, are more aggressive, and are at an advanced stage at presentation. Thus the focus should be on early screening, smoking cessation, HPV and HBV vaccination, treatment of Hepatitis C, and Hepatitis B.

Cardiovascular system: Long-term use of ART there is an increased risk of metabolic syndrome in the form of increase in centripetal fat, raised triglyceride & cholesterol levels, raised blood pressure, and insulin resistance, which are all risk factors for cardiovascular disease. The cardiovascular risk is also related to the duration of treatment with antiretroviral drugs and increases with uncontrolled disease, particularly in presence of other risk factors.[12]

The risk of acute myocardial infarction (MI) and advanced subclinical cardiovascular disease is increased in PLHIV when compared to age matched general population.[13] With increasing age, focus should be shifted on the treatment adherence and management of hypertension, dyslipidemia, obesity, and diabetes. Lifestyle modifications like smoking cessation, regular exercise, and healthy diet would also help in reducing cardiovascular mortality.

Central Nervous System

Neurocognitive disorders: It is estimated that the approximately 50% of the PLHIV on long-term ART have some amount of neurocognitive dysfunction. HIV-associated dementia is three times higher among patients ≥50 years than among patients aged 20–39 years. The most severe form of HIV-associated neurocognitive disorders is HIV-associated dementia (HAD), classically manifested as a subacute onset of impairments in subcortical function, such as decreased attention/concentration and psychomotor slowing. ART is known to have beneficial effect on the treatment and prevention of HAD. As HAD is associated with local replication of HIV in the CNS, it is

TABLE 1 Causes of morbidity in PLHIV

HIV-related pathology	*HIV treatment complications*	*Age-associated pathology*
• HIV-related increased risk for chronic conditions • HIV infection-related immunosenescence	• Lipodystrophy • Cardiac disease • Dyslipidemia • Diabetes • Metabolic syndrome	• Cardiovascular disease • Diabetes • Osteoarthritis/osteoporosis • Glaucoma/cataract • Sarcopenia • Neurocognitive diseases

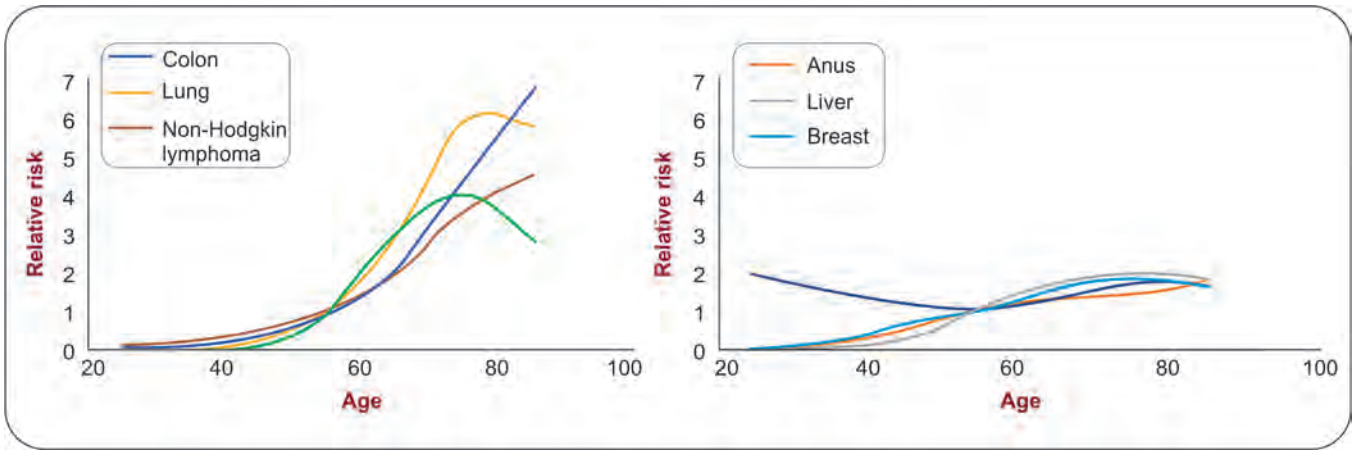

Fig. 1: Age-wise relative risk of malignancies in PLHIV compared to general US population. From Surveillance, Epidemiology and End Results (SEER) Study
Source: Justice AC et al. Journal of the International AIDS Society, 2019[11]

recommended that ART, which penetrates the CNS should be used. Some of the preferred regimens are Tenofovir-emtricitabine plus dolutegravir; Abacavir-lamivudine plus dolutegravir; or Tenofovir-emtricitabine plus ritonavir-boosted darunavir.

It is also important to distinguish between HIV-associated neurocognitive disorders and other neurodegenerative disorders, especially Alzheimer's disease. The incidence of neuropsychiatric manifestation especially depression is more in PLHIV as compared to the general population and it increases with age and should be recognized and treated early.[14]

Peripheral neuropathy: Ageing is a risk factor for peripheral neuropathy. In an observational study of 2,141 antiretroviral-naïve PLHIV who were seen annually between 2000 and 2007, ageing was associated with peripheral neuropathy despite virologic and immunologic control of HIV.[14] Almost 50% of the PLHIV are having some amount of HIV-associated sensory neuropathy (HIV-SN). This could be either be HIV-associated or as an adverse effect of ART. However, with the decrease in the use of antiretrovirals like stavudine, didanosine, etc. the incidence of ART induced neuropathy is decreasing.

Skeletal system: PLHIV are prone to a wide range of musculoskeletal problems including opportunistic bone infections, osteonecrosis, osteopenia, and osteoporosis, which could be either due to HIV itself or ART induced. The chronic inflammatory state, antiretroviral drugs like tenofovir, abnormal vitamin D metabolism, cigarette smoking, alcohol use, depression, opiate use, low testosterone levels, and premature menopause are the factors responsible for enhanced bone loss in PLHIV.[15] With increasing age, bone fractures (especially hip fracture) are responsible for very poor quality of life and a major physical and psychological impact on the patients and their family.[16]

Apart from the earlier mentioned problems, PLHIV also have sarcopenia, that is, loss of skeletal muscle mass. Many of the factors responsible for sarcopenia are already present in a PLHIV. Along with these factors, ART is also responsible for differential body fat distribution (already described earlier) and also sarcopenia.

Liver disease: Coinfection with hepatitis B and C viruses (HBV and HCV) is common among PLHIV and HIV coinfection increases the likelihood of chronic infection and a faster rate of liver fibrosis progression. Thus, chronic liver disease is a frequent finding in older adults with HIV. Thus, all efforts should be made to detect these chronic infections early and treat them. Vaccination for Hepatitis B should be done for all PLHIV at the time of diagnosis who are HBsAg negative.

Renal system: In general population, glomerular filtration rate (eGFR) decreases with increasing age normally. problems arising from age-associated diminished renal function may be compounded among older adults living with HIV. Kidneys are the reservoir for the virus, and

hence the risk of renal dysfunction is higher in PLHIV. Risk of acute renal failure is increased with Low CD-4 cell levels and long-term use of ART. HIV-associated nephropathy (HIVAN) has a high risk of developing end-stage renal disease (more often seen in African-Americans as compared to whites). Many ART drugs (tenofovir) are nephrotoxic, and hence may require dose modification in these patients or even require change in therapy.

Hypogonadism: Hypogonadism is common in men with HIV and has been associated with advanced disease and, in the ART era, persistent viremia. In one study of the Multicenter AIDS Cohort Study (MACS) cohort, the rate of decline in testosterone level decline over 10 years appeared similar between men with or without HIV, although HIV may be associated with greater loss of diurnal variation.[18]

Geriatric syndromes and functional impairment:[17] In addition to facing multimorbidity and polypharmacy, older adults with HIV may also be dealing with geriatric syndromes, such as falls, frailty, functional impairments, and disability. As with certain comorbidities, these geriatric syndromes may also occur at relatively younger age in adults with HIV compared with the general population.[18]

TABLE 2 Evaluation and monitoring of PLHIV

Cardiovascular risks	Blood pressure check	At baseline and annually
	Fasting sugar and/or HbA1C	• At baseline and every 6–12 months • 1–3 months after ART initiation
	Fasting lipid profile	• At baseline and every 6–12 months • 1–3 months after ART initiation
	Weight assessment	At baseline and follow-up visits
	Tobacco use assessment	At baseline and annually
Neuropsychiatric disorders	• Depression screening • Screening for cognitive deficits	• At baseline and annually • At baseline and annually
Medication toxicity	• Complete blood count with differential • BUN and creatinine • ALT, AST, and total bilirubin	At baseline, 2–8 weeks after ART initiation and every 3–6 months thereafter
	Urinalysis	• At baseline • At ART initiation or change • Annually
	Dilated fundoscopic examination	Every 6–12 months in patients with CD4 <50 cells/μL
Other metabolic complications	Bone densitometry	At baseline in postmenopausal women and men ≥50 years
Cancers	Colonoscopy	• At 50 years of age in asymptomatic person with average risk • Earlier screening in patients with strong family history • Subsequent testing based on baseline results
	Mammography	Annually in all patients of 50–74 year age
	Cervical pap smear	• At baseline and subsequent testing based on coinfection with HPV • Additional tests if abnormal results
	Anal pap smear	• Consider at baseline and annually • More frequent testing if abnormal results

Management of HIV Infection in Aging Population

Early diagnosis and prevention: Often older individuals are detected late as clinicians do not think that they are at risk for HIV infection. This mindset needs to be changed as early diagnosis and institution of therapy improves mortality in this group. Early screening of hypertension, diabetes, dyslipidemia, and counseling for weight loss, exercise, and tobacco cessation should be part of routine management. Screening for neurocognitive disorders, depression, bone health, and malignancies should be done routinely at baseline as well as part of follow-up **(Table 2)**. Vaccine against influenza, pneumococci, Hepatitis A and B should be given to older PLHIV.

Antiretroviral Therapy

Institution of early ART is recommended in this group so as to reduce the higher risk of non-AIDS-related complications. There are no preferred first-list ART regimens for older adults. However, while choosing the ART regimen focus should be given on concomitant medications and comorbidities, particularly liver and kidney disease. As this group patients are often on polypharmacy, that is, taking five or more medications it can lead to adverse drug events, drug-drug interactions, and inappropriate medication. This can also lead to poor adherence.

Age-associated physiologic changes like increased adiposity, increased gastric pH, decreased albumin levels, and changes in the cytochrome p450 enzyme system alter pharmacokinetics of drugs. Since both NNRTIs and PIs are metabolized by cytochrome p450, older patients with HIV may have significantly higher drug exposure when treated with antiretroviral agents and are thus prone to adverse effects. Moreover, cytochrome P450 interactions of PI and NNRTIs should be considered to minimize risk for drug-drug interactions.[19] Although integrase inhibitors have lesser interactions, interactions and timing of administration of polyvalent cations including calcium and iron supplements must be kept in mind as they can affect absorption of INSTI. Dolutegravir which is usually well tolerated causes increased neuropsychiatric problems in PLHIV more than 60 years of age and weight gain. Since both NNRTIs and PIs are metabolized by cytochrome p450, older patients with HIV may have significantly higher drug exposure when treated with antiretroviral agents and are thus prone to adverse effects. Moreover, cytochrome P450 interactions of PI and NNRTIs should be considered to minimize risk for drug-drug interactions.[19,20]

Conclusion

Health system is constantly working on enhancing the life expectancy of PLHIV. Early detection of HIV and prompt start of ART in older PLHIV should be done to decrease mortality. When considering any ART focus should be on drugs with excellent efficacy and minimal drug interaction and side effects. With the emergence of very effective ART the focus is now shifting on decreasing the functional and cognitive impairment, preventing cardiovascular mortality and morbidity, prevention and early detection of malignancy and decreasing the disability, and enhancing the quality of life in PLHIV. Screening and prompt detection of these comorbidities will go a long way in improving morbidity in these age groups. A public health approach that anticipates the needs of the ageing population with HIV will be best suited to prevent and manage these challenges.

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Section 14

Section Editor: **DP Singh**

Tuberculosis

CHAPTER

189 Newer Paradigms in the Management of Drug-resistant TB

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Abstract

Drug-resistant tuberculosis is an important impediment to successful TB control in any country. India has the highest number of MDR-TB cases in the world. Diagnosis and management of such cases are difficult; drugs are costly, of longer duration, and are associated side effects that are sometimes unacceptable. Further, treatment outcomes are not very encouraging. However, with availability of newer diagnostic opportunities, specifically CBNAAT, LPA for both the standard and second-line drugs and liquid culture and drug susceptibility testing have changed the approach. Further developments with availability of newer and efficacious drugs like bedaquiline, delamanid, and pretomanid have changed the paradigm of our approach for treating these cases with better outcomes. The duration of therapy has further come down with these new drugs and now we have the option of shorter courses of therapy to 6–9 months and the all oral longer duration of therapy for 18 months are now realities with success rates of more than 80%. Another important advantage is the no necessity of injectables so that patients accept these injection-free, all oral regimens with better compliance.

Introduction

The Revised National Tuberculosis Control Program (RNTCP), now known as the National Tuberculosis Elimination Program (NTEP) has notified around a total of 2.41 million TB patients of all types in 2019 according to the Nikshay dashboard.[1] More than a quarter of TB patients in India have drug resistance to one or the other anti-TB drug as per the 1st National Anti-TB Drug Resistance Survey (NDRS) of India (1914–1916).

A case of presumptive DR-TB includes the following:

- Positive sputum smear during any follow-up visit while on treatment with first line ATT;
- Pediatric TB non-responders;
- If the patient is a contact of a known DR-TB case;
- Earlier treated patient;
- TB-HIV coinfection;
- All notified new TB patients.

Results from a RNTCP (NTEP) accredited laboratory is taken as confirmed case of DR-TB. These patients are then classified according to the following definition:

Mono-resistance TB (MR): Biological sample—sputum or fluid or tissue shown to be resistant to any one anti-tubercular drug of the first-line only.

Polydrug resistance TB (PDR): When the biological sample shows resistance to more than 1 first-line anti-tubercular drug other than both INH (H) and rifampicin (R).

Rifampicin resistance (RR): When the sputum or the biological specimen shows resistance to rifampicin, when tested using phenotypic or genotypic methods and with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR, or XDR. Most of the rifampicin resistant cases will also show H-resistance, hence the

RNTCP (NTEP) has taken a considered decision that all R-resistance cases will be treated as MDR-TB cases.

Multidrug resistance TB (MDR): In this form of tuberculosis, the biological specimen is resistant to both INH and rifampicin with or without resistance to other first-line anti-TB drugs. These patients may also have additional resistance to any/all fluoroquinolones or any/all second-line injectable (amikacin, kanamycin, and capreomycin) anti-TB drug.

Pre-XDR-TB: MDR TB with demonstrable resistance to any one of the second-line injectable anti-TB drugs like amikacin, kanamycin, or capreomycin OR to any one of the fluoroquinolones.

Extensive drug resistance (XDR): When there is additional resistance to at least any fluoroquinolone (like ofloxacin, levofloxacin, moxifloxacin, etc) and a second-line injectables (like amikacin, kanamycin, or capreomycin) in a case of MDR TB.

The following technologies are used nowadays (besides culture and DST methods):

- Line Probe Assay (LPA) for detection of MTB complex and detection of resistance to first-line drugs rifampicin, isoniazid, and second-line drugs (fluoroquinolones, second-line injectables);
- CBNAAT (Catridge Based Nucleic Acid Amplification Test) Xpert MTB/Rif testing by using the Gene X pert platform; and
- TrueNat TB test.[2]

Drug-resistant tuberculosis is a great impediment to the achievement of End TB strategy because of the complexity of drug regimes against this form of tuberculosis, treatment outcome, and cost involved. However, with availability of newer drugs particularly bedaquiline (BDQ), delamanid, and pretomanid and experience of success with shorter durations of therapy have raised hope to handle this form of the disease. An estimated 484,000 incident cases of MDR/RR-TB were reported in 2018 globally. MDR/RR-TB was reported in 3.4% of all new cases and 18% in all previously treated cases of TB. The three high burden countries for this form of TB were India (27%), China (14%), and the Russian Federation (9%). Around 123 countries of the world have reported the presence of XDR-TB (extensive drug-resistant TB) in their population. The proportion of XDR-TB among MDR-TB patients is 6.2% worldwide.[3] About 214,000 deaths occurred from MDR/RR-TB in the word in 2018. INH mono-resistance was reported in 7.2% of cases of new TB and 11.6% in previously treated cases of TB globally in 2018. India in collaboration with WHO carried out the first National Anti-TB Drug Resistance Survey (NDRS) between 2014–1916. The survey carried out drug susceptibility testing (DST) for 13 anti-TB drugs using the automated liquid culture system, (the mycobacteria growth indicator tube, MGIT 960). The main findings were: MDR-TB in 6.19% of cases (2.84% among new and 11.60% among previously treated TB patients). Additional resistance to any fluoroquinolones was observed in 21.82%, and 3.58% of cases to any second-line injectable drugs amongst all MDR-TB cases. XDR TB was present in 1.3% of cases.[4] During 2007–2018, India tested 2,798,599 patients using CB-NAAT and line-probe assays (LPAs). These tests detected 236,725 drug-resistant TB patients. In 2019, the program notified a total of 66,359 Multi Drug Resistant/Rifampicin Resistant (MDR/RR) TB cases and 56,500 (85%) of them put on treatment, which is an improvement of 7.6% over last year as reported by the India TB Report, 2020.

Approach to Treatment of DR-TB

Drug resistance emerges when anti-TB drugs are used inappropriately, poor TB control program, delayed diagnosis, inappropriate drug regimen, inadequate initial therapy, incomplete duration of therapy, inappropriate treatment modifications, addition of a single drug to an already failing regimen, improper use of chemoprophylaxis, poor adherence and incomplete follow up, failure to isolate MDR TB, failure to employ DOTS, availability of over the counter anti-TB drug, and faked drugs. Use of second-line drugs can cure MDR TB cases. However, second-line treatment options are limited and require long durations (up to 2 years of treatment). Besides the longer duration of therapy, other problems associated with these drugs are that they are expensive and toxic. More severe drug resistance can develop in some cases.

An independent expert panel of the WHO reviewed the latest evidence for treatment of drug-resistant TB in July 2018. The committee recommended certain key changes and issued a rapid communication.[5]

The programmatic management of drug-resistant TB (PMDT) was initiated in India in 2007 and the National Guideline scaled up the same which was achieved

Flowchart 1: Diagnostic algorithm for drug-resistant TB

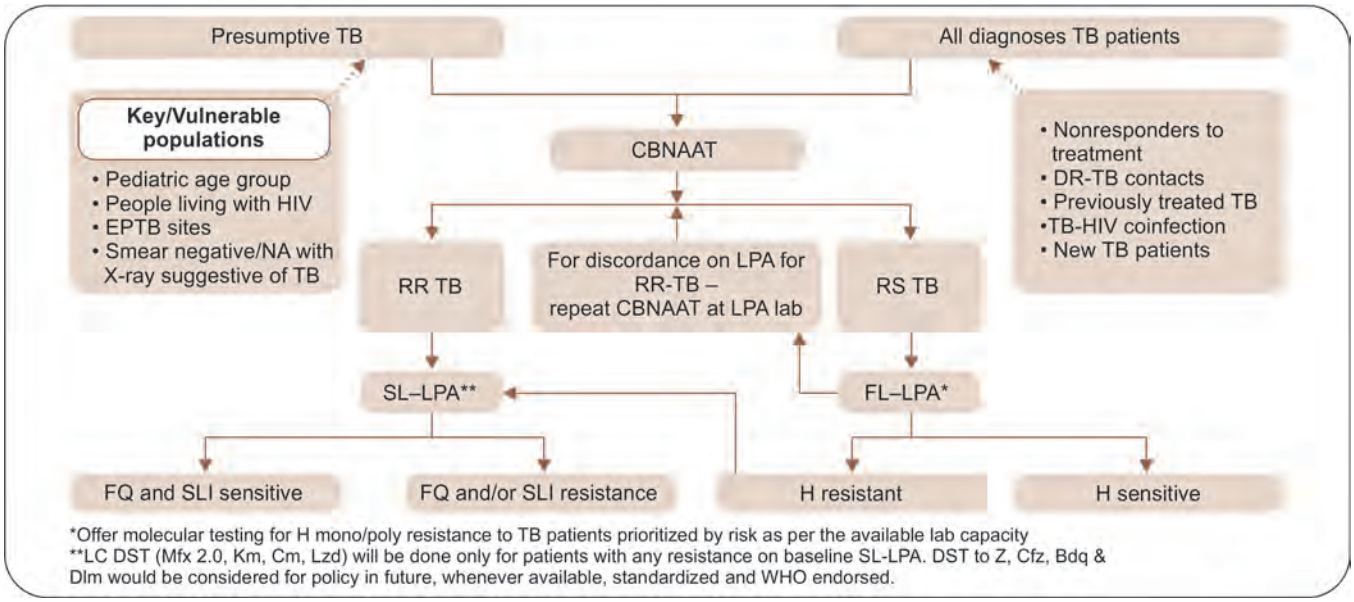

TABLE 1 Conventional drug regimen (previously used) for MDR/RR; and XDR-TB

Category of TB case	*Drug regimen (intensive phase)*	*Treatment regimen (continuation phase)*
MDR TB/RR-TB	(6–9 m) Kanamycin, Levofloxacin, Ethionamide, Cycloserine, Pyrazinamide, Ethambutol (duration 6–9 months)	(18 m) Levofloxacin, Ethionamide, Cycloserine, Ethambutol (duration 18 months)
XDR-TB	(6–12 m) Capreomycin; PAS-para Aminosalicylic Acid; Mfx-Moxifloxacin; High dose INH; Cfz-Clofazimine; Lzd-Linozolid; Amx/Clv-Amoxicillin-Clavulinic acid	(18 m) PAS-para aminosalicylic Acid; Mfx-Moxifloxacin; High dose INH; Cfz- Clofazimine; Lzd-Linezolid; Amx/Clv-Amoxicillin-Clavulinic acid

by March 2013. However, the success rate of MDR TB treatment has been around 46% consistently with a death rate of approximately 20% while the same figures at the global level has been 52% and 17%, respectively. Fluoroquinolone resistance in Indian patients was responsible for such high rates of treatment failure and death rates.[6]

The diagnostic algorithm for DR-TB is shown in **Flowchart 1**.

The conventional DR-TB regimens consisted of the following drugs, which many countries including India continued to use till recently. These are shown in **Table 1**. However, this regimen is no more used by the National program.

All MDR-TB isolates are subjected to liquid culture DST for kanamycin and levofloxacin at baseline to rule out pre-XDR and XDR-TB. Appropriate modifications have to be made if there is additional drug resistance. Pretreatment investigations are carried out and drugs are dispensed in patient-wise boxes on monthly basis. Follow-up is done with culture every month in intensive phase and every quarter in the continuation phase. However, the major issues with these regimens are the longer duration of therapy (24–27 months) resulting in poor compliance, side effects, and the overall success rate was below 50% with approximately 20% death rates. These regimens were continued till 2016 starting from 2007 when PMDT (Programmatic Management of Drug-resistant TB) was initiated in the country. With discovery and availability of BDQ (2012) and delamanid (2014) the situation changed.

Bedaquiline (BDQ) is a newly developed drug and is a diarylquinoline derivative. It targets the mycobacterial

ATP synthase.[7] It has strong bactericidal activity and tissue distribution is quite extensive and the distribution in the tissue can be there for up to 5.5 months after BDQ is stopped. The most significant benefit with the drug is that it shortens the time for culture conversion quite significantly. However, there was concern about cardiac toxicity with QTc prolongation, but subsequently it was found to be tolerated in most patients. The drug is given in the following doses:

- Week 0–2: BDQ in a dose of 400 mg (4 tablets of 100 mg) per day (all 7 days of the week) along with an optimized background regimen (OBR)
- Week 3–24: BDQ 200 mg (2 tablets of 100 mg) 3 times per week + optimized background regimen (OBR)
- After 24th week, and from Week 25 (start of month 7): Other drugs in OBR is to be continued

Delamanid (DLM) is a nitro-dihydro-imidazooxazole compound and acts by inhibiting the key mycolic acid synthesis of the *Mycobacterium tuberculosis*. The drug is administered orally as 100 mg twice daily (BID) for 2 months followed by 200 mg once daily (QD) for 4 months and is administered along with an optimized background regimen (OBR).

A number of societies, the WHO and the NTEP of India have recommended regimens for treating different forms of DR tuberculosis.[5,8-11] These recommendations are for the treatment of MDR-TB, XDR-TB, INH-resistant tuberculosis, or a mixed form of drug-resistant TB cases.

The WHO published the consolidated guidelines for DR TB in 2019 that include a set of comprehensive recommendations for the DR TB care and treatment.[5] It includes eight guideline documents developed by WHO over a period extending from 2011 till 2018. The document includes a consolidated policy recommendations for treatment regimens meant for INH-mono-resistant TB, (HrTB) and MDR/RR-TB. The treatment for the latter category includes both the longer and shorter regimens, monitoring guidelines using culture and the timing of starting antiretroviral therapy when this is associated. It also includes the recommendations for surgery for MDR-TB cases and an optimal model of care and treatment of such patients.

The recommended treatments of drug-resistant TB are in four groups:

- Treatment of INH-resistant cases
- Long duration (standardized) of therapy
- Shorter duration of therapy
- Treatment of mixed drug-resistant cases

The regimen may or may not include bedaquilline/delamanid and can be classified as treatment of:

- MDR/RR-TB
  - Shorter MDR-TB regimen
  - Conventional regimens for MDRTB
  - MDR or RR TB and additional resistance to any or all fluoroquinolones or second line injectable drugs
  - XDR-TB
- DR-TB (Mixed pattern)
  - with H mono + FQ/SLI/Lzd resistance
  - with MDR/RR-TB + FQ/SLI + Lzd resistance
- H-Mono/Poly Drug-Resistant TB

Treatment Regimens for INH-resistant Tuberculosis (HrTB)

The INH and other drug resistance produce significant problem in the success of TB treatment. **Table 2** shows the importance with various patterns of resistance that can ultimately lead to MDR/RR TB.

The World Health Organization (WHO) after reviewing many observational studies (–33 database, n-5418 INH mono-resistant cases) and individual patient data (IPD) came up with these specific guidelines for resistance to isoniazid in the absence of R-resistance. Rifampicin, levofloxacin, pyrazinamide, and ethambutol combination therapy is recommended for confirmed R-susceptible and H-resistant TB patients with confirmed rifampicin-susceptible and isoniazid-resistant tuberculosis. The treatment is for a period of 6 months. Streptomycin injection or other injectable drug is no more needed in this regimen. The duration can be extended up to 9 months. This will be true for extrapulmonary TB cases and TB with HIV also.

Conventional MDR-TB Regimen of MDR/RR-TB—Longer Duration Therapy

The regimen shown in Table 1 is recommended for R-resistant (RR) + H sensitive/unknown Or MDR–TB which was used till 2016. With the availability of new drugs, WHO has now grouped the anti-TB drugs used for DR-TB for longer MDR-TB regimens into three groups and has recommended how to include these drugs in

TABLE 2 Issues associated with H-mono- and polydrug-resistant TB (RNTCP data)

DST pattern *Total No. with DST available = 2,422 (%age out of 2,422)*	*Success (%)*	*Failure (%)*	*Progressed to Rif resistance (%)*
H-Mono (LJ/MGIT) n=819 (34%)	31	49	40
SH n=611 (25%)	25	54	52
SHE n=323 (13%)	16	67	53
S Mono n=442 (18%)	26	49	35
HE n=100 (4%)	31	54	64
SE n=68 (3%)	24	49	46
E Mono n=59 (2%)	29	56	59
H Mono (LPA) n=6426	53	24	41

TABLE 3 Grouping of drugs recommended for use in MDR-TB (longer regimens)

Group and steps	*Drugs*
Group A All the three drugs to be included	Levofloxacin, Moxifloxacin
	Bedaquiline
	Linezolid
Group B Add one or both drugs	Clofazimine
	Cycloserine, Terizidone
Group C Add to complete the regimen and when drugs from Group A and B cannot be used	Delamanid
	Pyrazinamide
	Imipenem-cilastatin OR Meropenem
	Amikacin (OR Streptomycin)
	Ethionamide or Prothionamide
	p-aminosalicylic acid

the regimen **(Table 3)**. This grouping is based on serious adverse events and relative risk for failure to treatment, or relapse and death compared to successful treatment.[5]

When a longer regimen is used for MDR/RR TB, all the three drugs in Group A and at least one agent from Group B must be included so that the treatment is ensured and is commenced with at least four anti-TB drugs which are likely to be effective, and at least three drugs should be included for the rest of the duration after BDQ is stopped after 6 months. If the regimen includes only one or two drugs belonging to Group A, then both the drugs listed in Group B are to be used. If it is not feasible and the regimen cannot include drugs from Group A or B, then Group C drugs are to be added so that the regimen is complete. Injectable agents like kanamycin and capreomycin are no more recommended in the longer regimen since BDQ is a part of the drug therapy. Levofloxacin or moxifloxacin are now a part of the longer treatment regimen for MDR/RR TB. BDQ can be and should be a part of the regimen for MDR/RR TB in patients above the age of 6 years. If susceptibility is demonstrated, amikacin can be used in adults above the age of 18 years with adequate measures for safety monitoring. Streptomycin may be considered if amikacin is not available.

The conventional regimen as indicated above (with BDQ for 6 months) is indicated in MDR/RR-TB with treatment duration of 24–27 months. If fluoroquinolone is used for more than 1 month or a second-line injectable drug like amikacin, kanamycin, or capreomycin, which is not a part of the shorter MDR-TB treatment regimen as described below, but that may cause cross resistance, then it should be excluded. However, if a reliable DST has excluded drug resistance to these two classes of drugs, the shorter regimen is a choice. BDQ is contraindicated (not administered) in pregnancy and extrapulmonary case. Drug susceptibility tests for pyrazinamide, isoniazid, ethambutol, ethionamide, and fluoroquinolones are not recommended to decide therapy because of unreliability of these tests.

Longer regimen for MDR/RR-TB is usually 18–20 months duration and can be used as a standardized one or in an individualized form. These regimens usually consist of at least five medicines that are considered to be effective. The following factors are taken into consideration to determine the choice of drugs:

- *Oral drugs are preferred over injectable drugs;*
- *drug-susceptibility test (DST results);*
- *reliability of the methods used for DST;*
- *drug resistance levels in the population;*
- *previous history of medicine used by the patient;*
- *tolerability of the drugs used; and*
- *issues pertaining to drug-drug interactions.*

NTEP Recommendations for Longer All Oral Regimen

This longer all oral regimen (there is no injectable now) is now recommended for *patients who are not suitable for receiving shorter MDR-TB regimen (see later) due to:*

- Exclusion criteria for the shorter regimen
- Adverse drugs reactions to any component of the shorter regimen
- If there is resistance to any of the drugs in the regimen (for inh A mutation ethionamide cannot be given, or pyrazinamide resistance obtained from a certified lab).

The all oral longer regimen consist of the following:
6–8 months of Bedaquiline (Bdq), Levofloxacin (Lfx), Linezolid (Lzd), Clofazimine (Cfz) Cycloserine (Cs)/12 Levofloxacin (Lfx), Linozolid (Lzd), Clofazimine (Cfz), Cycloserine (Cs).

All regimens under RNTCP (NTEP) of longer duration (conventional MDR/MDRFQ/SLI/XDR-TB) are to be replaced with this longer oral regimen in adults. The regimen can be used in children more than 6 years. If resistant to FQ class on SL-LPA, levofloxacin is to be replaced with high dose moxifloxacin.

This is the standard drug regimen now for all MDR/RR TH and XDR TB under the program.

Delamanid (Dlm) in DR-TB

WHO has given a conditional recommendation for the use of delamanid after reviewing all data and pending further review later. The recommendation states that delamanid should only be added to the longer regimen for MDR TB only when the said treatment regimen cannot be constituted according to the recommendations by the WHO. It further emphasizes that delamanid should not be added to an otherwise well tolerated and effective longer MDR regimen. WHO does not recommend delamanid to be a part of the shorter regimen for MDR TB as sufficient data for the same is not there.

The drug is indicated in patients who are 18 years of age or above and can be a part of the combination therapy for MDR TB.[12-14] Of course, now it is also recommended for children of 6 years age more.

The drug is recommended under RNTCP under the following conditions:

- Patients who are aged 6 years or above; and can also be used in patients with HIV, and who are not eligible for short course MDR TB treatment regimen due to resistance, other contraindications or inability to tolerate.
- Patients with MDR/RR TB and additional resistance to any or all fluoroquinolones and all second line injectable anti-TB drugs
- Extensively Drug Resistance TB (XDR TB)
- Patients with mixed pattern of Drug-Resistant TB and who are failing to any regimen for a drug-resistant TB regimen or who are not tolerating the drugs or there are other reasons of contraindication or those patients who come back after disruption or any new criteria of exclusion for shorter regimen or if the disease is extensive or advanced and when there is a possibility of poor outcome at the baseline risk **(Table 4)**.

Shorter MDR-TB Regimen

To reduce the duration of therapy, a shorter duration of therapy, and known as The Bangladesh regimen was first tried in Bangladesh.[15] The duration of therapy was for a minimum period of 9 months of treatment. The regimen consisted of gatifloxacin, clofazimine, ethambutol, and pyrazinamide all throughout the treatment period of 9 months and was supplemented by prothionamide, kanamycin injection, and high-dose isoniazid for a minimum of 4 months (intensive phase). The relapse-free cure was 87.9% (95% confidence interval, 82.7–91.6) observed among 206 patients. The regimen was well tolerated and infrequent major adverse drug reactions were observed and they could be manageable. The only issue with this regimen was that it was not a case control study, but an observational study. To establish the effectiveness further, a case control study was carried out subsequently.[16] This short regimen consisted of high dose moxifloxacin, clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, with additional kanamycin, isoniazid, and prothionamide in the first 16 weeks.[16] There was provision of extension of the intensive

TABLE 4 Use of delamanid according to drug resistance

Resistance pattern	*DST-guided regimen class*	*Intensive phase*	*Continuation phase*	*Principle of regimen design*
Regimen with new drugs for MDR-TB + FQ/SLI resistance:				
MDR/RR + resistance to FQ class OR SLI class	MDR/RR + res to FQ class	(6–9) Km Eto Cs Z Lzd Cfz + (6) Dlm	(18) Eto Cs Lzd Cfz	0 GpA + 1GpB + 2 GpC + Z + add on 2 GpC + 1 GpD2
	MDR/RR + res to SLI calss	(6–9) Lfx Cm Eto Cs Z LzD Cfz + (6) Dlm	(18) Lfx Eto Cs Lzd	1 GpA + 1GpB + 2 GpC + Z + add on 2 GpC + 1 GpD2
Regimen with new drugs for XDR-TB:				
XDR-TB (res to both FQ and SLI)	XDR-TB	(6–12) Cm Eto Cs Z Lzd Cfz E + (6) Dlm	(18) Eto Cs Lzd Cfz E	0 GPA + 1 GPB + 2 GpC + Z + add on 2 GpC + 1 GpD1 + 1 GpD2
Regimen with new drugs for mixed pattern DR-TB:				
Mixed pattern DR-TB	MDR/RR-TB + res to FQ/SLI + Lzd or more	Modifity the regimen with new drugs for XDR-TB		

phase to 20 or 24 weeks for those who did not have sputum conversion by 16 or 20 weeks, respectively. The regimen was similar to that of the Bangladesh Regimen except that moxifloxacin was substituted for gatifloxacin because quality-assured gatifloxacin was not available. A similar prospective observational study was carried out in nine African countries in 1,006 MDR-TB patients. The regimen similarly comprised of a standardized 9-month regimen (moxifloxacin, clofazimine, ethambutol) (EMB) and pyrazinamide (PZA) throughout and additional kanamycin, prothionamide, and high-dose isoniazid during the intensive phase of 4–6 months.[17] The cohort included 200 (19.9%) patients who were infected with the human immunodeficiency virus (HIV). Of these 1,006 patients, 728 (72.4%) were cured and 93 (9.2%) completed therapy; thus causing a success rate of 81.6%. Failure rate was 5.9%, 78 (7.8%) died, and 48 patients (4.8%) were lost to follow-up. Death among HIV positive cases was more (19.0% vs. 5.0%). The treatment success rate was not affected by HIV status. The main factor of failure was fluoroquinolone resistance. The bacteriological outcome was not affected by resistance to other drugs like pyrazinamide, ethambutol, or ethionamide. Hearing impairment of 11.4% was the most important adverse drug reaction with severe deterioration after 4 months. The observations of the trial supported the efficacy, and hence the use of shorter regimens.

The WHO recommends the use of short regimens of 9–12 months in place of long regimens in MDR/RR TB patients provided that the patient has not received second-line drugs for more than 1 month and there is no resistance to fluoroquinolones and second-line injectable anti-TB drugs.[4]

The National Technical Expert Group (NTEG) of the NTEP, India, has now recommended the use of shorter regimens in all cases of MDR TB except under the situations discussed in **Table 5**.

BPaL Regimen

Pretomanid, a new anti-TB drug was approved by the US FDA in August 2019 for use along with BDQ and linezolid (high dose); this regimen, referred to as the *BPaL regimen*, is administered for 6 months (extendable to 9 months) to treat adults with pulmonary form of the extremely drug-resistant TB (XDR-TB), or treatment-intolerant or non-responsive multidrug resistant TB (MDR-TB). It inhibits the biosynthesis of mycolic acid, thus blocking the production of cell wall by the

TABLE 5 Contraindications for shorter duration therapy

DST-based criteria	*Non-DST-based criteria*
• If DST/DRT result for FQ or SLI is resistant or • Presence of INH A mutation (for Eto) or • Resistance to Z (whenever available) • If result for DST (FQ, SLI, INH A mutation, Cfz & Z) is not available, history of use of high dose moxifloxacin (Mfx(h)), Kanamycin (Km), Ethionamide (Eto) or Clofazimine (Cfz) for >1 month	• Pregnancy • Any extrapulmonary disease in HIV positive cases • If the tuberculosis is disseminated, or TB meningitis, or tuberculosis of the central nervous system • If the patient does not tolerate any drug in the shorter MDR TB regimen or if there is a risk of toxicity to a drug in the regimen like drug-drug interactions

mycobacteria. It acts in non-replicating mycobacteria as a respiratory poison releasing nitric oxide under anaerobic situation. The regimen of the three drugs was investigated in three sites in South Africa. The drug regimen was as follows:

- BDQ in a dose of 400 mg once daily for 2 weeks that was to be reduced to 200 mg thrice weekly for a period of 24 weeks;
- Pretomanid—200 mg daily for a period of 26 weeks; and
- Linezolid of 1,200 mg daily for up to 26 weeks.

The dose was adjusted according to toxicity.[18] The study enrolled 109 patients (XDR TB and unresponsive MDR TB patients). After 6 months of the trial, an intention to treat analysis was done. Around 98 patients (90%; with CI of 83–95) showed favorable and 11 patients (10%) had unfavorable outcomes. There were 7 deaths. One patient withdrew consent during treatment, relapse occurred in two cases, and one patient was lost to follow-up. The linezolid toxicity included peripheral neuropathy (81%) and myelosuppression (48%). Although these were common toxicities, they were manageable. Very often reduction of dosages or in some cases interruption of linezolid resolved the toxicities. The trial is named as the *Nix-TB Trial*. This BPaL regimen consisting of BDQ, pretomanid and linezolid continued to show favorable outcome till 6 months after treatment completion in most cases even with high degrees of DR TB although some toxic effects were observed.

Salvage Regimen

In spite all the above approaches, some patients continue to have sputum-culture-positive despite therapy with second-line TB drugs. For them treatment options are limited, especially if there is no scope of resectional surgery because of advanced and bilateral disease. Salvage therapy may be an option. Salvage therapy refers to the design of a regimen that combines both new and previously used drugs in a final effort to attain sputum conversion before declaring treatment to have failed. A combination of BDQ and delamanid along with other drugs may sometimes help with good results.[19-22]

General

Surgery in very few cases will be required and whenever possible, should be offered. It is imperative that pretreatment evaluation including detailed drug history, confirmation of DR TB using molecular methods, or liquid culture is a must to ascertain the type of drug-resistant TB. Pretreatment evaluation will need complete blood count, liver, and kidney function tests including thyroid function test, audiometry, cardiac assessment (for BDQ and DLM) and psychosocial evaluation. Nutrition is also important. The Government of India is providing Rs. 500 every month to these patients through direct transfer (DBT). Provision of ancillary drugs, initial admission (not mandatory now), and prescribing appropriate drugs is very essential. Besides, adverse drug reactions monitoring is equally important. Whenever there are associated conditions like HIV, diabetes, COPD, or other ailments they need to be looked after with equal emphasis. Treatments of these cases are usually carried out at the DR-TB center or DR-TB nodal center.

Major Recommendations of NTEG (National Technical Expert Group) for the treatment of MDR/XDR TB are as follows: (held from 9-11 September 2020)

There will be only two types of regimens for treating MDR/XDR-TB –

- All oral Longer MDR-TB reagimen (12-18 months); and
- Shorter all oral bedaquiline (BDQ) containing regimen.

- Shorter all oral bedaquiline (BDQ) containing regimen, (4-6) Bdq (6 m) Lfx Cfz Z E Hh Eto/ (5) Lfx Cfz Z E ((recommended by WHO) in adults (>18 yrs) in individuals confirmed with pulmonary MDR/RR-TB, uncomplicated extra-pulmonary TB disease and in PLHIV to be introduced in a phased manner starting with an implementation pilot in selected states to gain programmatic experience to guide future expansion. This recommendation may be considered for children (6-17 years) given their special needs pan-India in consultation with NTEG for paediatric TB.
- Only those patients with mutations in both inhA and katG will not be eligible for shorter regimen. However, patients with only inhA or only katG mutations will be eligible for the shorter regimen provided other conditions are met.
- **Preventive treatment** among close contacts of MDR-TB index patients (in whom FQ resistance has been ruled out) using 6Lfx for all age groups to be introduced in a phased manner starting with an implementation pilot in selected states to gain programmatic experience to guide future expansion. This recommendation may be considered for children given their special needs pan-India in consultation with NTEG for paediatric TB.
- For all oral longer MDR-TB regimen, the revised replacement drugs sequence recommended would be Delamanid, Amikacin, Pyrazinamide, Ethionamide, PAS, Ethambutol, Carbapenems.
- Extension of BDQ beyond 6 months to be considered in patients in whom an effective regimen cannot be otherwise designed if only 2 of 5 drugs are available from Groups A & B and adequate number of Group C drugs are not available due to high background resistance, non-availability or unreliability of DST.
- Use of BDQ in pregnancy needs further discussion with the concerned experts before taking a policy decision for its use under the program setting.
- Combined use of BDQ and DLM in the regimen is recommended for those M/XDR-TB patients in whom an appropriate regimen cannot be designed using all 5 drugs from Group A and B.
- BPaL research proposal may be considered with flexibility to adapt with anticipated results of ZeNix trial and submitted to the National Operational Research Committee for approval and implementation. BPaL can be considered as a last resort by NTEP under prevailing ethical standards in individual patients for whom the design of an effective regimen not possible as per recommendations.
- Post-treatment completion follow-up of all successfully treated TB patients at 6th, 12th, 18th and 24th months to be initiated under NTEP. Plan and expedite introduction of Xpert-XDR test and drug susceptibility testing for the drugs Lzd, Z, Cfz, Bdq, Dlm
- Consider second line drugs procurement adjustments and forecasting (including child friendly formulations) and capacity building planning.
- Strengthen mechanisms for improved patient follow-up and implementation of aDSM (Active TB drug-safety monitoring and management) as per the PMDT guidelines.
- Expedite up-gradation of Nikshay for diagnostic module, DR-TB case finding report and aDSM module for improving monitoring of DR-TB patients.
- Build capacity of all providers (labs, DR-TBC, field staff) in optimally utilizing Nikshay (electronic data monitoring system) for real-time data entry as well as monitoring at state and district level in order to improve the quality of care and timely regimen change in DR TB patients.
- Programme to issue DO to all DRTB Centres to consider admitting children requiring in-patient care for management of DRTB as per PMDT guidelines and proactively engage the available paediatricians (in-house/honorary) for the management of paediatric DR-TB patients.
- Programme to issues Demi-Offcial letter for use of BDQ in children in the age-group 12-17 years for management of DR-TB
- National Task Force (NTF) mechanism to support the establishment and functioning of DR-TB centres in remaining Medical Colleges across India (also engaging Paediatric Dept. for management of paediatric DR-TB patients).
- Programme to establish the mechanism to ensure dissemination of any policy change to all stakeholders especially Nodal/District DR-TB sites including medical colleges. NTEP website to have all important communications sent to states periodically uploaded so that it can be easily accessed by all concerned.

Conclusion

The previously used longer but less effective drug regimen that contained an injectable drug has now been replaced with all oral, injection free short-course and longer duration (~18 months) therapy and is more effective. The National TB Elimination Program has quickly adopted these changes and has introduced these forms of therapy throughout the country so that DR-TB cases are treated more successfully. These are important developments that have been adopted by the program so that marching toward End TB will be a reality. However, prevention, early diagnosis, and completion of therapy are important keys to success.

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CHAPTER

190 National DR-TB Guidelines in 2021

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Abstract

Drug resistant-tuberculosis (DR-TB) is relatively difficult to treat than drug-sensitive-TB. Nearly 27% of global multi-drug resistant/rifampicin resistant-TB (MDR/RR-TB) patients are in India. National guidelines for the treatment of DR-TB in India [programmatic management of drug resistant-TB (PMDT)] have been essentially adapted from 'WHO consolidated guidelines for DR-TB treatment (2020)'. These national guidelines emphasize access of universal DST to all TB patients and categorize DR-TB into rifampicin susceptible but isoniazid monoresistant-TB (Hr-TB), MDR/RR-TB, and extensively drug resistant-TB (XDR-TB). As per PMDT guidelines, patients should be examined for Hr-TB and should be treated with uniphasic rifampicin, ethambutol, pyrazinamide, and levofloxacin regimen for 6 months. Preferably, 7-drug injection-free, pan-oral shorter (9–11 months) or 5-drug pan-oral longer (18–20 months) DST-guided, bedaquiline-containing individualized MDR-TB treatment regimen should be constituted for intensive phases and 4-drug regimen for continuation phases, respectively. Monthly smear and culture should be done during follow-up. Active TB drug-safety monitoring and management (aDSM) is strongly recommended. Post-treatment, follow-up at 6th,12th,18th, and 24th months of all successfully treated DR-TB cases under national-TB elimination programme (NTEP) is recommended.

Introduction

National Guidelines on drug resistant-tuberculosis (DR-TB) in India [programmatic management of drug resistant-TB (PMDT)][1] have been adapted from WHO Consolidated Guidelines on DR-TB treatment (2020).[2] Recently, American Thoracic Society/Centers for Diseases Control and Prevention/European Respiratory Society/Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) have jointly published comprehensive guidelines on treatment of DR-TB.[3] **Table 1** compares various differences between these three guidelines.[1-3]

DR-TB Definitions

The term DR-TB is a broader one encompassing several subentities, and is primarily a laboratory diagnosis confirming the presence of *Mycobacterium tuberculosis (Mtb)* and subsequently demonstrating its resistance to first-line and second-line anti-tuberculosis drugs on drug-susceptibility testing (DST). Various sub-entities of DR-TB are defined in **Box 1**.[1]

Epidemiology

DR-TB is highly prevalent[1,2] and continues to be a serious public health threat. According to the WHO Global TB report 2020,[4] worldwide there were 465,000 people (range 400,000–535,000) with new rifampicin resistant-TB (RR-TB) diagnosis and 78% of these had multidrug resistant-TB (MDR-TB). India (27%), China (14%), and Russian Federation (8%) contributed to almost half of these cases in 2019.[4] Globally, 3.3% of new and 17.7% of previously treated patients had MDR/RR-TB.[4]

TABLE 1 Comparison of WHO, ATS/CDC/ERS/IDSA and PMDT, India guidelines for the treatment of drug-resistant TB (DR-TB)

	WHO consolidated guidelines, 2020	***ATS/CDC/ERS/IDSA guidelines, 2019***	***PMDT, India, 2019-20***
Types of DR-TB	Deals with Hr-TB, MDR/RR-TB and MDR-TB with additional FQs resistance	Deals with Hr-TB, MDR-TB, pre-XDR-TB and XDR-TB Does not cover RR-TB	Deals with Hr-TB, MDR/RR-TB and XDR-TB
DST if *Mtb* isolated	Comprehensive DST if *Mtb* is isolated	Microbiological data are required to constitute an individualized treatment regimen based on DST of the *Mtb* strain isolated	Universal DST is strongly recommended to constitute treatment regimen for DR-TB
Hr-TB	Information on *katG* and *inhA* mutations on genotypic (molecular) DST is essential.	No specific recommendation for genotypic DST	Recommendation for genotypic DST is similar to WHO 2020 guidelines
	Hr-TB is treated with rifampicin, ethambutol, pyrazinamide and levofloxacin for 6 months [(6) R E Z Lfx]. If Lfx can't be used, R E Z treatment is recommended	For HR-TB patients should be treated with rifampicin, ethambutol, isoniazid and pyrazinamide for 6 months. Duration of pyrazinamide can be shortened to 2 months in selected situations such as non-cavitary disease, low- burden disease, or intolerance to pyrazinamide	About 10% of the Indian patients have *inhA* mutations where H^h can be administered and Eto can't be used because of cross-resistance About 90% have *katG* mutations and where Eto can be used. Addition of levofloxacin (Lfx) is done without a split for 6 months [(6) R E Z Lfx]
Classification of Drugs	Drugs are classified into ABC groups depending on safety and efficacy profiles. Treatment regimen is preferably constituted from Groups A and B and if it is not possible then from drugs can be added from Group C	**Recommendations:** **STRONG FOR:** Bdq, later generation fluoroquinolones (Lfx and Mfx) **CONDITIONAL FOR:** Lzd, Cfz Cs/Trd, E, Z (provided susceptibility to Z). **CONDITIONAL FOR:** Injectables Am and S, Imp-Cln and Mpm/Amx-Clv (if one of these is essential to constitute a regimen) **CONDITIONAL AGAINST:** Eto/Pto, Km and Cm, PAS **STRONG AGAINST**: macrolides (azithromycin and clarithromycin), Amx-Clv	*Grouping of drugs has been adapted from WHO guidelines 2020
Pan-oral Bdq- containing longer regimen (based on DST)	Intensive phase = at least 4 drugs Continuation phase= 3 drugs Pan-oral 5-drug longer regimen is constituted from Group A and B drugs and if it is not possible then Group C drugs are included from the replacement sequence depending upon drug susceptibility profile and tolerance	Intensive phase = 5 drugs Continuation phase= 4 drugs	Intensive phase =5 drugs Continuation phase =4 dugs Regimen: (6- 8) Bdq (6) Lzd Lfx Cfz Cs/12 Lfx Lzd^l Cfz Cs

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	WHO consolidated guidelines, 2020	*ATS/CDC/ERS/IDSA guidelines, 2019*	*PMDT, India, 2019-20*
Pan-oral Bdq- containing shorter regimen	A shorter all-oral Bdq-containing 7-drug regimen of 9-12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for > 1month, and in whom resistance to FQs has been excluded	Standardized 9- to 11-month shorter MDR-TB regimen is not preferred as it has injectables. A research recommendation has been given for the conduct of RCTs to evaluate the efficacy, safety and tolerability of newer oral drugs	9- to 11-month shorter pan-oral Bdq-containing 7-drug regimen comprising of (4-6) Bdq (6) Lfx Lfz Cfz Z E H^h Eto/ (5) Lfx, Cfz Z E to be administered if there are no contraindications
BPaL regimen	Bdq, Pa and Lzd (BPaL) for pre-XDR-TB (MDR-TB *plus* FQs) under operational research (OR) conditions who have no previous exposure or <2 weeks exposure to Bdq and Lzd	A total duration of treatment between 15 and 24 months after culture conversion is recommended in patients with pre-XDR- and XDR-TB	Combined use of Bdq and Dlm is recommended for M/XDR-TB patients in whom an appropriate regimen can't be made using all 5 drugs of groups A and B A 20-month treatment is recommended for XDR-TB patients BPaL regimen to be tried under OR conditions
Use of injectable	Amikacin may be included in patients aged ≥ 18 years on longer regimens to constitute a regimen. Use of injectables (especially Kanamycin and Capreomycin) is avoided as far as possible. Although, if all other options are exhausted, for the use of streptomycin *in vitro* drug sensitivity must be demonstrated	Use of injectables is not recommended. However, Am/S may be included if one is unable to constitute a 5-drug regimen and *Mtb* is drug-sensitive	Amikacin or streptomycin can be used to constitute a 5-drug regimen in patients with aged >18years, if it is essential and *Mtb* is susceptible to the drug depending upon tolerance of drugs and *in vitro* drug resistance
Duration of treatment for longer MDR-TB	Intensive phase=6-7 months Total duration=18-20 months After culture conversion= 15-17 months In MDR/RR-TB patients, on longer regimens containing amikacin or streptomycin an intensive phase of 6-7 months is suggested for most patients. However, the duration may be modified according to response to treatment	Intensive phase=5–7 months after culture conversion Total duration= 15–21 months	Intensive phase= 6–8 months (Bdq given for 6 months) Continuation phase= 12 months (fixed duration) Total duration = 18–20 months Extension of intensive phase will depend on culture conversion report at 4^{th} month or beyond

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	WHO consolidated guidelines, 2020	*ATS/CDC/ERS/IDSA guidelines, 2019*	*PMDT, India, 2019-20*
Surgery for lung resection	In patients with RR-TB or MDR-TB, elective partial lung resection (lobectomy or wedge resection) may be done along a constituted drug regimen in a centre with a skilled and experienced thoracic surgeon and with careful selection of candidates	According to guidelines, an elective partial lung resection (e.g., lobectomy or wedge resection) with a DST-guided MDR-TB treatment regimen is more beneficial compared with medical therapy alone when clinical judgment, supported by bacteriological and radiographic data, suggests a strong risk of relapse or treatment failure Pneumonectomy is not recommended	Lung resection surgery is not done usually due to lack of infrastructure and well-trained and skilled thoracic surgeons
Preventive therapy	No specific recommendation for LTBI	For LTBI for MDR-TB patients' contacts, 6 to 12 months of treatment with a later-generation fluoroquinolone alone or with a second drug, on the basis of DST of the *Mtb* isolate of the source- case	No specific recommendation for LTBI

*Replacement drugs sequence consists of the following order: delmanid (Dlm), amikacin (Am), pyrazinamide (Z), ethionamide (Eto), *para*-aminosalicylic acid (PAS), ethambutol (E), penems. Use of Bdq during pregnancy is under consideration. Bdq may be used beyond 6 months if only 2 of 5 drugs from Groups A and B are available and adequate no. of Group C drugs are not available due to high background resistance non-availibility or unreliability of DST

Note: ATS/CDC/ERS/IDSA guidelines (2019) and WHO Consolidated DR-TB guidelines (2020) categorise following drugs, Am/S and E, H^h differently whereas in PMDT, 2019-20 PAS has been preferred over E and carbapnems

Am, amikacin; Amx/Cln, amoxicillin -clavulanic acid; ATS/CDC/ERS/IDSA, American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America; Bdq, bedaquiline; Cfz, clofazimine; Cln, cilastatin; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid; DST, drug-susceptibility testing; E, ethambutol; EPTB, extrapulmonary TB; Hh, high-dose isoniazid; Hr-TB, rifampicin sensitive but isoniazid resistant-TB; Imp, imipenem; Km, kanamycin; Lfx, levofloxacin; LTBI, latent TB infection; Lzd, linezolid; Lzd^l, low dose linezolid (300mg); MDR/RR-TB, multidrug-resistant/ Rifampicin resistant-tuberculosis; Mfx, moxifloxacin; Pa: pretomanid; PAS, p-aminosalicylic, acid; PLHIV, people living with HIV; PMDT, programmatic management of drug-resistant tuberculosis; S, streptomycin; WHO, World Health Organisation; XDR-TB, extensively drug- resistant TB; Z, pyrazinamide

Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2020; Treatment of Drug-Resistant Tuberculosis-An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline, 2019; Guidelines on programmatic management of drug-resistant tuberculosis in India, 2019-20.

BOX 1 DR-TB diagnosis methods and definitions

Laboratory methods for DR-TB diagnosis

- Genotypic (rapid molecular tests): provide early diagnosis
  - Nucleic acid amplification tests
    - ♦ Cartridge-based nucleic acid amplification test (CBNAAT): 1.5 hours
    - ♦ *TrueNat (chip based): 1 hour for *Mtb* detection + 1 hour for Rifampicin resistance testing
  - First-line and second-line line probe assays (FL-LPAs and SL-LPAs): 48 hours turn-around time
- Phenotypic methods (culture methods): time-consuming, used for confirmation and drug susceptibility testing (DST)†:
  - Liquid culture: 42 days
  - Solid culture: 56 days

DR-TB definitions

Monoresistance: refers to *Mtb* resistance to one of the first-line anti-TB drugs. Isoniazid monoresistance (Hr-TB) is commonly encountered

Polydrug resistance (PDR): resistance to more than one first-line anti-TB drugs other than both isoniazid and rifampicin

Multi-drug resistant TB (MDR-TB): *Mtb* resistance to both rifampicin and isoniazid

Pre-XDR-TB: includes MDR-TB and resistance to either of flouroquinolones (FQs) or second-line injectables (SLIs)

‡**Extensively drug resistant TB (XDR-TB):** a subset of MDR-TB that includes additional resistance to FQs and SLIs.

*TrueNat is a chip based battery operated nucleic acid amplification test system made in India.

In FL-LPA, mutations in *Mtb* for rifampicin and isoniazid resistance and in SL-LPA the mutations for FQs (Mfx and Lfx) and injectables (amikacin, kanamycin and capreomycin) are tested

†**DST definitions:** Critical concentration (CC), is the lowest concentration of an anti-TB drug in vitro that will inhibit the growth of 99% of phenotypically wild-type strain of *Mtb* complex. Minimal inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent that inhibits growth of > 99% of a microorganism in a solid or broth dilution susceptibility test. Critical breakpoint (CB) concentration(s) of an antimicrobial agent which defines an MIC above the critical concentration that separates strains that will likely respond to treatment. The CB is used in to guide individual clinical decisions in patient treatment

‡As SLIs will no longer be recommended in the revised DR-TB treatment guidelines, XDR-TB definition will require revision in future

Source: Guidelines on programmatic management of drug-resistant tuberculosis in India, 2019–20

BOX 2 Risk factors for drug-resistant tuberculosis

- Factors related to previous treatment
  Incomplete and inadequate treatment
  Inadequate treatment adherence
- Virulence of *Mtb* strain, e.g., W-Beijing genotype is well-known for multidrug resistance
- Presence of multidrug transporter proteins may lead to drug resistance in *Mtb* strain
- Lower anti-TB drugs levels due to either malabsorption of anti-TB drugs or drug-drug interactions like rifampicin and moxifloxacin
- Male gender
- Older age
- Low BMI
- Diabetes mellitus
- HIV/AIDS
- Factors such as psychiatric illness, alcoholism, drug addiction, and homelessness do predict non-adherence to treatment

BMI, body mass index; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency virus; Mtb, *Mycobacterium tuberculosis*

Source: Adapted from Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest. 2006;130:261-72.

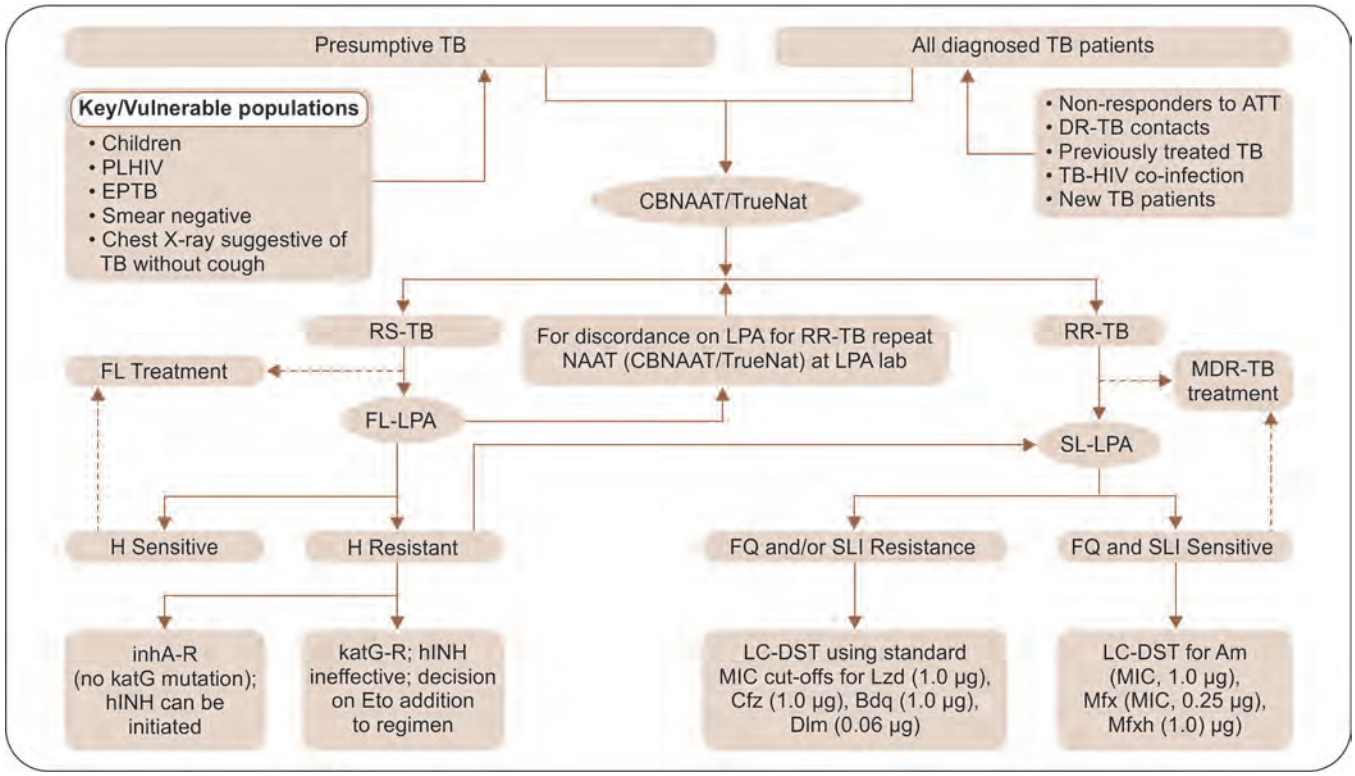
India had 66,255 laboratory-confirmed MDR/RR-TB in 2019, 55.5% of these were tested for second-line anti-TB drugs and 3.5% had extensively drug-resistant-TB (XDR-TB). MDR-TB developed among 2.8% of new and 14% of previously treated patients had MDR/RR-TB.[4] Globally, only one in three diagnosed MDR/RR-TB accessed DR-TB treatment, and in India 48% of laboratory confirmed MDR/RR-TB and 30% of XDR-TB cases were initiated on treatment. Various risk factors for DR-TB are described in the **Box 2**.[5]

According to National Anti-tuberculosis Drug Resistance Survey (NDRS) in India,[6] ~8% of Hr-TB patients are resistant to any fluoroquinolone (FQ) drug whereas resistance to linezolid (Lzd) is uncommon in MDR/RR-TB and minimal in isoniazid (H) mono/poly-DR-TB. In India, H resistant-TB (Hr-TB) occurs due to *kat*G gene mutations in ~90% patients and high dose H (H^h) may be ineffective in these patients whereas in the remaining (~10%) *inh*A gene mutation confers low-level resistance to H[7] and cross resistance to ethionamide (Eto). In this situation, H^h can be administered.[1]

Integrated Diagnosis of DR-TB

According to National Guidelines,[1] it is essential to rapidly characterize *Mtb* sensitivity or resistance to H, FQs, and second-line injectables (SLIs) with first line-line probe assay (FL-LPA) and second line-line probe assay (SL-LPAs) respectively after receiving nucleic acid amplification tests (NAAT) amplification report and treat according to DST report in order to avoid further amplification of DR-TB. Subsequently, although time-consuming, phenotypic culture with DST is required to establish the diagnosis. DST-guided treatment is strongly recommended in the

Flowchart 1: Integrated DR-TB diagnostic algorithm



Note: Vulnerable populations: As per WHO, children, pregnant women, elderly people, malnourished people, and people who are ill or immunocompromised, are particularly vulnerable when a disaster strikes, and take a relatively high share of the disease burden associated with emergencies. In H resistant Mtb ioslates, katG gene and inhA gene mutations can co-exist and it is considered as 'high-level' resistance only.
Am, amikacin; ATT, anti-tuberculosis treatment; Bdq, bedaquiline; CBNAAT, cartridge-based NAAT; Cfz, clofazimine; Dlm, delamanid; Eto, ethionamide; FL-LPA, first-line drug-line probe assay; FQ, fluoroquinolone; H, isoniazid; hINH, high dose isoniazid; inhA-R, inhA gene mutation resistance; katG-R, katG gene mutation resistance; LC-DST, liquid culture drug susceptibility test; Lzd, linezolid; Mfx, moxifloxacin; Mfxh, high dose moxifloxacin; MIC, minimum inhibition concentration of drugs; NAAT, nucleic acid amplification test; PLHIV, people living with HIV; RR, rifampicin resistant; RS, rifampicin sensitive; SLI, second line injectable agents; SL-LPA, second-line drug-line probe assay; TureNat, Chip based NAAT system made in India
Source: Guidelines on programmatic management of drug-resistant tuberculosis in India, 2019–20.

National TB Elimination Program (NTEP)[1-3] erstwhile known as Revised National TB Control Program (RNTCP) known to avoid further amplification of resistance and the integrated diagnostic algorithm **(Flowchart 1)** can be used for this. As mentioned previously, it is established that rapid molecular tests such as NAAT and LPAs provide early diagnosis of DR-TB and are helpful when used in tandem with phenotypic methods (solid and liquid cultures) as latter take longer for DST results.

The standard smear microscopy test has some inherent limitations as it is usually difficult to diagnose TB when the bacillary load in the sputum specimen is $<10^3$/mL.[8] The DST can be growth-based (phenotypic DST) on liquid culture (Bactec MGIT 960) or solid culture (Lowenstein-Jensen culture) or genotypic DST which employs rapid molecular tests for the diagnosis of DR-TB. Various molecular tests include NAAT (cartridge based NAAT or chip based TrueNat) and FL-LPAs (GenoType MTBDR*plus* V1, GenoType MTBDR*plus* V2) and Nipro (NTM *plus* MDRTB detection kit) and SL-LPAs (MTBDR*sl* V1 and MTBDR*sl* V2).[9] The NAAT test uses real time-polymerase chain reaction (RT-PCR) principle and the result is reported as *Mtb* detected/not detected with additional finding of *Mtb* rifampicin sensitive or resistant. Under programmatic conditions where the laboratory capacity is limited and facilities for FL-LPAs and SL-LPAs are not available, the report of NAAT as RR-TB is considered as a surrogate marker of MDR-TB and the patient is treated as MDR-TB as phenotypic tests with DST usually take from weeks to months. While the test report from FL-

LPAs provides additional information of *Mtb* sensitivity or resistance to H, SL-LPAs provide additional information on resistance to fluoroquinolones and SLIs.[9]

LPAs are a family of deoxyribonucleic acid (DNA) strip-based tests that determine the drug-resistance profile of an MTB[1] complex strain through the pattern of binding of amplicons (DNA amplification products) to probes targeting the most common resistance associated with the mutations to first- and second-line agents and to probes targeting the corresponding wild type (WT) DNA sequence.[9] LPAs are WHO-approved tests for rapidly detecting drug resistance to the first- and second-line agents. They can be used for testing of culture isolates (indirect testing) and direct testing of acid-fast bacilli (AFB) smear microscopy specimens (FL-LPA), and both smear positive and smear negative sputum specimens (SL-LPA). Mutations are detected by the binding of amplicons to probes targeting the most commonly occurring mutations (MUT probes) or inferred by the lack of hybridization (lack of binding) of the amplicons to the corresponding WT probes.[9] The post-hybridization reaction leads to the development of the colored bands on the test strip detecting probe binding. LPA results are reported as "Resistance not detected" instead of "Susceptible" to define the bacteria resistance profile.[9]

Given the limitations of LPA and in particular the fact that the resistance cannot be completely excluded even in the presence of all WT probes as not all mutations that confer resistance are covered by these tests or mutations that are covered may be below the limit of detection, it is more appropriate to report the result as "resistance detected" or "resistance not detected."[9] The term "resistance detected" is used whenever one or more MUT probes identifying specific mutations conferring resistance to the drugs are developed regardless of whether WT probes are developed or not.[9] The term "resistance inferred" is used whenever one or more WT probes in regions of the gene known to confer resistance to the drug are not developed and none of the MUT probes in the corresponding region is developed. In this case the precise mutation cannot be reported, only the region where the mutation lies is identified.[9]

FL-LPA showed sensitivity and specificity for the detection of rifampicin resistance 96.7% and 98.8%, respectively, and for the detection of H resistance, sensitivity and specificity 90.2% and 99.2%, respectively.[10] SL-LPA (GenoType MTBDR*sl* V1) showed pooled sensitivity and specificity for the detection of fluoroquinolone resistance by direct testing of 86.2% and 98.6% respectively, and a pooled sensitivity and specificity for the detection of second-line injectable drugs resistance of 87% and 99.5%, respectively.[9]

Treatment of DR-TB

Treatment of Isoniazid-resistant Tuberculosis (Hr-TB)

Substitution of H with levofloxacin (Lfx) is recommended for the treatment of Hr-TB. Drug regimen consisting of rifampicin, ethambutol, pyrazinamide, and levofloxacin (REZ-Lfx) is administered for 6 months without split of intensive and continuation phases.[2] Although, moxifloxacin (Mfx), arguably more potent than Lfx, has several limitations due to drug-drug interactions,[2] and QTc-prolonging ability when coadministered with drugs with similar properties. Further, Mfx peak plasma concentration and exposure declines when coadministered with rifampicin, however, unlike Lfx, does not require dose modifications in chronic kidney disease. Recent ATS/CDC/ERS/IDSA guidelines provide option of shortening the duration of pyrazinamide (Z) to 2 months in presence of non-cavitary and low-burden disease, intolerance, or toxicity to Z.[3]

Treatment can be extended to 9–12 months as per clinical, radiological, and microbiological responses, especially in extrapulmonary TB involving bone, central nervous system (CNS) and/or miliary TB. Use of injectable agents like streptomycin and others is not recommended in the guidelines.[1-3] In case of additional resistance, intolerance or toxicity to a drug, its substitution can be effected by, in order of preference with linezolid (Lzd), clofazimine (Cfz), or cycloserine (Cs).

Treatment of MDR/RR-TB

Two evidence-based guidelines on DR-TB treatment have been published in 2019. A propensity score-matched meta-analysis of an individual patient data meta-analysis (IPDMA) from 12,030 patients in 50 studies from 25 countries was used for making recommendations in these guidelines. Major differences between WHO Consolidated Guidelines, ATS/CDC/ERS/IDSA Guidelines, and current Indian Guidelines, 2019–20, are listed in **Table 1**. Current

BOX 3 Principles of drug-resistant TB management

- Drug susceptibility testing(DST)-guided treatment is recommended for DR-TB and universal DST should be available to all TB patients
- A bedaquiline based 5-drug regimen (3 drugs from Group A, two from Group B and if not possible from Group B then one or two drugs from Group C; refer Table 2) should be constructed for MDR/RR-TB
- A fully oral regimen is preferred and injectables like kanamycin and capreomycin are no longer recommended
- Long-term bedaquiline-based drug regimen should have at least 5 drugs for initial 6 months and afterwards 4 drugs should be continued for rest of the treatment duration
- The individualized, longer MDR-TB regimen is to be administered for the duration of 18–20 months, and the duration is primarily based on patient's response to treatment or 15–17 months after culture conversion
- In addition to smears, monthly follow-up cultures should be done from 1st month till the end of intensive phase. Decision on treatment extension should be based on culture reports at 4^{th}, 5^{th} and 6^{th} month
- If patient's culture is positive after 8 months from the specimen submitted at the end of 6^{th} month, treatment failure will be declared
- If drugs need to be discontinued due to intolerance or resistance on DST, then sequence of drug replacement should be according to the guidelines
- If fluoroquinolone (FQ) class resistance is detected on SL-LPA, replace Lfx with high dose moxifloxacin (Mfx^h)
- Fluoroquinolone should not to be used, if resistance to high dose moxifloxacin with LC-DST (MIC, 1.0 µg) is reported,
- In case of fluoroquinolone-resistant pre-extensively drug resistant (pre-XDR)-TB, a second line injectable drug (SLID) may be considered
- Duration of XDR-TB treatment should be longer than MDR/RR-TB
- Cascades of training are recommended for implementation and adoption of rapid changes in DR-TB management integrated with efficient mechanism of active drug-safety monitoring and management (aDSM).
- aDSM should focus on QTc monitoring (along with observation of serum K^+, $Mg^{2+}$and Ca^{2+} levels), myelosuppression, optic and peripheral neuropathy and lactic acidosis
- Ensure treatment adherence by different methods complemented with information and communication technology based adherence monitoring and reminder systems

Note: As per WHO consolidated guidelines on drug-resistant tuberculosis treatment, duration of standardized shorter MDR-TB regimen is 9-12 months which is one month more than the original standardised shorter MDR-TB regimen used in trial, given that some patients required slightly more than 11 months to complete a shorter regimen owing to brief interruptions.
LC-DST, liquid culture DST; Lfx, levofloxacin; MDR-TB, multi-drug resistant TB; Mfxh, high-dose moxifloxacin; MIC, minimum inhibitory concentration; SL-LPA, second-line-LPA
Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment (2020).

Indian guidelines for MDR/RR-TB have been primarily adapted from WHO Consolidated Guidelines, 2020 **(Box 3)**.

A new feature of guidelines is regrouping of DR-TB drugs into A, B, and C categories and the ranking is based on the efficacy profiles of drugs **(Table 2)**.[1,2] Based on 6-month culture conversion results in the Delamanid (Dlm) Phase III trial, Dlm has been placed in group C.[11,12] Dosages of drugs for MDR/RR-TB treatment as per weight categories are detailed in **Table 3**.[1] Interim analysis of an Indian study on safety and efficacy of bedaquiline under conditional access program (CAP) for MDR-TB in India was recently published.[13] This feasibility study was conducted between June 2016 and August 2017 under programmatic conditions in the field settings at six sites of India. Of 620 MDR-TB patients, 57% patients had MDR-TB with additional drug resistance to fluoroquinolones (MDR_{FLQ}) and 5% with additional second-line injectable (MDR_{SLI}) and 16% had extensively drug-resistant TB (XDR-TB), 39% had severe malnutrition [body-mass index (BMI<16)]. After 6 months of treatment, the *Mtb* culture conversion was achieved in 83% of patients. The median time to culture conversion was 60 days, higher BMI was associated with faster culture conversion. Mortality was 12% and a majority of deaths (56%) occurred within the first 6 months of treatment. While Bdq was permanently discontinued in about 2%, its administration was temporarily interrupted in about 3% due to QTc interval prolongation and after correction of abnormalities of Mg^{2+}, Ca^{2+}, and K^+, it could be successfully reintroduced. Based on these results it was concluded that Bdq-based treatment for MDR/RR-TB is safe and can be scaled up with careful monitoring of QTc interval. According to WHO Guidelines, decisions to start the standardized shorter MDR-TB regimen should be made according to patient preference and clinical judgment **(Box 4)**. Since some geographical areas in India are still implementing standardized shorter MDR/RR-TB, a pan-oral, injection-free drug regimen is strongly recommended in the current National Guidelines of India.

TABLE 2 Grouping of anti-TB drugs for longer MDR regimen

Group and steps	*Drug*	*Standard abbreviations*
Group A Include all three drugs	• Levofloxacin *or* Moxifloxacin	Lfx/Mfx
	• Bedaquiline	Bdq
	• Linezolid	Lzd
Group B Add one or both drugs	• Clofazimine	Cfz
	• Cycloserine *or* Terizidone	Cs/Trd
Group C Add to complete the regimen and when drugs from Groups A and B can't be used because of drug intolerance, toxicity or some other contraindication	• Ethambutol	E
	• Delamanid	Dlm
	• Pyrazinamide	Z
	• Imipenem-cilastatin *or* Meropenem	Imp-Cln/Mpm
	• Amikacin (*or* Streptomycin)	Am (S)
	• Ethionamide *or* Prothionamide	Eto/Pto
	• *p*-aminosalicylic acid	PAS

- This table is intended to guide the design of individualized, longer MDR-TB regimens. Group C drugs are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 Individual Patient Data-Meta-analysis (IPD-MA) for longer regimens included no patients on thioacetazone (T) and too few patients on gatifloxacin (Gfx) and high-dose isoniazid (H^h) for a meaningful analysis.
- Evidence on the safety and effectiveness of Bdq beyond 6 months and below the age of 6 years was insufficient for review.
- Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review.
- Use of linezolid for at least 6 months was shown to increase efficacy, however, drug toxicity may limit use. The analysis suggested that using linezolid for the whole duration of treatment would optimise its effect (about 70% of patients on Lzd with data received it for >6 months and 30% for 18 months or the whole duration). From the IPD-sub-analysis no patient predictors for early cessation of Lzd could be identified.
- Evidence on the safety and efficacy of delamanid beyond 6 months, below the age of 3 years was insufficient for review.
- Pyrazinamide is to be used only if DST results confirm susceptibility.
- Every dose of Imp-Cln and meropenem is administered with clavulanic acid, which is only available in formulations combined with amoxicillin (Amx-Clv). Amx-Clv is not counted as an additional effective TB agent and should not be used without Imp-Cln or meropenem.
- Amikacin and streptomycin are only to be considered if DST results confirm susceptibility and high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be used only if amikacin cannot be used (unavailable or documented resistance) and if phenotypic DST results confirm susceptibility (streptomycin resistance is not detectable with second-line molecular line probe assays). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.
- These agents only showed effectiveness in regimens without bedaquiline, linezolid, clofazimine or delamanid, and therefore only proposed when other options to compose a regimen are not possible.

Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2020.

Current Indian guidelines recommend bedaquiline-based, preferably pan-oral 5-drug regimen as per DST in the Intensive Phase and 4-drugs in the Continuation Phase: 6–8 Bdq (6) Lfx, Lzd, Cfz, Cs/12 Lfx, Lzd[l], Cfz, Cs[14] **(Box 5)**. Similar regimens have been endorsed in the ATS/CDC/ERS/IDSA Guidelines **(Table 4)**. Bedaquiline should be stopped after 6 months and linezolid dose should be reduced to 300 mg once daily. Monthly sputum smear and cultures should be done. In case sputum culture positivity persists after 3 months then treatment failure should be strongly suspected and the DST should be repeated.

If SL-LPA detects FQ class resistance, then addition of two drugs is preferred in the previous regimen from class C drugs.[9] High dose Mfx (Mfx^h) is effective provided susceptibility is proven in LC-DST to Mfx^h (MIC,1.0µg)[15] [in many settings SL-LPA detects specific mutations such as A90V, S91P, D94A (*gyrA*) which contribute to low-level Mfx resistance]. In all MDR/RR-TB patients, SL-LPA is recommended which clarifies the additional FQ class resistance and second-line injectable drugs resistance. **Table 5** details the sequence of replacement drugs to modify the ongoing treatment in case of specific situations like drug toxicity or resistance.[1]

Management of extrapulmonary TB (EPTB) is similar to pulmonary MDR/RR-TB and patients are monitored for clinical, radiological, and microbiological outcomes

TABLE 3 Dosage of MDR/RR-TB drugs in adults

Drugs	*16–29 kg*	*30–45 kg*	*46–70 kg*	*>70 kg*
Rifampicin (R)*	300 mg	450 mg	600 mg	600 mg
High-dose H (H^h)	300 mg	600 mg	900 mg	900 mg
Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
High-dose Mfx (Mfx^h)	400 mg	600 mg	800 mg	800 mg
Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
Linezolid (Lzd)	300 mg	600 mg	600 mg	600 mg
Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
Cycloserine (Cs)†	250 mg	500 mg	750 mg	1000 mg
Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6–11 years of age 100 mg twice daily (200 mg) for 24 weeks for ≥12 years of age			
Imipenem/cilastatin (Imp/Cls)†	1000 mg imipenem/1000 mg cilastatin twice daily			
Meropenem (Mpm)†	1000 mg three times daily (alternative dosing is 2000 mg twice daily)			
Amikacin (Am)‡	500 mg	750 mg	750 mg	1000 mg
Capreomycin (Am)‡	500 mg	750 mg	750 mg	1000 mg
Kanamycin (Km)‡	500 mg	750 mg	750 mg	1000 mg
Ethionamide (Eto)	375 mg	500 mg	750 mg	1000 mg
Na-PAS (60% weight/vol)†‖	10 g	14 g	16 g	22 g
Amoxyclav (Amx-Clv) (In child: WHO 80 mg/kg in two divided doses)	875/125 mg BD	875/125 mg BD	875/12 mg (2 morning plus 1 evening)	875/125 mg BD (2 morning plus 1 evening)
Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

*For H mono/poly resistant TB
†Drugs can be given in divided doses in a day in the event of intolerance
‡For adult more than 60 yrs of age, dose of SLI should be reduced to 10 mg/kg (max up to 750 mg)
‖In patient of PAS with 80% weight/volume the dose will be changed to 7.5 g (16–29 kg); 10 g (30–45 kg); 12 g (46–70 kg) and 16 g (>70 kg)
Source: Guidelines on programmatic management of drug-resistant tuberculosis in India, 2019–20.

BOX 4 Criteria to decide when the shorter MDR-TB regimen may be offered

A shorter all-oral Bdq-containing regimen (4–6) Bdq (6m) Lfx Cfz E H^h Eto/(5) Lfx Cfz Z E of 9–12 months duration is recommended in eligible patients with MDR/RR-TB in the following situations:

- Without resistance or suspected ineffectiveness of a medicine in the shorter regimen (except H resistance)*
- Without exposure to previous treatment with second-line medicines in the regimen for >1 month (unless DST confirms susceptibility to these medicines)†
- No pregnancy
- Age >6 years
- No extensive TB disease‡ and with no severe EPTB
- PLHIV

*H resistance determined by mutations in either *inhA* or *katG* genes (not both) or phenotypic DST. The presence of both mutations suggests that isoniazid at high dose and thioamides are not effective and therefore, in such patients, shorter regimen should not be used.
†Phenotypic DST for some medicines included in the regimen (ethambutol and ethionamide) is not considered reliable and reproducible.
‡Extensive TB disease: bilateral cavitary disease or extensive parenchymal damage on chest X-ray. In children under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest X-ray.
Bdq, bedaquiline; Cfz, clofazimine; DST, drug susceptibility testing; E, ethambutol; EPTB, extrapulmonary TB H, isoniazid; H^h, high-dose isoniazid; Lfx, levofloxacin; MDR/RR-TB, multidrug-resistant/ Rifampicin resistant-tuberculosis; PLHIV= people living with HIV, Z, pyrazinamide
Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2020.

TABLE 4 ATS/CDC/ERS/IDSA criteria to build an individualized treatment regimen for MDR-TB

• Constitute a drug regimen consisting of five or more drugs to which the *Mtb* isolate is susceptible (or has low likelihood of resistance), preferably with drugs that have not been used to treat the patient previously • Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preferences/values (choices therefore subject to program and patient safety limitations) • In children with TB disease who are contacts of infectious MDR-TB source cases, the source case's isolate DST result should be used if one is unable to obtain from the child • **TB expert medical consultation is recommended (ungraded good practice statement).**	
Step 1: Choose one of the later-generation fluoroquinolones	Lfx Mfx
Step 2: Choose both of these prioritized drugs	Bdq Lzd
Step 3: Choose both of these prioritized drugs	Cfz Cs/Trd
Step 4: If a regimen can't be assembled with five effective oral drugs, *and the isolate is susceptible*, use one of these injectable agents*	Am S
Step 5: If needed or if oral agents preferred over injectable agents in Step 4, use the following drugs‡	Dlm‡ Z E
Step 6: If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs	Eto or Pto§ Imp–Cln or Mpm-Cln‖ PAS¶ H[h]**
The following drugs are no longer recommended for inclusion in MDR-TB regimens:	Cm and Km Amx/Clv (when used without a carbapenem) Azithromycin and clarithromycin

* Amikacin and streptomycin should be used only when the patient's isolate is susceptible to these drugs. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs in the intensive phase.

† Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory), the capacity to appropriately monitor for significant adverse effects, consideration of drug–drug interactions, and patient comorbidities should be considered in selecting Step 5 agents over injectables. Ethambutol and pyrazinamide had mixed/marginal performance on outcomes assessed in our PS-matched IPDMA; however, some experts may prefer these drugs over injectable agents to build a regimen of at least five effective oral drugs. Use pyrazinamide and ethambutol only when the isolate is documented as susceptible.

‡ Data on dosing and safety of delamanid are available in children ≥3 years of age.

§ Mutations in the *inh* A region of the *Mycobacterium tuberculosis* genome can confer resistance to ethionamide/prothionamide as well as to INH. In this situation, ethionamide/prothionamide may not be a good choice unless the isolate is shown to be susceptible with in vitro testing.

‖ Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined.

¶ Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.

** Data not reviewed in our PS-matched IPDMA (propensity score-matched individual patient data meta-analyses), but high-dose isoniazid can be considered despite low-level isoniazid resistance but not with high-level INH resistance.

Note: pepQ mutations were associated with low-level resistance to Bdq and cross-resistance to Cfz. These mutations reduced the efficacy of both drugs *in vivo* but did not lead to complete resistance to these drugs. The value of using loading doses and the optimal dosing for Cfz requires additional research.

Am, amikacin; Amx/Clv, amoxicillin -clavulanic acid; Bdq, bedaquiline; Cfz, clofazimine; Cln, cilastatin; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid; DST, drug susceptibility testing; E, ethambutol; Hh , high-dose isoniazid; Imp, imipenem; INH, isoniazid; IPDMA, individual patient data meta-analyses; Km, kanamycin; Lfx, levofloxacin; Lzd, linezolid; MDR, multidrug-resistant, PS: propensity score; Mfx, moxifloxacin; PAS, p-aminosalicylic, acid; S, streptomycin; TB, tuberculosis; Trd, terizidone; Z, pyrazinamide

Source: Treatment of Drug-Resistant Tuberculosis-An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline, 2019.

TABLE 5 Sequence of using replacement drugs to modify the regimen

Regimen	*Sequence of using replacement drug to modify the regimen*	
All oral H mono/poly	If SL LPA detects Lfx resistance; replace Lfx with Mfxh. LC DST should be used for detection of resistance to Mfx^h and Z If Mfx^h or Z can't be used; substitute with Lzd. If Lzd cannot be administered, replace with Cfz. If both Lzd and Cfz cannot be given, use Cs as replacement If both Mfx^h and Z can't be used; add two drugs of these Lzd, Cfz, Cs, in the order of preference Treat for 9 months in any of the above three situations; duration of the treatment can be extended to 12 months especially in CNS-TB, spinal, miliary, bone, and lymph node TB If R resistance; switch to appropriate regimen, i.e., MDR/RR-TB regimen	
Pan-oral Bdq-containing shorter MDR-TB regimen	If there is a need for stopping/replacing any drug, stop the regimen and switch to DST-guided all oral longer regimen	
Pan-oral Bdq-containing longer MDR-TB regimen	Replacement situations	Proposed composition of regimen after replacement
	Initial 6 months of treatment	
	Initiate treatment **If Lfx can't be used**, replace Lfx with Mfx^h if SL LPA pattern suggests **If Mfx^h can't be used**, replace it with Dlm **If Mfx^h & Dlm both can't be used**, add two drugs from replacement sequence†	**Lfx, Bdq, Lzd, Cfz, Cs** **Mfx^h*,** Bdq, Lzd, Cfz, Cs **Dlm*,** Bdq, Lzd, Cfz, Cs Bdq, Lzd, Cfz, Cs *plus* **two drugs** from replacement sequence†
	If Bdq can't be used, replace with Dlm If Dlm can't be used, replace with two drugs from replacement sequence†	Lfx, Dlm*, Lzd, Cfz, Cs Lfx, Lzd, Cfz, Cs *plus* two drugs from replacement sequence†
	If **one of Lzd, Cfz or Cs can't be used**, **no replacement** (if Bdq and Lfx/Mfx^h can be given) If **two or all three of Lzd, Cfz or Cs can't be used, replace with two or three drugs** respectively from replacement sequence† If **three out of five drugs from A & B group cannot be used, replaced with three drugs** from replacement sequence†	
	After 6 months of treatment	
	If **one of the drugs from Lfx, Lzd, Cfz, Cs can't be used**; no replacement is required If two drugs **from Lfx, Lzd, Cfz, Cs** cannot be used, replace with **two drugs** from Z*, Eto*, PAS, E in given order to complete the four drugs regimen	

*Use Dlm: if available, no history of prior use and no exclusion criteria for its use, Z: if resistance not detected, Eto: If inhA mutation not present, Am: if SL LPA pattern suggests. DST for Bdq, Dlm, Lzd, Cfz, and Z will be considered whenever it is available. DST for E and Eto is not reliable and reproducible

†Replacement sequence: Dlm, Am*, Z*, Eto*, PAS, E, Imp/Cln or Mpm *plus* Amx/Clv

Am, amikacin; Amx/Cln, amoxicillin-clavulanic acid; Bdq, bedaquiline; Cfz, clofazimine; Cln, cilastatin; Cm, capreomycin; Cs, cycloserine; Dlm, delamanid; DST, drug-susceptibility testing; E, ethambutol; H^h, high-dose isoniazid; Hr-TB, rifampicin sensitive but isoniazid resistant-TB; Imp, imipenem; Km, kanamycin; Lfx, levofloxacin; Lzd, linezolid; MDR/RR-TB, multidrug-resistant/Rifampicin resistant-tuberculosis; Mfx, moxifloxacin; Pa, pretomanid; PAS, p-aminosalicylic, acid; S, streptomycin; Z, pyrazinamide

Source: Guidelines on programmatic management of drug-resistant tuberculosis in India, 2019-20.

depending on EPTB site and the treatment duration is 18–20 months. Drug treatment preferably a regimen containing FQ, Bdq, Lzd, and Cs (injectables Am/S only if *Mtb* is susceptible); Cfz, Eto (provided *inh*A mutations are absent) may be used if required. Efavirenz may be replaced with nevirapine in patients with HIV/AIDS.[14,16] Treatment of MDR/RR-TB patients with pregnancy is done with a 4-drug regimen according to the DST and with drugs having a low-teratogenic potential. In children with seizures Mpm is preferred over Imp.

Nix-TB Trial: Bedaquiline, Pretomanid, and Linezolid (BPaL) Regimen for MDR-TB Treatment

Nix-TB is a clinical trial, conducted by TB alliance in three South African sites (April, 2015 to November, 2017) in which the 3-drug pan-oral BPaL regimen, consisting of

TABLE 6 Characteristics of drugs* used for DR-TB

Group	*Dosage*	*Adverse events*	*Special precautions*
Group A Include all three medicines (unless they cannot be used) Levofloxacin (Lfx) or Moxifloxacin (Mfx) Bedaquiline (Bdq)	500–1000 mg daily 400 mg daily 400 mg daily for initial 2 weeks and subsequently 200 mg thrice weekly for next 22 weeks (can be given longer)	In advanced CKD, class effect of fluoroquinolones may pose a higher risk of neuropsychiatric adverse events and tendinopathy; QTc prolongation on ECG more with Mfx than Lfx, a combination of Bdq, Cfz and Lfx (rather Mfx) preferred QTc prolongation, arthralgias, hepatitis, headache, anorexia, nausea	Dose adjustment required in CKD Cr cl 30–50 mL/min = 750–1000 mg daily <30 mL/min = 750–1000 mg thrice weekly No dose adjustment in CKD; predominantly hepatobiliary excretion; may increase hepatic enzymes; has good CNS penetration; avoid concomitant administration of antacids, phosphate binders, calcium, iron, or aluminum containing medications to avoid malabsorption; Administration with meal increases bio-availability; no dose adjustment with renal or liver disease; ECG should be done to monitor QTc prolongation at baseline, 2,12 and 24 weeks and stop the drug if QTc >500 ms, serum K^+, Mg^{2+} and Ca^{2+} monitoring required for QTc prolongation; QTc monitoring required when co-administered with clarithromycin, Cfz, Lfx/Mfx
Linezolid (Lzd)	600 mg once daily; the dose can be decreased to 300 mg after 3–6 months; linezolid should be discontinued in case toxicity occurs and can be re-introduced at a lower (300 mg daily) dose following recovery	Hematological toxicity, lactic acidosis, peripheral and optic neuropathy and serotonin syndrome. Drug toxicity is related to dose and duration of linezolid. Hematological toxicity and lactic acidosis occur early in few weeks to months while neurological toxicity occurs late after 3–4 months	Main route of excretion is hepatic with some renal clearance. No dose adjustment is required in CKD; careful monitoring of hematological toxicity, lactic acidosis, peripheral and optic neuropathy (often reversible) required. Pyridoxine 100 mg daily can be administered to prevent hematological toxicity. Avoid concomitant use of food items rich in tyramine and medications (SSRIs and other medicines) known to increase serotonin production to prevent development of serotonin syndrome
Group B Add both medicines (unless they cannot be used) Clofazimine (Cfz)	100 mg daily	Ichthyosis and dry skin, sun burn, pink-brownish-black discoloration of skin, cornea, retina and urine; acne flare	QTc monitoring on ECG is required when co-administered with Bdq, Lfx/Mfx and Cfz; serum potassium, magnesium and calcium monitoring required for QTc prolongation. Not to be used in pregnancy and severe hepatic insufficiency. Skin problems can be prevented by application of sunscreen and lubricants
Cycloserine (Cs) OR Terizidone (Trd)	10–15 mg/kg/day in divided dose or 250 mg morning 500 mg evening 300 mg morning 300 mg evening	Dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression, and altered behavior, suicidal tendency, generalized hypersensitivity reaction or hepatitis	Cr cl ≥ 30 mL/min: no dose adjustment required; < 30 mL/min: 250 mg daily or 500 mg on alternate days; therapeutic drug monitoring is recommended if facility is available; avoid if possible in renal disease as the main route of excretion is renal. Cs (and Trd) should be avoided in patients with history of epilepsy, psychiatric illness or alcoholism, to prevent minor adverse reactions like insomnia administration of small dose of a tranquilizer is recommended or pyridoxine 50 mg/250 mg of administered cycloserine can be given to prevent neurotoxicity

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Group	Dosage	Adverse events	Special precautions
Group C Add to complete the regimen and when medicines from Group A and B cannot be used Ethambutol (E)	15–25 mg/kg/day	Dose dependent optic (retrobulbar) neuropathy (> 30 mg/kg/day or 15-25 mg/kg in CKD); generally, reverses on prompt discontinuation; hyperuricemia Uncommon: interstitial nephritis, cholestatic jaundice, neutropenia and thrombocytopenia, reversible cutaneous hypersensitivity disappearing on desensitization	Cr cl ≥ 30 mL/min, no dose adjustment required; < 30 mL/min: 15–25 mg/kg thrice weekly. Patients should be monitored at baseline and regularly thereafter for visual acuity and red-green color discrimination
Delamanid (Dlm)	100 mg twice weekly for 6 months (can be administered longer)	QTc prolongation, nausea vomiting and abdominal pain, dizziness	QTc monitoring at baseline, 2, 12, and 24 weeks. Stop if > QTc 500 ms; monitor serum K^+, Mg^{2+} and Ca^{2+}
Pyrazinamide (Z)	25–30 mg/kg/day (1.5 g for 50 kg, 2 g for > 50 kg)	GI upset, hyperuricemia, arthralgia, hepatotoxicity (not dose related)	Cr cl ≥ 30 mL/min: no dose adjustment required; < 30 mL/min: 25–30 mg/kg three times/week
Imipenem - cilastatin (Imp-Cln) OR Meropenem Amoxycillin-Clavulanate (Mpm/Amx-Clv)	1g IV every 12 h 1g every 8–12 h IV administered with clavulanate (as amoxycillin clavulanate 250/125 mg every 8–12 h)	GI upset, transaminitis	Dose adjustment required in CKD Dose adjustment required in CKD
Amikacin (Am)	15 mg/kg-maximum 1 g; five to seven times weekly or 20–25 mg/kg 2–3 times/ week	Vestibular, auditory and renal toxicities	Baseline audiogram and renal functions. Dose adjustment required in CKD; *prefer to avoid if possible*. Periodic monitoring of audiogram and renal functions every 2-4 weeks
Ethionamide (Eto) Or Prothionamide (Pto)	15–20 mg/kg/day in divided doses. The usual dose is 250–1000 mg/day. Most patients should be started on 250 mg doses daily or twice daily and gradually increased over several days to 750 or 1000 mg total daily dose	Pto is generally considered to be less unpleasant and better tolerated than Eto. However, profile of adverse events is similar. GI disturbances, metallic taste and sulphurous belching; psychotic reactions, hypoglycemia (especially in diabetes mellitus patients); hepatitis; other rare side-effects include gynaecomastia, menstrual disturbance, impotence in males, acne, alopecia and peripheral neuropathy	Should not be administered in pregnancy (teratogenicity in animals). Careful monitoring is required if administered in patients with diabetes mellitus, liver disease, alcoholism or mental instability. No dose adjustment required in CKD. Serum TSH monitoring required periodically especially when co-administered with PAS
p-aminosalicyclic acid (PAS)	150 mg/kg or 10–12 g daily in 2–3 divided doses	GI disturbances (diarrhea is self-limiting), hypothyroidism (more chances if given along with ethionamide), hypokalemia, hepatitis, thrombocytopenia, aggravation of metabolic acidosis in patients with CKD	Although no dose adjustment required in CKD. However, caution should be exercised, since main route of excretion is renal. Periodic serum TSH monitoring required especially when co-administered with ethionamide

*All are bactericidal except Cs and PAS which are bacteriostatic; Cfz and Eto are weak bactericidal

Note: Creatinine clearance (CrCl) is best calculated with estimated glomerular filtration rate (eGFR) using CKD Epidemiology Collaboration (CKD-EPI) creatinine equation.

CKD, chronic kidney disease; CKD, chronic kidney disease; Cr Cl, creatinine clearance; ECG, electrocardiogram; GI, gastrointestinal; SSRIs, selective serotonin reuptake inhibitors; TB, tuberculosis; TSH, thyroid stimulating hormone

Source: Dheda K, Theron G, Calligaro G, Limberis J, Davids M, Esmail A et.al. Drug resistance tuberculosis. eds. Sharma and Mohan's Textbook of Tuberculosis and Nontuberculous Mycobacterial Diseases, 3rd ed. New Delhi. Jaypee Brothers Medical Publishers;2019. pp. 592-5.

TABLE 7 Important rug cotoxicity and drug-drug interactions in patients with HIV/DR-TB coinfection

Description	*Responsible ARV drugs*	*Responsible anti-TB drugs*	*Considerations*
Renal toxicity	TDF	Aminoglycosides, Cm	• TDF causes renal failure with hypophosphatemia and proteinuria • Avoid TDF in patients receiving aminoglycosides and Cm • Serum creatinine should be checked before switching patients onto TDF after completion of aminoglycoside • Caution is advised when administering TDF or aminoglycosides in patients with underlying co-morbidities, such as, diabetes mellitus or in patients who are receiving concomitant nephrotoxic agents such as NSAIDs and amphotericin B • If TDF is necessary, close monitoring of serum creatinine is required
Electrolyte abnormality	TDF	Aminoglycosides, Cm	• Exclude exacerbating factors, such vomiting, diarrhoea, dehydration, diuretics, etc.
Hepatitis/hepatotoxi-city	NVP, EFV, PI (especially RTV), NRTI	Z, Bdq, PAS, FQ	• When severe stop both ARVs and anti-TB agents, restart TB drugs first • Assess for other contributing factors such as alcohol abuse, viral aetiologies and other drugs like co-trimoxazole • Avoid concomitant use of NVP and Z • The risk of NVP hepatotoxicity is highest in the first 3 months of starting therapy with higher risk in patients with CD4+ >250/mm^3, the risk of NVP hepatotoxicity is lower if VL is suppressed
Myelosuppression	AZT	Lzd, H	• Stop Lzd if myelosuppression occurs. Blood transfusion is indicated if haemoglobin falls below 8 g/dL • Avoid co-administration of AZT and Lzd • Adverse events should be managed with a combination of temporary suspension of linezolid, dose reduction and/or symptom management • Reduction dose of 300 mg daily may be associated with fewer neuropathic effects but is not supported by pharmacokinetic data • Consider stopping cotrimoxazole
Peripheral neuropathy	ddI, d4T	Lzd, Cs, H, Eto, E	• Avoid use of D4T or ddI in combination with Cs or Lzd • Use pyridoxine as prophylaxis in patients receiving Cs, H and Lzd
QTc prolongation		Bdq, Mfx, Cfz Lfx, Ofx	Close monitoring of QTc is recommended when using these agents in combination

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Contd...

Description	*Responsible ARV drugs*	*Responsible anti-TB drugs*	*Considerations*
Central nervous system toxicity	EFV	Cs, H, Eto/Pto, FQ	• EFV toxicity occurs in first 2–3 weeks of treatment • Concurrent use of EFV with CS needs close monitoring
Headache	AZT, EFV	Cs, Bdq	• Headaches may be self-limited in case of AZT, EFV and Cs • Advice analgesia and hydration
Nausea and vomiting	RTV, d4T, NVP	Eto, PAS, H, Bdq, E, Z	• Most drugs will cause some degree of nausea • If persistent consider drug-induced pancreatitis, hepatitis
Lactic acidosis	d4T, ddI, AZT, 3TC	Lzd	• High index of suspicion needed to detect hyperlactatemia to prevent overt symptoms of lactic acidosis
Pancreatitis	d4T, ddI	Lzd	• Avoid co-administration where possible • If pancreatitis occurs discontinue the ARVs completely
Diarrhea	PI, ddI	PAS, FQ, Eto	• For mild diarrhea anti-motility drugs can be used • May be self-limited. Exclude opportunistic infections
Optic neuritis	ddI	E, Lzd, Eto	• Stop all suspected agents causing optic neuritis • Screen patients using the Snellen chart and Ishihara chart
Hypothyroidism	d4T	Eto, PAS	Monitor serum TSH for patients receiving these agents
Joint pain	PI (Indinavir)	Z, Bdq	Mild symptoms can be managed with simple analgesics

ARV, anti-retroviral drugs; ARVs, anti-retroviral drugs; AZT, zidovudine; Bdq, bedaquiline; Cfz, clofazimine; Cm, capreomycin; Cs, cycloserine; d4T, stavudine; ddI, didanosine; DR-TB, drug-resistant tuberculosis; E, ethambutol; EFV, efavirenz; Eto, ethionamide; FQ, fluoroquinolones; Gfx, gatifloxacin; H, isoniazid; HIV, human immunodeficiency virus; Lfx, levofloxacin; Lzd, linezolid; Mfx, moxifloxacin; NRTI, nucleoside reverse transcriptase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; NVP, nevirapine; Ofx, ofloxacin; PAS, para-amino salicylic acid; PI, protease inhibitor; Pto, prothionamide; RTV, ritonavir; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; TSH, thyroid stimulating hormone; VL, viral load; Z, pyrazinamide

Source: Dheda K, Theron G, Calligaro G, et al. Drug resistance tuberculosis. Sharma and Mohan's Textbook of Tuberculosis and Nontuberculous Mycobacterial Diseases, 3rd ed. New Delhi: Jaypee Brothers Medical Publishers; 2019. pp. 592-5.

BOX 5 Composition of pan-oral longer MDR-TB treatment regimen

- 6–8 Bdq (6) Lfx Lzd Cfz Cs / 12 Lfx Lzd^{l} Cfz Cs
- Resistance to FQ likely to be high among RR/MDR-TB
- May need to stop Lzd due to ADRs
- Mfx^{h} fear of high cardiac ADRs with Bdq, Cfz, Mfx^{h}

Selection of fluoroquinolones:

- In presence of FQ class resistance by LPA, in-country data (BDQ CAP, NITRD, NIRT) show in ~80% patients Mfx^{h} may be sensitive. No such data are available for Lfx
- Lfx has been used in India for~8 years, while Mfx^{h} has not been used: concerns about efficacy of Lfx vs. Mfx^{h}. Both Lfx and Mfx have similar efficacy
- Lfx More likely to cause nephrotoxicity compared to Mfx
- Very limited data (SALVAGE regimen, BDQ CAP): combination of Bdq, Cfz, Mfx^{h} may be tolerated
- Systematic review (2018) also shows low incidence of cardiac ADRs with BDQ + other drugs

ADRs, adverse drug reactions; Am, amikacin; Bdq, bedaquiline; CAP, conditional access program; Cfz, clofazimine; Cs, cycloserine; E, ethambutol; FQ, fluoroquinolones; Lfx, levofloxacin; Lzd, Linezolid; Lzd^{l}, low dose linezolid; Mfx^{h}, high dose moxifloxacin; NIRT, National Institute for Research in Tuberculosis, Chennai, India; NITRD, National Institute of Tuberculosis and Respiratory Disease, New Delhi, India

Source: Guidelines on programmatic management of drug-resistant tuberculosis in India, 2019-20.

bedaquiline, pretomanid, and linezolid was administered in 109 XDR-TB patients.[17] Patients received bedaquiline 400 mg once daily for 2 weeks followed by 200 mg three times a week for 24 weeks, plus pretomanid 200 mg daily for 26 weeks and linezolid 1,200 mg daily for up to 26 weeks. Nix-TB data have demonstrated a successful outcome in 95 (89%) of the first 107 patients after 6 months of treatment with BPaL drug regimen and 6 months of post-treatment follow-up. With the advantages of pan-oral shorter treatment duration and very low rates of adverse drug reactions, in future BPaL regimen can be adopted as a standard DR-TB regimen.

Active TB Drug-safety Monitoring and Management

Several drugs used for the treatment of MDR-TB have additive toxicities and may cause adverse events (AEs) and serious adverse events (SAEs).[18] Active TB Drug-Safety Monitoring and Management (aDSM) has been strongly recommended for better adherence and successful treatment outcome. **Table 6** details serious adverse reactions of the drugs and special precautions required while treating MDR/RR-TB patients.[19] During treatment of HIV DR-TB patients, clinicians should be careful and need to carefully monitor additive drug cotoxicities and drug-drug interactions **(Table 7)**. Linezolid is a very potent anti-TB drug and its irrational use because of its free availability over-the-counter for other bacterial infections such as staphylococcus should be avoided. Its use in MDR-TB patients for the entire duration of treatment is desirable but its adverse events must be monitored carefully and the dosage may be decreased from 600 to 300 mg after 6 months. Lactic acidosis and hematological toxicity occurs early while peripheral and optic neuropathy occur late **(Table 6)**. Optic neuropathy is usually reversible if recognized early. Serotonin syndrome is known to occur with linezolid[20,21] and can be fatal at times **(Table 6)** and a heightened awareness is required. Cutaneous hyperpigmentation with clofazamine is usually reversible after stopping the drug **(Table 6)**. Similar to current Indian MDR/RR-TB guidelines, the ATS/CDC/ERS/IDSA guidelines[3] have emphasized health education regarding adverse events and serious adverse events of drugs in MDR/RR-TB patients. Post-treatment, follow-up at 6th,12th,18th and 24th months of all successfully treated DR-TB cases under national-TB elimination programme (NTEP) is recommended.

Acknowledgments

Professor SK Sharma is sponsored by JC Bose National Fellowship of the Science & Engineering Research Board (SERB; no. SB/S2/ JCB-04/2013) of the Ministry of Science & Technology, Govt. of India. Mr. Vishwanath Upadhyay is a Junior Research Fellow pursuing his PhD course in Jamia Hamdard Institute of Molecular Medicine at Jamia Hamdard (Deemed-to-be-University), Hamdard Nagar, New Delhi. He is supported by Prof. SK Sharma through JC Bose Fellowship of the Science & Engineering Research Board.

Conflicts of Interest

Prof. SK Sharma is a member of the National Technical Expert Group (NTEG) on treatment of TB, (National Tuberculosis Elimination Programme erstwhile known as Revised National Tuberculosis Control Programme) Central TB Division, Ministry of Health & Family Welfare, Government of India.

Conclusion

All efforts should be made to have quality laboratory network with regular accreditation. Universal DST is strongly recommended to enable individualized pan-oral long-term MDR/RR-TB regimens to prevent further amplification of drug resistance. Smear and mycobacterial cultures should be done monthly during follow-up, aDSM should be rigorously followed to have good adherence for better treatment outcome. All these concerted efforts will go a long way toward achieving the goal of TB-free world.

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CHAPTER

191 Tuberculosis with Diabetes: How to Tackle?

Shailendra Kumar

Abstract

Diabetes is one of the largest causes of non-communicable morbidity and mortality worldwide and in India. Tuberculosis is the leading infectious disease in India and some other Asian countries including china. Tuberculosis and diabetes are frequently encountered together. About 10% of TB cases are globally linked to diabetes. Diabetes affects the presentation and treatment outcomes of tuberculosis. On the other hand tuberculosis also affects the treatment of diabetes due to significant drug interaction and some other factors. So, theoretically, treatment of both diseases needs to be modified. In this context many studies have been published which indicates that TB-diabetes need special considerations in treatment. It will help in improving the treatment outcome and preventing the emergence of drug resistance cases.

Introduction and Epidemiology

Globally tuberculosis is the leading cause of death from an infectious disease and in India the incidence of tuberculosis in 2018 has been estimated to be 27 lakhs, about 16% increase from previous year.[1,2]

Recent estimation of diabetic population worldwide is about 463 millions.[3] The proportion of people with diabetes are increasing in many countries. India has an estimated 77 million people with diabetes, which makes it second most affected country after China. India alone contributes to about 17% of world diabetic population.

TB and Diabetes Comorbidity

About 10% of TB cases globally are linked to diabetes. The precise biological mechanism is still not very clear but it has been observed that diabetes accounts for 20% of smear-positive pulmonary TB. Recent analysis have indicated that increase in diabetes prevalence in India has been an important obstacle in reducing TB incidence.[4] More recent studies suggest that DM increases the risk of active TB up to three- to fourfold. In an Indian study the prevalence of DM among TB patients was 13.1% (known diabetic 9.1% and new diabetic 4%).[5] TB and diabetes when present together affects each other in various ways:

- Diabetics have weaker immune system so they are at higher risk of progressing latent TB to active TB.
- Diabetes can lengthen the time for sputum culture conversion and thus may be potential cause for development of MDR-TB.
- People with TB and diabetes have four times higher risk of death during treatment and higher risk of relapse. Higher reported rate of mortality in TB patients with diabetes may be caused by cardiovascular complications rather than by TB itself.[6]
- Diabetes is complicated by the presence of infectious diseases, including TB. It is important that proper care for diabetes should be provided to patient suffering from TB-diabetes comorbidity.
- TB is associated with worsening of glycemic control in diabetics; good glycemic control can improve the outcome. Furthermore diabetics may have many other

comorbidities like hypertension, dyslipidemia, and needs to take many pills, so chances of developing complications due to other comorbidities and unwanted drug interaction are more.

How Diabetes Affects Clinical Spectrum of Tuberculosis?

Clinical Presentation

Major biochemical manifestation of diabetes is hyperglycemia which favors growth, viability, and pathogenicity of the tubercle bacilli.[7] Increased production of glycerol, and nitrogenous substance further aids to the growth of tubercle bacilli.[8] Tuberculosis runs more aggressive course in a diabetic. In diabetic subject increased prevalence of pulmonary TB and relatively infrequent extrapulmonary form of TB have been noticed. In a series of studies 82.6% of diabetics with TB were found to be above 45 years with male preponderance.[9] In another Indian study it has been observed 55% of TB-DM group were underweight and age group was above 45 years.[10] In DM-TB group prolonged duration of illness and more significant weight loss has been observed than in non-diabetic subjects.[9,11] Low grade fever and productive cough were observed with almost equal frequencies in both groups.[12]

Diagnosis

Sputum microscopy and X-ray chest are two most important investigations used for the diagnosis of pulmonary tuberculosis in RNTCP. Apart from that we have CBNAAT for detection of RR, LPA, and culture sensitivity test for individual DST. Now RNTCP has a well designed program structure from national level to PHI level. RNTCP was launched in 1997 and achieved full nationwide coverage by March 2006. DMC is the most peripheral laboratory under RNTCP. There are 13,000 DMCs across the country.[13] HIV screening of all patients undergoing sputum examination has also been included. In 2010, an integrated National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke,(NPCDCS) has been launched.

Effect of Diabetes on Sputum Examination

Sputum positivity indicates the infectivity of pulmonary tuberculosis and culture conversion the effectiveness of treatment. In a study it has been found that diabetics are five times more prone to develop sputum positive pulmonary tuberculosis than non-diabetics.[14] These factors were analyzed in a recent Turkish study containing 737 pulmonary tuberculosis patients hospitalized during 2000 to 2005.[14] They concluded that those who are diabetic, radiologically having extensive and cavitatory lesions, take longer sputum and culture conversion time than the other group. Another larger study concluded that pulmonary tuberculosis patients with diabetes had a higher bacillary load before initiation of treatment and DM was found to be an independent risk factor for more AFB on sputum smear examination.[15]

Effect on Chest X-ray

Comparative studies of radiological findings in TB-diabetes with tuberculosis alone group have yielded contrasting results. In a study by Perenez-Guzman et al. in Mexico, 192 diabetic patients were compared with radiological findings of tuberculosis alone.[16] They found that the TB-DM patients were older and have a decreased frequency of upper (17% vs. 56%), and an increased frequency of lower (19% vs. 7%) and increased frequency (64% vs. 36%) both upper and lower lung field lesions. In TB-DM group cavitatory lesions were more (82.5% vs. 59%) than control and that were more often in lower lung field (29% vs. 3%). Cavities were more often multiple in the TB-DM patients (25% vs. 2%).

Treatment Outcome and Complications

At the end of intensive phase treatment a slightly lower sputum conversion rates were observed in diabetics as compared to non-diabetic group. Regarding treatment outcome some reports suggest adverse effects of diabetes on treatment outcome of TB patients with increased rate of failure, death, defaults, and relapses.[17] Mortality rates in these patients are reported to be several times higher than the non diabetic TB patients.[7] However, in contrary recent study concludes that as far as tuberculosis is concerned, the survival rate and socioeconomic rehabilitation of adequately treated patients with diabetes and pulmonary TB are the same as that of TB patients without diabetes.[15]

How to Tackle?

Screening for Diabetes

Ideally WHO and International Union against Tuberculosis and Lung Disease recommend that all adult TB patients

TABLE 1 Recommended thresholds and cut-off points for diabetes and pre-DM

Blood test	*Diabetes mellitus*	*Pre-diabetes*
2 hrs plasma glucose after oral glucose tolerance test (OGTT)	≥11.1 mmol/L ≥200 mg/dL	7.8–11.0 mmol/L 140–199 mg/dL
Fasting plasma glucose (FPG)	≥7.0 mmol/L ≥126 mg/dL	6.1–6.9 mmol/L 110–125 mg/dL
Glycosylated hemoglobin (HbA1c)	≥6.5% ≥48 mmol/mol	6.0–6.4% 42–47 mmol/mol

should be screened for diabetes. But in country like India where resources are tight it may be more cost effective to go for the targeted screening policy for high risk patients; above 40 years of age, those who are overweight or obese, those with family history of diabetes, those who consume excess alcohol, those with a previous history of gestational DM or previous pre-DM.

When to screen a tuberculosis patient for diabetes is very important aspect for the ease of programmatic management and to alleviate fallacies like stress related diabetes. It has been recommended that TB patients should be screened for diabetes at the time of diagnosis and registration. The fasting blood glucose and HbA1c are the two most suitable tools in programmatic setting and in those patients who have symptoms of diabetes—polyuria, polydipsia, and polyphagia. In asymptomatic persons fasting after glucose both should be done **(Table 1)**.

Treating a diabetic-tuberculosis has many challenges with treatment of tuberculosis as well as treatment of diabetes. Both diseases alter each other management in many ways. Medications used for their management affect each other in terms of—efficacy, drug interaction, adverse reactions. More over TB adversely affects control of diabetes too. Diabetics have often cardiovascular complications and risk factors which may be worsened by tuberculosis. So there are some considerations which must be taken into account while dealing with this complex duel problem:

- Inflammation related with TB can lead to temporarily elevated blood suger—"stress induced hyperglycemia," sometimes quite pronounced but usually improve during TB treatment.
- Our initial priority should be successful initiation of TB treatment and with optimizing blood glucose control.
- Referral of TB patients to specialized DM treatment centre is not recommended in the early phase of treatment because of the risk of transmission of tuberculosis.

Treatment of Tuberculosis

For treating diabetic tuberculosis patients, under RNTCP a National framework for joint TB-diabetes collaborative activities has been launched in 2017 in co-ordination with NPCDCS (National Program for Cancer, Diabetes, Cardiovascular Diseases and Stroke). Currently recommended anti-tuberculosis treatment is similar for patients with combined TB and diabetes compared to those with TB only. This strategy needs proper evaluation because DM is associated with ATT drug resistance,[18] slower treatment response, higher rate of toxicity, treatment failure, and recurrent TB. Points to be considered for ATT in diabetics:

- The length of ATT might have to be adjusted. This is common practice in some countries including China. In a retrospective cohort study in Taiwan, a 9-months treatment regimen was associated with a lower rate of recurrent TB than the 6 months regimen.[19]
- Higher dose of ATT may be needed, especially rifampicin due to interaction with sulphonyl urea derivatives. In an observational study in the USA it has been found that therapeutic drug monitoring for INH and rifampicin, after 2 weeks of treatment was associated with significantly shorter time of sputum culture conversion among patients with combined TB and DM.[20]
- TB-DM should be prioritized for DST at least for RR by CBNAAT. Nowadays CBNAAT is recommended as initial DST for all patients with high MDR/TB burden

TABLE 2 Important drug interactions in TB-DM patients

Medication	*Refampicin*	*Isoniazid*	*Aminoglycosides*
Metformin	No clinically relevant Interaction Drug of choice in TB-DM	No important interaction May worsen neupatic symptoms	My worsen renal toxicity
Sulfonylurea (Glyburide, Glipizide, Glimepiride)	Decreased ↓ Glyburide level (39%), Glipazide (22%), Glimepiride (30%)	↑ Sr Conc. of Glimepiride and my cause Hypoglycemia	No significant interaction
DPP IV inhibitor (Sitagliptin, Saxagliptin)	May ↓ blood level of gliptines	Not significant	No significant interaction
Thiazolidinedione (Pioglitazone)	↓ Pioglitazone level (54%)	No interaction	No significant interaction
Insulin	None	None	None

Source: Adopted from www.heartlandntbc.org

but on ground level this is not happening due to resource issues.

- Close monitoring of ATT is needed due to risk of side effects and drug interaction particularly if more toxic second line drugs used for MDR-TB.
- Close monitoring for renal, hepatic function, and neuropathic sign and symptoms because OHA and ATT may have combined toxicity or diabetes may have impaired renal function. INH may aggravate neuropathic symptoms.
- Drug compliance needs more close observation because of high pill burden **(Table 2)**.

Treatment of Diabetes

Treatment of diabetes itself is a vast subject but here while treating a diabetic patient with tuberculosis following points to be considered:

- It should be noted that TB-diabetes form a heterogeneous group consisting of previously diagnosed (known) diabetic and "New" diabetic. In the TANDEM cohort, around 74% of TB-DM patients have previously diagnosed DM (74%), while 26% were newly detected as a result of screening.[21] The relationship between tuberculosis and diabetes is bidirectional. TB is a known cause of pancreatitis and tuberculosis pancreatitis might reveal itself only after the development of diabetes.[22]
- Management of diabetes should be aggressive and optimal glycemic control results in a better patient outcome. If tuberculosis is not extensive or severe there may not be much difference for treatment of diabetes alone, i.e., it may be treated as per general guideline for the treatment of diabetes. Some important drug interaction should be kept in mind while adjusting the dose of OHA.
- Refampicin, through enzyme induction, accelerates the metabolism of sulphonylureas and biguanides, reducing their plasma level and thereby leading to hyperglycemia.[23] Isoniazid antagonizes the action of sulphonylureas and worsen glycemic control. Isoniazid also inhibits the release of insulin even among none diabetics and causes hyperglycemia.[24] Metformin is the drug of choice having no clinically relevant drug interaction. It has some anti-tuberculous activity also.[25] DPPIV inhibitors causes immune paresis and probably worsen treatment outcome of tuberculosis. Thiazolidinediones efficacy may be decreased by enzyme inducing effect of refampicin.
- Insulin is the preferred agent for type 2 DM treatment with TB.[24] The rational for the choice of insulin includes:
  - Severe TB infection
  - Body tissue loss
  - The need for increased anabolism
  - Pancreatic hypofunction
  - Interaction between OHA and ATT
  - Possibility of associated liver disease which would preclude the use of oral agent

  So, usually in case of severe TB-DM with profound systemic sign and symptoms patient is switched over to insulin. After few weeks of treatment tuberculosis get controlled then dose requirement of insulin falls, patient may again be switched over to OHA. Choice of insulin should be based on safety, effectiveness, cost, and patient characteristics.

- Cardiovascular risk assessment is very important in patients with TB-DM. The higher reported rate of mortality in TB patients with diabetes may be caused by these cardiovascular complications rather than TB itself. Cohort study in Taiwan has shown that patients with newly diagnosed pulmonary TB have a 40% increased risk of ACS and a 50% higher risk of ischemic stroke.[26,27]

Conclusion

Our country India has very large number of tuberculosis cases as well as diabetics. Clinical presentation as well as treatment outcome of tuberculosis is largely affected by other comorbidities. Diabetes is an important comorbidity which affects all aspects of tuberculosis management and vise-versa. TB-DM is a commonly encountered situation which needs special attention in RNTCP (NTEP) to improve the treatment outcome and prevent complications.

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CHAPTER

192 Molecular Assays as Initial Tests for the Diagnosis of Tuberculosis

DP Singh, SK Ghosh, Krishna Kumar

Abstract

Tuberculosis remains a major public health problem in developing countries like India due to undue diagnostic delay in diagnosis, and hence treatment of TB. While diagnosis of TB has entered into an era of molecular detection of tubercle bacilli which is faster and rapid, we are still sticking to sputum microscopy as initial test for diagnosing TB, which has comparatively less sensitivity.[1] WHO has recommended molecular assays (Gene X-pert MTB/RIF, Gene X-pert Ultra, and TrueNat) as initial tests for diagnosis of TB and rifampicin resistance in a recent communication, which will bring a paradigm shift in to End TB program.[2]

Introduction

A tribute to Robert Koch is the discovery of tubercle bacilli as a causative organism of tuberculosis (TB) on 24th March, 1882, but the mystery of TB continues even today. TB attacks lungs in 80% of cases called pulmonary tuberculosis (PTB), but it can also affect any extrapulmonary organ named extrapulmonary TB. Global burden of TB is still quite high. In 2018, 10 million people contracted TB and 1.5 million died. There are more than 0.5 million new cases of multidrug resistant TB.[3] Globally, diagnosis of TB and drug-resistant TB remains a challenge, because a third of people with TB and two-thirds of people with drug-resistant TB are not being detected. Accelerated efforts to diagnose TB and drug-resistance are crucial to end the global TB epidemic. India which accounts for 1/5 of global burden of TB needs adequate policy reforms and a high-quality laboratory system which utilizes modern diagnostics for early and rapid diagnosis of TB and rifampicin (RIF) resistance.

Diagnosis of TB

Standards of TB care in India (STCI)[4] have laid down clear diagnostic criteria for different types of TB:

- *Pulmonary TB:* Any adult patient complaining of cough more than 2 weeks, fever more than 2 weeks, significant weight loss, and any abnormality in chest X-ray must be evaluated for TB.
- *Pediatric TB:* Children with persistent fever and/or cough more than 2 weeks, loss of weight/or no weight gain, and/or contact with pulmonary TB cases must be investigated for TB.
- *Extrapulmonary TB:* For all patients with presumptive EPTB, appropriate specimens from the presumed site of involvement must be obtained for microscopy/culture and drug sensitivity/molecular assay to pathological examinations.

WHO urges countries to expand access to rapid molecular tests for detection of TB. Molecular assay (CBNAAT) is already the preferred first diagnostic tool for childhood TB and TB-HIV coinfection. A systemic review of 23 studies has shown that TB is diagnosed in India after a delay of about 2 months.[5] Molecular assay as initial test will lead to early diagnosis. It will also promote reduction in transmission and faster life-saving treatment of this deadly communicable disease.

Paradigm Shift[3]

There has to be a paradigm shift in the approach to TB diagnosis by using newer molecular tests in place of conventional sputum microscopy, if we want to achieve the ambitious goal of ending TB early and accurate diagnosis of TB and RIF resistance is a prime step in this direction.

- *Sputum microscopy:* It has been a diagnostic tool for TB for over a century and still most conventional method for diagnosing TB in India. It takes less than an hour during the examination. At least 5–10 thousand tubercle bacilli per mL of sputum (limit of detection LOD) are needed to demonstrate bacilli in the sample.[6] But this methodology lacks sensitivity and so misses many TB cases.
- *Mycobacterium culture:* Culture of mycobacterium TB is the gold standard for diagnosis of TB. In contrast to sputum microscopy only 10–100 tubercle bacilli are needed for culture positivity. Conventional L J Media takes longer time (4–8 weeks), but liquid culture media like BACTEC or non-radiometric MGIT (mycobacterium Growth Indicator Tube) takes 2–3 weeks times. But this process is cumbersome and time consuming. Hence, there is a dire need of a diagnostic tool which can provide a rapid and confirmed diagnosis of TB. Molecular assay is most suitable to perform this role.
- *Molecular assays:*[1,7] Science is moving from biology to microbiology and from microbiology to molecular biology. Molecular assay have ushered to a new era of rapid and early diagnosis of not only TB, but also RIF resistance.

Probe-based Methods/DNA Chip- based Methods:

- Cartridge Based Nucleic Acid Amplification Test (CBNAAT): Gene X-pert, Gene X-pert Ultra, and TrueNat are endorsed by WHO
- Line Probe Assay (LPA)
- Loop-mediated isothermal amplification (LAMP)

Rapid Molecular Tests:[2,8-10]

- Nucleic Acid Amplification Test (NAAT) is a molecular system that detects pathogenic DNA (deoxyribonucleic Acid) of *Mycobacterium tuberculosis* (MTB).

  Molecular assays have several advantages in their arms:
  - NAAT amplifies mycobacterium specific DNA sequences using a nucleic acid probe
  - It increases the rate of detection
  - It requires only 16–131 bacilli to give positive results in a given sample
  - It lessens the time of detection
  - It is more accurate diagnosis with sensitivity at least 80% in most studies and specificity 98–99%

  Disadvantage: It has one disadvantage that it is not able to differentiate active infections from old ones as DNA from a dead organism can be detected and amplified by PCR.

  X-pert MTB/RIF (USA) is an automated PCR test, which detects MTB and RIF resistance within 2 hours of starting the test.[7]

  X-pert Ultra is the new version of X-pert MTB/RIF, which is much more sensitive than X-pert. Its sensitivity is comparable to liquid TB culture. Gene Ultra is an advanced version of Gene X-pert with better TB detection capabilities and more definitive identification of RS and RR bacilli. Gene Ultra can be used as an alternative to Gene X-pert for initial testing in pts with s/s of TB. It is also planned to phase out Gene X-pert to be replaced by Gene Ultra.
- Line Probe Assays (LPAs) are active molecular tools. LPA of TB was endorsed by WHO in 2008. Meta analyses have shown that LPAs are highly accurate for the detection of first-line drug resistance of isoniazid (INH), RIF, and other first line drugs in sample positive specimens. By using LPA it is possible to diagnose MDR early and rapidly within 2 days.

  INH and RIF drug resistant strains are identified by detecting the most common single nucleotide polymorphism associated with resistance.
- *Loop-mediated isothermal amplification (LAMP):* LAMP is an isothermal nucleic acid amplification technique. It was recommended by WHO in 2016 for diagnosis of TB as a replacement of smear microscopy. Characteristics of TB-LAMP have been compared to those of Gene X-pert and LPA **(Table 1)**.

Evidences of Molecular Assays as Initial Test for TB Diagnosis[2,11,12]

- *X-pert TB/RIF:* WHO in 2010 has approved X-pert MTB/RIF machine, which utilizes molecular technique for

TABLE 1 Characteristics of rapid molecular assays[7,12,13]

Test specification	*TB LAMP*	*X-Pert MTB/RIF*	*X-Pert MTB/RIF Ultra*	*LPA*
Technology	LAMP	R-T PCR	R-T PCR	Multiplex PCR
Detects	MTB	MTB + RIF resistance	MTB + RIF resistance	MTB + resistance to RIF and INH
Targets	IS6110	rpoB gene	rpoB gene	rpoB, katG, inh genes
Time of detection	<1 hour	2 hours	<90 min	5 hours

LAMP, loop mediated isothermal amplification; LPA, line probe assay; R-T PCR, real-time polymerase chain reaction.

TABLE 2 Overall sensitivity and specificity of all samples sputum positive (SP) and sputum negative (SN) in Gene X-pert

	Sensitivity (%)	*Specificity (%)*
Non-HIV group	85	98
HIV group	81	98

rapid diagnosis of TB and RR.70 studies involving more than thirty thousand patients from 37 countries have shown high diagnostic accuracy of gene X-pert in pulmonary TB **(Table 2)**.

If a patient is rifampicin resistant (RR), can Gene X-pert give false rifampicin sensitive (RS) results? Answer is yes and this paradox is caused by silent mutation.

Data from JLNMCH, Bhagalpur, confirm clear-cut superiority of cartridge based NAAT (CBNAAT) over sputum microscopy.[14] Conventional approach using LED microscopy SP was 10.3% while CBNAAT detected 22% positivity. An addition advantage was 19% positivity in SN samples.[11,14]

- *Molecular assays are pillars in diagnosis of EPTB:* Difficulties were always encountered in confirming the diagnosis of EPTB because of its paucibacillary nature and obtaining tissues from unreachable sites. By using X-pert MTB increased numbers of bacteriologically confirmed EPTB cases were found.

  X-pert MTB/RIF ultra: X-pert MTB/RIF-ultra is much more sensitive than X-pert MTB/RIF.[13] **Table 3** shows the limit of detection (LOD) of different diagnostic tests of TB.

  In samples where MTB detected was very low false RMP resistance was seen in Gene X-pert, not in Gene Ultra. Such sample must be subjected to Gold Standard test of TB diagnosis-culture DST. For HIV-positive patients sensitivity of Ultra was 90% versus 77%, i.e., 13% more.

TABLE 3 Limit of detection (LOD)

Diagnostic tests for TB	*Limit of detection (bacilli per mL of sample)*
Sputum microscopy	5,000–10,000
Mycobacterium culture	10–100
Gene X-pert	131
Gene Ultra	16
TrueNat	29

It is as sensitive as mycobacterial culture. In other words Ultra will result in greater TB case detection rate in subjects with paucibacillary TB such as smear negative-culture-positive TB, those with HIV coinfection, pediatric TB, and those with extrapulmonary TB.

High diagnostic accuracy of Gene X-pert Ultra in adults with PTB: 5 studies from 12 countries (including high-burden TB countries) overall sensitivity was found to be 90%, which includes all specimens smear-positive and smear-negative ones. Overall specificity was 96% in both types of specimens.

- *Pediatric TB:* There are difficulties in obtaining sputum specimens in children and due to this limitation various non-pulmonary specimens (gastric, nasopharyngeal, and stool) are used for bacteriological confirmation. Data from 21 countries involving more than 6,000 patients show.

In pediatric TB these are variable sensitivity in different specimens (nasopharyngeal—46%, stool—61%, sputum—65%, and gastric—73%) and Specificity 98–100%.

X-Pert MTB/RIF to Detect RIF Resistance in Pediatric TB

Using Gene X-pert when RIF resistance was tested with reference to phenotypic drug sensitivity testing it was found to have high overall sensitivity (90%) and specificity

TABLE 4 Sensitivity and specificity of extrapulmonary samples by Gene X-pert[15]

Samples	*Sensitivity (%)*	*Specificity (%)*
Lymph nodes	84.9	92.5
CSF	79.5	98.6
Pleural fluid	43.7	98.1
Gastric lavage	83.8	98.8

(98%). Data from six studies which involved 200 patients from four high-burden countries supported the above findings.

EPTB: Similar to pediatric TB difficulties are faced in obtaining extrapulmonary specimens and in aiding bacteriologically confirmed diagnosis in EPTB.

Gene X-Pert as Initial Test for EPTB

Data was assessed from 59 studies from 26 countries, which used MTB/RIF in adults with extrapulmonary TB.[11] Sensitivity and specificity of extrapulmonary TB varied with specimen types **(Table 4)**.

Another studies group using X-pert Ultra showed high performance of detection of RIF resistance sensitivity 96–97% and specificity 99%.[8]

TrueNat as Initial Test for Diagnosis of TB[2,16]

TrueNat TB test is a new molecular assay, which is in fact a real time PCR system. It is simple and user friendly. It is a point of care (POC) tool and battery operated. Therefore, it is suitable for diagnosis of TB and RIF resistance for poor countries like India where it can be used in rural primary health centers (PHC).

WHO Endorses TrueNat Test

In December 2019, WHO considered the latest evidence on the use of Molbio TrueNat MTB/RIF test. Multicentric study of TrueNat assays done in India, Peru, Ethiopia, and Papua-New-Guinea involving 744 patients examined the performance of TrueNat MTB, MTB plus, and MTB RIF Dx assays, which showed comparable efficacy to X-pert MTB/RIF and X-pert Ultra in TB diagnosis and RIF resistance. Overall sensitivity of the TrueNat MTB assay was 83% and that of MTB plus 89% while specificity for MTB and MTB Plus assay was 99% and 98%, respectively. The endorsement of TrueNat by WHO will help the low and middle income countries to use TrueNat in elimination of the disease (TB).

To evaluate the performance of TrueNat assay in comparison with Gene X-pert, 274 samples were processed. The overall sensitivity of TrueNat and Gene X-pert was 94.7% and 96%, respectively.

Conclusion[3]

- There are robust data to support that molecular assays (X-pert MTB/RIF and X-pert Ultra) should be used as initial tests for diagnosis of pulmonary TB in adults.
- A large number of studies support the use of X-pert MTB/RIF and X-pert Ultra as initial diagnostic work-up of extrapulmonary TB.
- These molecular assays show clear superiority over conventional sputum microscopy in the diagnosis of pediatric TB.
- Both molecular assays X-pert and X-pert Ultra show high accuracy in the simultaneous detection of RIF resistance.
- Low cost and Indian molecular assay TrueNat MTB, MTB plus, and MTB-RIF Dx show comparable accuracy with both Gene X-pert and Gene X-pert Ultra in diagnosis of TB and RIF resistance.

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CHAPTER

193 Association of Tuberculosis and COPD

SM Mishra

Abstract

COPD and Tuberculosis are common respiratory diseases in our country. Past history of Tuberculosis is considered an important risk factor for COPD. Chronic airflow obstruction in tuberculosis patients occurs due to tuberculosis-associated lung damage leading to COPD. A number of factors associated with COPD may increase the progression of Tuberculosis in these patients, most important factors are- use of inhaled/oral corticosteroids in the treatment of COPD and smoke related exposure related altered protective response to *M. tuberculosis*. There is bidirectional relationship between tuberculosis and COPD. Early diagnosis and standardized treatment of Tuberculosis and COPD is essential. Action to increase awareness regarding COPD is essential.

Introdution

Tuberculosis and chronic obstructive pulmonary disease (COPD) are major causes of morbidity and mortality worldwide. As per recent reports the prevalence of COPD is increasing worldwide. Past history of tuberculosis is an important risk factor of COPD. It is well known that COPD patients have an increased risk of developing tuberculosis. Thus, there is bidirectional relationship between COPD and tuberculosis. It is alarming for our country since both these diseases are prevalent in our country. These diseases have adverse impact on each other as far morbidity and mortality is concerned. We are committed to eliminate TB, if we have to fulfill our commitment, timely intervention and action for early diagnosis and institution of appropriate treatment of tuberculosis is essential. In addition to adequate steps for diagnosis and treatment of tuberculosis, common risk factors for tuberculosis and COPD must be addressed properly to prevent development of both these diseases in future, otherwise we cannot achieve the target of TB elimination.

COPD and pulmonary tuberculosis are two very important disease of respiratory system, worldwide. These diseases primarily affects lung, COPD is a non-communicable disease, and pulmonary tuberculosis is an infective disease caused by Mycobacterium tuberculosis. As per a number of studies conducted worldwide, there is bidirectional relationship between two diseases and effects each other adversely.

Due to recent advancement in medical field incidence of infective diseases are showing decreasing trend. Due to economic development epidemiological transition is going on globally, the incidence of infective diseases are decreasing, but there is increase in the incidence of non-communicable diseases like COPD. But due to rapid urbanization, overcrowding, lack of awareness, weak health-care system in our part of world (low and middle income countries), there is double burden of infective diseases like tuberculosis and non-communicable diseases like COPD.[1]

We are committed to eliminate tuberculosis, from India by 2025, 5 years ahead of global target, if we have to achieve the target we must take steps to control both COPD and tuberculosis simultaneously. Early diagnosis and proper and standardized treatment of tuberculosis

is mandatory to reduce the future burden of COPD and tuberculosis both. Similarly, steps must be taken to reduce air pollution and other common risk factors, which may help in prevention of these diseases. Fortunately a number of programs are going on in our country, so we can expect favorable results in near future.

Current Global Burden of Tuberculosis

As per global TB report (2019), this is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent. About a quarter of the world's population is infected with *Mycobacterium tuberculosis* and thus at risk of developing TB disease.[2] Globally, an estimated 10 million people fell ill with TB in 2018, and there were about 1.5 million death due to this disease. With timely diagnosis and treatment, most people who develop TB can be cured and transmission of infection reduced in the society, thus decreasing mortality and morbidity.

Current Global Burden of COPD

COPD is a major public health problem worldwide, due to its high prevalence, morbidity and mortality.[3,4] Mortality due to COPD is showing an increasing trend. At present it is the third leading cause of death globally.[5] Chronic obstructive disease is a progressive disease, treatment can relieve symptoms and thus, improve quality of life and reduce the risk of death.[6] Air pollution and smoking both active and passive is very important risk factor. Use of conventional fuel is prevalent in our country, this is also an important risk factor. By risk reduction measures we can reduce the burden and socioeconomic consequences. Fortunately, a number of initiatives have been taken in our country, this may have a positive impact and reduce the burden of COPD in our country.

Tuberculosis and COPD Different Aspects of Association

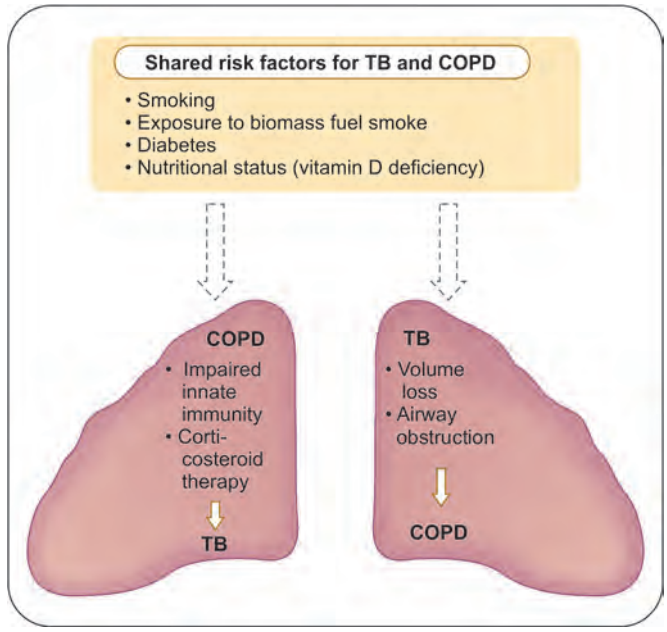
COPD and Tuberculosis Shared Risk Factors

There are some common risk factors for COPD and Tuberculosis, that is, they share some of the risk factors and these are shown in **Figure 1**.

Tuberculosis as the Risk Factor for COPD

Past history of tuberculosis is well recognized as risk factor for development of COPD, particularly in developing countries.[7,8] This relationship of TB and COPD is dangerous for our country since the prevalence of both diseases are high in our country. The pathological process due to tuberculosis leads structural changes in the lungs. These structural damage of the lungs increases with increasing number of episodes and they persists despite anti-tubercular chemotherapy.

Fig. 1: Common risk factors for COPD and tuberculosis



The structural damage leads to air flow obstruction and impairment of lung function. Impairment in airflow can occur during active phase of tuberculosis or may be detected after the treatment. Patients usually develop maximum loss of lung function within 6 months of diagnosis of tuberculosis and generally stabilize about 18 months after the completion of treatment.[9,10] Antitubercular treatment leads to improvement in lung function, but the residual lung function impairment depends on both pre- and post-treatment radiological extent of disease. Delay in initiation of treatment lead to more extensive disease and more structural damage leading to more impairment of lung function.

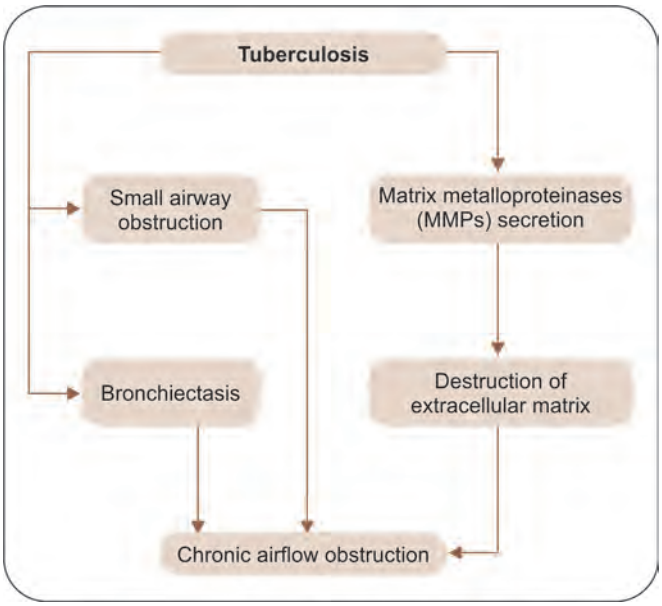
Mechanism of Airflow Obstruction Due to Tuberculosis

The sequence of pathological process leading to chronic airflow obstruction in post-tuberculosis patient is not clear, following mechanisms have been proposed:

- *Role of macrophages:* Macrophages are one of the key cells concerned in the pathological process of tuberculosis, these cells play an important role in wound healing and resolution, they may cause remodeling of airways, leading to chronic airflow obstruction.
- *Small airway involvement:* The pathological process undergoing in lungs in tuberculosis may involve the small airways leading to airflow obstruction. The observation of Allwood et al. during their study supports this concept, they observed that patients with chronic airflow obstruction with definite previous TB had higher gas trapping, fibrosis, and emphysema score than subjects with no previous tuberculosis. The diffusion capacity was also significantly lower in patients with definite previous TB.[11]
- *Bronchiectasis:* Post-tuberculosis bronchiectasis is very common finding and probably most common cause of Bronchiectasis in our country. Endobronchial obstruction or peribronchial fibrosis or obstruction by enlarged lymph nodes found in tuberculosis, may lead to bronchiectasis and chronic airflow obstruction.[12]
- *Accelerated parenchymal destruction:* Lung parenchymal inflammation occurs in tuberculosis, this leads to destruction of pulmonary extra-cellular matrix (ECM). As described earlier remodeling occurs in the lung due to ongoing pathological and healing process, Matrix metalloproteinases (MMP) are considered to mediate tissue remodeling in tuberculosis. MMPs are a family of calcium dependent zinc containing endopeptidases. There are different kinds of MMPs. Different MMPs plays different role in Mycobacterial infection. MMP-9 is concerned in the formation of stable granuloma, thus containing the infection. Reactivation of latent TB leads to MMP-1 secretion, which causes alveolar destruction and is responsible for cavitation in tuberculosis.[13] Type II pneumocyte makes MMP-1.[14] MMPs lead to degradation of ECM and thus involved in the pathogenesis of both tuberculosis and COPD, the scaffold of alveolar wall.

The pathological process in tuberculosis leading to chronic airflow obstruction maybe summarized in the **Flowchart 1**.

Flowchart 1: Pathological process leading to chronic airflow obstruction in post-TB patients



Impact of COPD on Tuberculosis

It is well known that patients suffering COPD have increased risk of developing tuberculosis. Lee et al. in his study observed that COPD is an independent risk factor for tuberculosis.[15]

Exact mechanism or the factors which leads to increased risk is not well known, inhaled and oral corticosteroids are used for the treatment of COPD. Corticosteroids are known to produce immune-suppression; this may increase the risk of tuberculosis.[16]

Use of corticosteroids is not the only factor responsible for immune impairment in COPD and tuberculosis, but other factors also involved in immune impairment in these cases are:

- *Cigarette smoke exposure:* According to study conducted by patients Shang et al., the cigarette smoke exposure alters the protective response to *M. tuberculosis*.[17]
- *High levels of cytokines:* High levels of some of cytokines like sIL-2R, IL-6, TNF-alpha, IFN-y are found in COPD patients. These cytokines by producing an exuberant inflammatory response may cause progression of tuberculosis in COPD patients.[18]
- *Dysfunction of alveolar macrophages:* In patients suffering from COPD, dysfunction of alveolar macrophages develops, which is considered independent of steroids, this leads to an additional risk of developing tuberculosis.[19,20]

Conclusion

COPD and tuberculosis are most common respiratory problem in our country. As per different studies conducted, past history of tuberculosis is considered an important risk factor for COPD. Chronic airflow obstruction in tuberculosis patients occurs due to tuberculosis associated lung damage leading to COPD. A number of factors related to COPD may increase the risk of progression of tuberculosis in these patients—use of inhaled and oral corticosteroids in the treatment of COPD, may increases the risk of progression of tuberculosis by causing immune suppression. Other factors are—smoke exposure related altered protective response to *M. tuberculosis*, high levels of some of the cytokines and dysfunction of alveolar macrophages observed in COPD patients, which is independent of steroids. Thus, above mentioned facts indicates that there is bidirectional relationship between two diseases.

Early diagnosis and timely initiation of standardized and complete of treatment of tuberculosis and COPD is essential. Government of India under 'National Tuberculosis Elimination' has increased facility for early diagnosis and proper treatment of tuberculosis, definitely this will have a positive impact. Diagnosis of COPD is based on clinical suspicion, confirmed by respiratory function tests , it is essential to increase general awareness regarding this disease and improvement in facility for diagnosis of COPD. Action to reduce shared risk factors for COPD and tuberculosis is the prerequisite to reduce the burden of both tuberculosis and COPD in our country. These steps may improve the quality of life, morbidity, and mortality due to these diseases.

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CHAPTER

194 Exudative Pleural Effusion—Diagnostic Approach

Sanjay Kumar

Abstract

The exudative pleural effusion caused either by infections like tuberculosis or due to other diseases like cancer, is associated with a lot of complications and even mortality. The proper history and pleural fluid examination is the first step in differential diagnosis of exudative pleural effusion, but sometimes other investigation techniques like imaging, closed pleural biopsies, and pleuroscopy or video associated thoracoscopy are needed to clinch the diagnosis and proper management.

Introduction

Pleural effusion is a common condition in day to day practice. It develops when more fluid enters the pleural fluid than is removed. The first step in the evaluation of pleural effusion is to determine whether it is exudate or transudate. In cases of exudative effusion the stepwise approach to find out the etiology is needed. Thoracentesis and pleural fluid examination are useful in differential diagnosis of such cases. Other tests like CT scan, Pleuroscopy, etc. may help in reaching an etiological diagnosis.

Pleural effusion may be caused by variety of diseases. Traditionally to simplify the diagnostic approach the pleural effusion is first dichotomized as transudative or exudative. Exudative effusion usually develops due to inflammatory or malignant disorders. The basic pathophysiological mechanism of exudative pleural effusion is increased capillary permeability, which leads to accumulation of large molecular weight compounds in the pleural space.

There are numerous causes of exudative pleural effusion. The most common cause of this in areas where tuberculosis is endemic is secondary to pleural TB.[1] The other common causes are pneumonic, malignancy (primary or secondary) and pulmonary embolus with infarction. The less common causes are—rheumatoid arthritis, other connective tissue diseases, pancreatitis, esophageal rupture, post coronary artery bypass surgery, etc.

Initial Evaluation

The careful history, including the occupational history & history of past illness, symptoms, and signs on physical examination are the first vital measure in guiding the evaluation of pleural effusion.

Pleuritic chest pain, cough, and dyspnea are three basic symptoms of exudative pleural effusion besides other symptoms like fever may be present. Pleuritic chest pain is due to inflammation of parietal pleurae and it likely indicates some infectious cause, while dull aching chest pain is very much suggestive of pleural malignancy. Non-productive cough is also a common symptom. Although the exact mechanism of cough is not clear, but pleural inflammation is again implicated as possible cause.

The third symptom dyspnea is basically due to space occupying process in the thoracic cavity and reappearance

of fluid quickly after therapeutic thoracentesis is most likely due to malignant involvement of pleura.

Thoracentesis and Examination of Pleural Fluid

After the initial evaluation, the next step is diagnostic thoracentesis and examination of pleural fluid. It not only settles the issue of transudative versus exudative effusion, but also diagnoses the cause of exudative effusion in most cases.

The usual tests that should be performed on fluid obtained during diagnostic thoracentesis are—cell counts and differentials, glucose, adenosine deaminase (ADA) estimation, and cytologic analysis. The pH measurement and bacterial cultures should be done when acute infection is suspected. The routine pleural fluid tests are summarized in **Table 1**.

For proper total white blood cell count and differential cell count, it is necessary to send the pleural fluid in anti-coagulated tube. Otherwise the fluid is likely to clot leading to an inaccurate count.[3]

The main WBC cell type is determined by the mechanism of pleural injury and the time interval between the onset of pleural pathology and thoracentesis. So, the neutrophil-rich fluid is highly suggestive of an acute process like parapneumonic effusion, while lymphocyte predominant fluid profile is indicative of chronic process like tuberculosis or malignancy.

A low pH value of fluid has important therapeutic and prognostic implications with parapneumonic and malignant pleural effusion. Low pH value less than 7.20 in patients with parapneumonic effusion is indicative of drainage of the fluid.[4]

In the unavailability of pH value determination, a pleural fluid glucose concentration of less than 60 mg% helps in detecting complicated parapneumonic effusion.[4]

The enzyme ADA plays a very important role in lymphoid cell differentiation. Pleural fluid ADA level greater than 40 U/L is highly sensitive and specific marker for the diagnosis of tuberculous pleural effusion. The sensitivity varies between 90% and 100%, while specificity is as high as 85% and 95%.[5]

Pleural fluid culture for both aerobic and anaerobic bacteria may identify the culprit microorganism in almost 40% of parapneumonic effusion.[2]

Pleural fluid smears for mycobacterium are positive very rarely found in about 5% of cases[2] and about one third of patients with tuberculous pleural effusion have negative tuberculin skin test.[6]

Pleural fluid cytology is very important to diagnose malignant pleural effusion. Cytology positivity is almost 60% in malignant pleural effusion.[7]

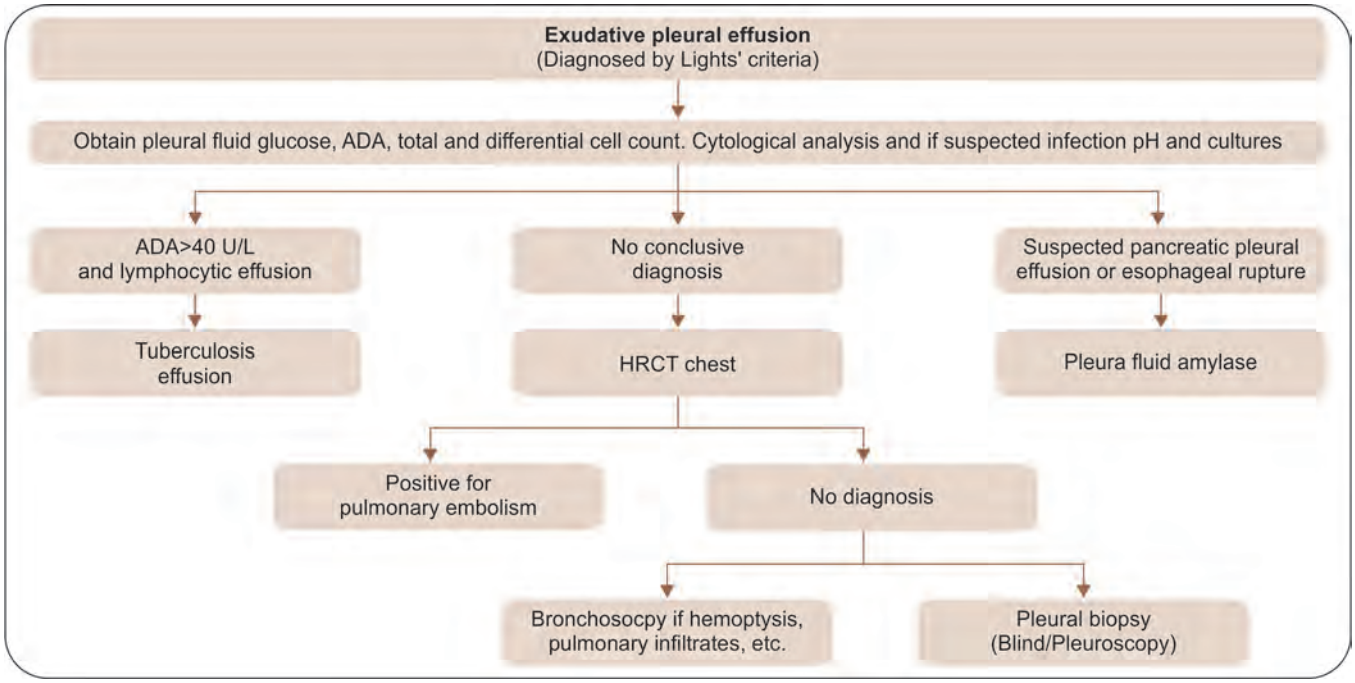
The test result negativity are related to different factors such as type of tumor (usually negative in mesothelioma, sarcoma, and lymphoma), the tumor burden in pleural space and the expertise of the person performing the job. An amount of 10 mL of pleural fluid is adequate for cytologic processing. Additional pleural taps increase the diagnostic yield further.

A second thoracentesis may be considered in suspected malignant effusion and the initial pleural fluid cytology examination is negative for malignancy.

TABLE 1 Routine pleural fluid tests for pleural effusion

Test	*Test value*	*Suggested diagnosis*
ADA	>40 U/L	Tuberculosis (>90%), Empyema (60%) complicated parapneumonic effusion (30%), malignancy (5%), Rheumatoid arthritis[2]
Cytology	Atypical cells/Malignant cells	Malignancy (primary or secondary)
Glucose	<60 mg/dL	Acute infection like parapneumonic effusion, tuberculosis, malignancy, rheumatoid arthritis[2]
RBC count	$>100\times10^6$/L	Malignancy, trauma, parapneumonic effusion, pulmonary embolism
WBC count & differential	10×10^9/L	Infection, empyema, etc.
Lymphocytes	>50%	Tuberculosis-most likely, malignancy, and post-CABG
Neutrophils	>50%	Parapneumonic effusion, pulmonary embolism, abdominal diseases

Flowchart 1: Exudative pleural effusion



Other Diagnostic Modalities

There are occasions when we need to further investigate the case in order to get a cause of exudative pleural effusion. The further work up includes:

- *Imaging techniques:* High resolution helical CT scan is the investigation that is used as first line modality for delineating pulmonary circulation in patients suspected to have pulmonary embolism. CT can distinguish malignant from benign pleural disease also as it detects nicely pleural nodules or nodular pleural thickening. The detection and differentiation of benign and malignant pleural disease is further enhanced using positron emission tomography scan.[8]
- *Bronchoscopy:* Endobronchial malignancy may lead to exudative pleural effusion also. Whenever this is suspected in chest radiography or CT scan images, or patient has symptoms of hemoptysis or there is massive pleural effusion or shift of mediastinum to the side of pleural effusion, bronchoscopy is useful.
- *Closed pleural biopsy:* In cases of undiagnosed exudative pleural effusion, percutaneous closed pleural biopsy (CPB) is recommended. Image guided biopsy is superior to blind closed biopsy. The sensitivity of image guided biopsy is much higher than closed biopsy. Histological examination associated with culture of pleural biopsy tissue confirms the diagnosis of tuberculosis in 90% of patients.[5]
- *Pleuroscopy:* Pleuroscopy, usually referred to as medical thoracoscopy, is gradually gaining importance and now recognized as procedure of choice both for diagnosing and treating exudative pleural effusion, which eludes diagnosis after thoracentesis. It is diagnostic in more than 90% of patients with pleural malignancy where cytology is negative.[9] Pleuroscopy offers the additional benefit of effective pleurodesis during the procedure.

Conclusion

The careful stepwise approaches starting from proper history taking, evaluation of symptoms & signs, and diagnostic tests help in finding out the exact cause of exudative pleural effusion in majority of cases. Despite the best of efforts, approximately 15% of patients of pleural effusion remain undiagnosed.[10]

The suggested algorithm for the investigation of exudative pleural effusion is shown in **Flowchart 1**.

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CHAPTER

195 Tubercular Lymphadenitis—Challenges in Treatment

Deependra Kumar Rai

Abstract

Tubercular lymphadenitis is most common form of extrapulmonary tuberculosis. The most common Lymph node involved is cervical followed by Supraclavicular, Axillary, submandibular and, Inguinal region. Majority of patient presented as isolated chronic nontender lymphadenopathy. The regimen and duration of tuberculosis is same as pulmonary tuberculosis. Treatment is complicated by paradoxical reaction in almost 1/5th of patients, which does not require change in treatment and most of the patient subside by its own.

Introduction

We are living in the second-most populous country after China in the world and one-fourth of the global incident tuberculosis (TB) cases occur in India annually as per the WHO Global TB Report.[1] Extrapulmonary TB (EPTB) is defined as occurrence of TB other than lung is more common in immunocompromised individual with HIV infection. Lymph node TB was found as most common EPTB (37.14%) found in 517 EPTB cases.[2] Cervical lymphadenitis is also known as scrofula.[3] Tubercular lymphadenitis also caused mainly mycobacterium TB, rarely by nontuberculous mycobacteria (NTM), especially in children or patient who immunocompromised.

Pathogenesis

Tubercular lymphadenitis is considered as local manifestation of systemic disease while lymphadenopathy due to NTM is purely a localized disease. Tubercular bacilli generally enter the body via respiratory tract and undergo hematogenous and lymphatic dissemination. Hilar and mediastinal lymph node are first lymphoid organ involved when spread from lung parenchyma occur. This can occur during primary infection or may occur due reactivation of previous infection. In NTM lymphadenitis, the bacilli enter through oropharyngeal mucosa, salivary glands, tonsil, or conjunctiva.

There are five stages of lymph node TB described by Jones and Campbell:[4]

- *Stage 1:* Enlarged, firm mobile discrete lymph nodes showing non-specific reactive hyperplasia
- *Stage 2:* Large rubbery lymph nodes fixed to surrounding tissue due to periadenitis
- *Stage 3:* Central softening due to abscess formation
- *Stage 4:* Collar stud abscess formation
- *Stage 5:* Sinus tract formation

Clinical Presentation

Most common clinical presentation as slowly enlarging lymph node. Constitutional symptoms like fever, weight loss, anorexia, and fatigue rarely found. We found[5] almost one-fourth of study patients (25.38%) having a symptom for more than 1 year before getting diagnosed as tubercular lymphadenitis before putting on anti-tubercular treatment. Cervical lymph node is the most

commonly involved followed by axillary and inguinal lymph node. Fever has been reported in 20–50% of cases in HIV-negative patients and 60–80% in HIV-positive patients.[3] Our study[5] showed fever, anorexia, and weight loss in 72.30%, 50.76%, and 41.53%, respectively. More than half of study patients (55.38%) received homoeopathic or ayurvedic treatment before putting on anti-tubercular treatment that could be one of the causes of delayed presentation. Physical examination finding depends upon stage of disease. Enlarged lymph node may be firm, discrete mass or matted nodes fixed to surrounding structures; the overlying skin may be indurated.[6] The lymph nodes are usually non tender unless secondary bacterial infection has occurred. Sometimes, lymph node abscess ruptured leading to non-healing sinus formation. The typical TB sinus appears thin, bluish, undermined edges with watery discharge. There is various complication occur especially due to mediastinal TB. These include dysphagia due to pressure on esophagus, esophagomediastinal fistula and tracheoesophageal fistula. Node may cause thoracic duct obstruction presenting as chylothorax, chylous ascites, or chyluria.

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Differential Diagnosis

- Hodgkin lymphoma and non-Hodgkin lymphoma
- Reactive lymphadenitis (secondary to bacterial or viral infections)
- NTM infection
- Cat scratch disease
- Fungal infection
- Sarcoidosis
- Kikuchi disease (idiopathic histiocytic necrotizing lymphadenitis)

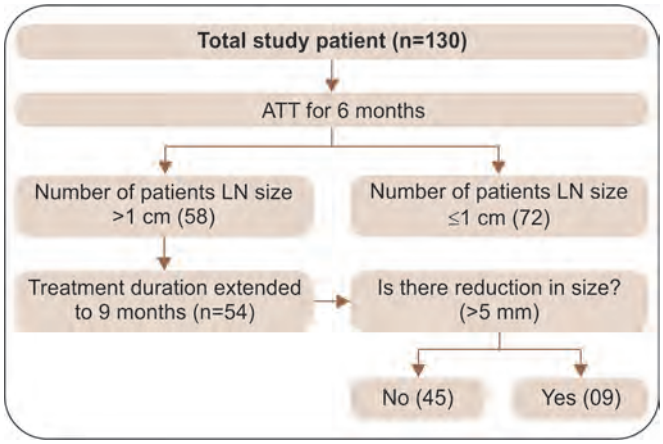
Diagnosis

Diagnosis of tuberculous lymphadenitis is confirmed by histopathology showing caseating granuloma and/or bacteriological evidence in form of smear positive for acid-fast bacilli (AFB), molecular test, or culture positivity. Fine needle aspiration (FNA) is appropriate for initial evaluation of cervical lymphadenopathy to evaluate for tuberculous lymphadenitis. The yield of FNA appears to be highest in the setting of HIV infection and in regions where the prevalence of TB is high. Specimens should be subjected for microscopy, culture, cytology, and polymerase chain reaction/GeneXpert testing. Excisional lymph node biopsy is indicated when FNA is not diagnostic. The finding of caseating granulomas on histopathology is highly suggestive of TB but it is not confirmatory because other disease like sarcoidosis and fungal infection may have granuloma. Multiplicity, matting and causation are three features which help in differentiating TB from other differential. In our study among 130 study patients, 62 (47.69%) were classified as having confirmed TB based on AFB positivity in FNAC sample. The remaining 68 (52.30%) patients had probable TB.

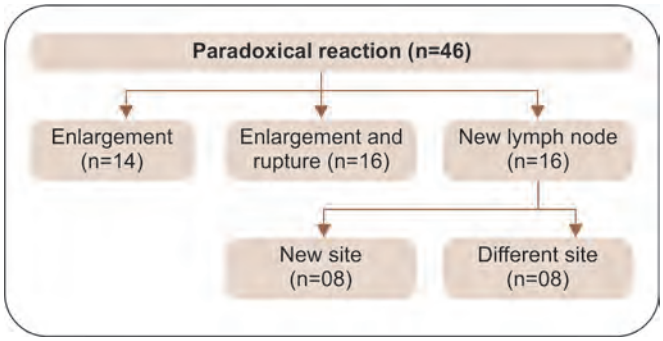
Treatment

Treatment options for tubercular lymphadenitis are surgical excision of involved node and/or anti-tubercular treatment. It is generally agreed that anti-tubercular treatment is sufficient for majority of cases and surgical treatment required in selected cases. INDEX TB guideline recommends 6-month therapy with first-line anti-tubercular drug of isoniazid, rifampicin, ethambutol, and pyrazinamide.[7] The studies evaluated 6–9 months regimen and found no difference as far as cure rates (89–94%) or relapse rates (3%) are concern.[8] Anti-tubercular treatment may be complicated by paradoxical reaction or increase in size of primary lymph node and/or appearance of new lymph nodes in up to 20% of patients during or even after cessation of treatment. These nodes may show histopathological features characteristics of TB but sterile on culture. These phenomena are transient and nodes ultimately regress in size. We did a study[5] to identify incidence of paradoxical reaction and residual lymph node at the end of 6 months of treatment. Forty-six (35.38%) patients out of 130 developed paradoxical reaction, and most of this occurred in the first 2 months of the initiation of anti-tubercular treatment. Fifty-eight patients (44.61%) had a residual lymph node of size more than 1 cm after 6 months of treatment. Only 9 patients out of 54 patients had significant reduction in the size of the lymph node with extended 9 months of treatment **(Flowcharts 1 and 2)**. So, presence of residual lymph node at the end of treatment does not require extended duration of treatment rather just close observation required but if there is increase in size of lymph node, send sample for histopathological examination, GeneXpert, and AFB culture.

Flowchart 1: Treatment outcome of standard 6 months and extended 9 months of lymph node tuberculosis patients



Flowchart 2: Characteristics of paradoxical reactions (number in bracket showing number of patients)



Conclusion

Lymph node TB is the most common forms of EPTB and is different from pulmonary TB in terms of diagnosis and treatment. Treatment regimen and duration is similar to pulmonary TB, but complicated by paradoxical reaction or residual lymph node at the end of treatment. So, patient might be given multidrug-resistant (MDR) treatment for paradoxical reaction and extended the duration of treatment for residual lymph node. Sample should always be processed for molecular test like GeneXpert and culture in all worsening lymph node with treatment to differentiate paradoxical reaction from drug resistance.

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CHAPTER

196 Gastric Tuberculosis: An Often Unrecognized Entity

Piyush Manoria, Vishal Yadav

Abstract

Tuberculosis of stomach is a very rare manifestation of mycobacterium tuberculosis and presents as a diagnostic challenge to physicians. Gastrointestinal tuberculosis is the sixth most common cause of extrapulmonary tuberculosis, and stomach is the sixth most common site of it. It mostly occurs as a part of disseminated tuberculosis or in an immunocompromised state and presents as non-healing gastric ulcer or gastric outlet obstruction. It's mostly diagnosed after surgical intervention as yield of endoscopic biopsies is low due to submucosal location of granulomas. It's treated with conventional antitubercular therapy, and surgery is only needed when it presents with complications.

Introduction

Tuberculosis is endemic and a major health problem in India. Gastric tuberculosis is a rare manifestation of gastrointestinal tuberculosis and usually occurs in association with pulmonary tuberculosis or in immunocompromised states. It mostly presents as a diagnostic dilemma and often masquerades as peptic ulcer disease or gastric malignancy.

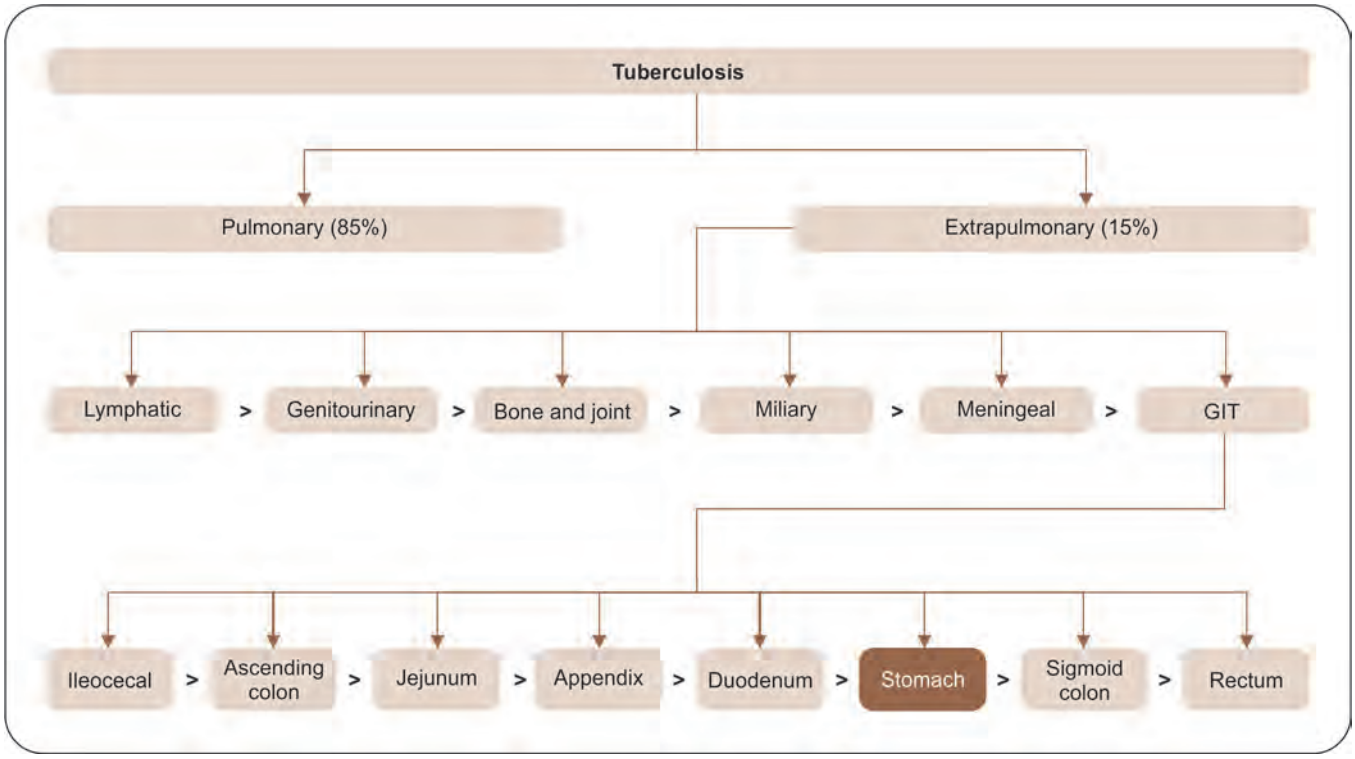
Epidemiology

Pulmonary tuberculosis accounts for 85% and extrapulmonary tuberculosis accounts for 15% of all cases of tuberculosis in an immunocompetent person. Gastrointestinal tuberculosis is the sixth most common cause of extrapulmonary tuberculosis after lymph node, genitourinary, bone and joints, miliary, and meningeal tuberculosis.[1] Tuberculosis can involve any part of gastrointestinal tract but it most commonly involves the ileocecal region followed by ascending colon, jejunum, appendix, duodenum, stomach sigmoid colon, and rectum.[2] The incidence of tuberculosis reduces as we move proximally and distally from ileocecal region. Stomach is the sixth most common cause of gastrointestinal tuberculosis and it accounts for 0.5–3% of its all cases.[3] The various sites of tuberculosis have been shown in **Flowchart 1**. It occurs mostly between ages of 15–62 years with a male preponderance.[4]

Pathogenesis

Gastric tuberculosis usually occurs as a part of disseminated disease or in immunocompromised states. Isolated gastric tuberculosis in immunocompetent person is very rare and only few case reports are published till date. We have published a case of isolated gastric tuberculosis in a healthy female presenting as non-healing gastric ulcer[5] **(Figs. 1A to C)**. Stomach as a site for tuberculosis is very rare due to bactericidal properties of gastric acid, absence of lymphoid tissue, and rapid transit of food in stomach due to its continuous motor activity.[6] The possible routes of infection in stomach are: direct infection of mucosa due to swallowing of sputum, direct infection from neighboring tubercular lesion, hematogenous spread or

Flowchart 1: Various sites of tuberculosis in an immunocompetent person



retrograde lymphatic spread.[7] Most commonly it occurs from neighboring celiac lymph nodes.[8]

Pathology

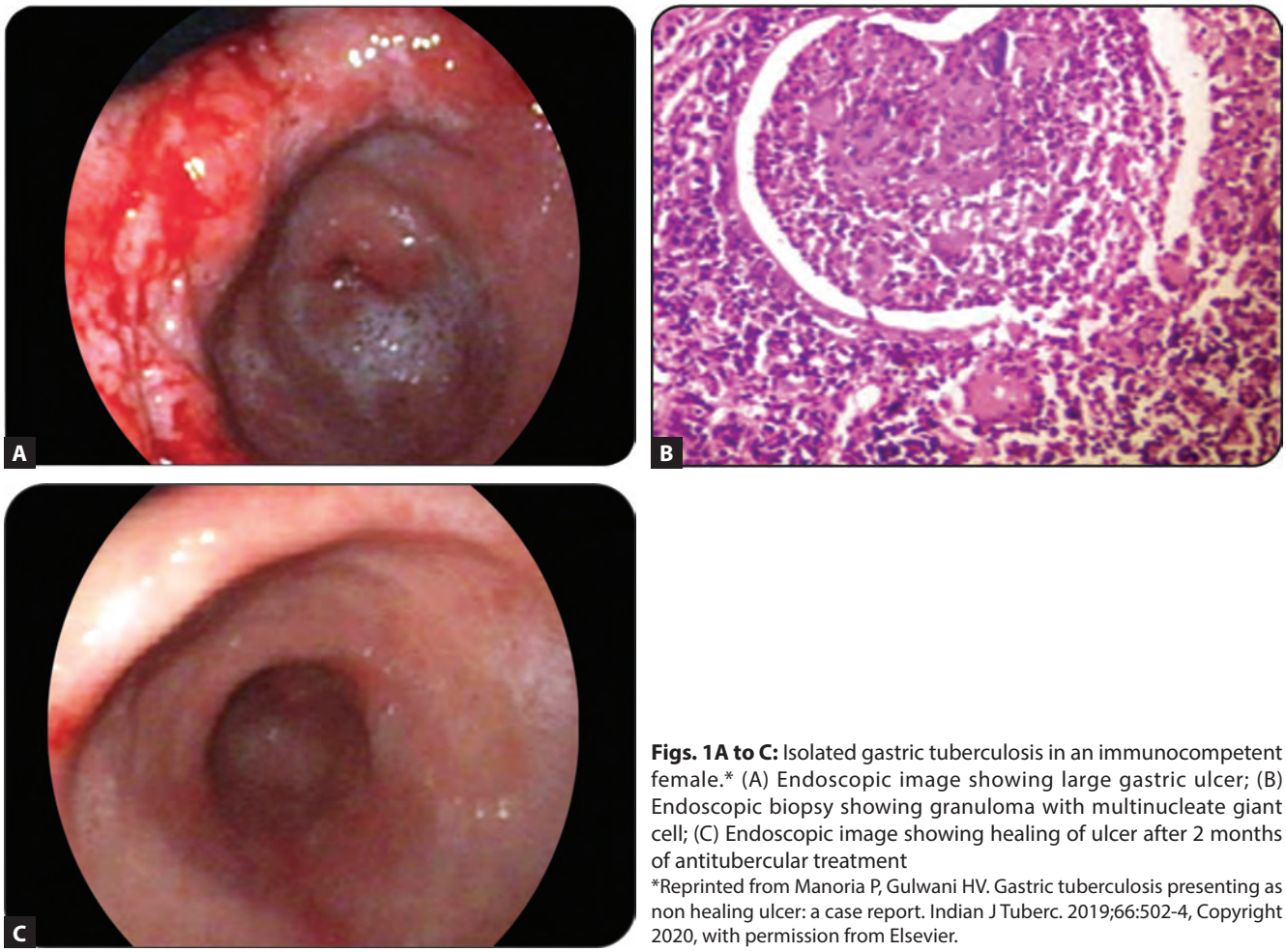
Gastric tuberculosis can present as an ulcer, hypertrophic mass, or ulcerohypertrophic lesion in the stomach.[9] It most commonly presents with non-healing gastric ulcer. Hypertrophic lesions mimic gastric carcinoma and present with gastric outlet obstruction. It mostly involves the antrum or prepyloric region in the lesser curvature.[10] The granulomatous lesions can involve the mucosa, submucosa, or serosa but most commonly it involves the submucosa. Granulomas in stomach can be caused by various disorders like tuberculosis, Crohn's disease, sarcoidosis, fungal and parasitic infection, Whipple's disease, xanthogranulomatous gastritis, lymphoma, Churg-Strauss syndrome, exposure to beryllium and silicates and syphilis, but most commonly it is caused by tuberculosis and Crohn's disease. Granulomas are more common in gastrointestinal tuberculosis compared to Crohn's disease. Caseation is present in around 40% cases. Granulomas in tuberculosis are more in number, larger in size, and confluent compared to Crohn's disease.[11]

Clinical Features

Clinical presentation of gastric tuberculosis is nonspecific. Its most common symptom is abdominal pain followed by vomiting. Constitutional symptoms of tuberculosis like fatigue, evening rise of temperature, loss of weight and appetite, etc. can also be present in some patients. Due to delay in its diagnosis it can also present with its sequelae like:

- Gastric outlet obstruction, which presents with postprandial vomiting, pain, and distension of abdomen
- Gastrointestinal bleed in the form of hematemesis and melena
- Perforation peritonitis and rarely
- Gastrocolic and gastrobronchial fistula.

Gastric tuberculosis most commonly presents as a case of non-healing gastric ulcer, which is resistant to proton pump inhibitor and negative for helicobacter pylori or as



Figs. 1A to C: Isolated gastric tuberculosis in an immunocompetent female.* (A) Endoscopic image showing large gastric ulcer; (B) Endoscopic biopsy showing granuloma with multinucleate giant cell; (C) Endoscopic image showing healing of ulcer after 2 months of antitubercular treatment

*Reprinted from Manoria P, Gulwani HV. Gastric tuberculosis presenting as non healing ulcer: a case report. Indian J Tuberc. 2019;66:502-4, Copyright 2020, with permission from Elsevier.

a case of a gastric outlet obstruction mimicking gastric malignancy but negative in histopathology. In both these clinical scenarios we should be highly suspicious of its diagnosis.

Diagnosis

Diagnosis of gastric tuberculosis is difficult and often delayed and it's mostly diagnosed after surgical intervention. The gold standard for its diagnosis is presence of acid fast bacilli in the histopathology specimen which is very rare.

Upper gastrointestinal endoscopy is the most important initial investigation. It can detect

- solitary or multiple ulcers in prepyloric region in lesser curvature
- ulceroproliferative mass in antrum causing gastric outlet obstruction, or
- submucosal lesion with normal overlying mucosa.

Endoscopic biopsies have a low yield for granuloma as majority of lesions are submucosal in location.[4] So it's advisable to take multiple deeper biopsies during endoscopy to increase the yield. *Helicobacter pylori* should always be ruled out in tissue biopsy and by doing rapid urease test. Colonoscopy should always be done in suspected cases as ileocecal tuberculosis can coexist with it.

Endoscopic ultrasonography (EUS) is very helpful and should be performed when it presents with submucosal mass or if there are associated adjacent lymph nodes. EUS guided fine needle aspiration cytology (FNAC) and biopsies should be taken from submucosal lesions and lymphnodes as it has a high yield for its diagnosis.

Imaging modalities like ultrasonography (USG) and contrast enhanced computed tomography (CECT) of

abdomen is not much useful in diagnosis as their findings are non-specific. They can show gastric wall thickening, hypodense lesion in antrum, multiple enlarge lymph nodes, peritoneal thickening, ascites, etc. CT or USG guided FNAC from enlarged lymph nodes should be done if they are accessible for making diagnosis. X-ray chest should always be done in any suspected patient as 25% of patients will have coexisting pulmonary tuberculosis.[12]

The yield of mycobacterial culture is from 0–69% in gastrointestinal tuberculosis in various studies. Bhargava et al. has suggested to do routine culture of biopsy specimen to increase the diagnostic yield.[13] The sensitivity and specificity of polymerase chain reaction (PCR) in endoscopic biopsies for gastrointestinal tuberculosis is 44% and 95%, respectively.[14] Kim et al. has suggested to do PCR testing as it also helps in ruling out Crohn's disease.[15] So, in any suspected cases of gastric tuberculosis, culture and PCR testing of biopsy should also be done to increase the yield of diagnosis.

Tuberculin test is non-specific test and is not done routinely for its diagnosis. There is no specific biochemical or hematological test for it.

Treatment

Treatment of gastric tuberculosis is conventional 6 months antitubercular therapy (ATT) with initial 2 months of intensive therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months of continuation phase with isoniazid and rifampicin. Few guidelines recommend longer duration of treatment of 1 year for it.[4] For uncomplicated cases ATT alone is sufficient for its treatment. Asia Pacific Association of Gastroenterology and Indian Society of Gastroenterology consensus on Crohn's disease have suggested a trial of ATT in cases where there is doubt in diagnosis.[16,17] Empirical ATT should always be given in any granulomatous lesion of stomach without a definitive diagnosis.

Surgery or endoscopic therapy is needed if it presents with complications.

- Surgery in the form of distal gastrectomy or primary closure is the main stay of treatment if it presents with perforation peritonitis.
- Gastric outlet obstruction secondary to tuberculosis can be dealt with endoscopic or surgical intervention. Endoscopic balloon dilatation followed by starting of antitubercular therapy should be the preferred initial treatment for it. For unresponsive cases surgery in the form of gastric resection with gastrojejunal anastomosis is usually done.
- Patient presenting with gastrointestinal bleeding should be initially managed with endoscopic hemostatic procedures like adrenaline spray, adrenaline injection, hemoclipping, etc. Non-responsive cases are treated surgically with partial gastrectomy.

Conclusion

Tuberculosis can involve any part of gut even in immunocompetent person. Gastric tuberculosis though rare should be kept as one of the differential diagnosis in any case of chronic infiltrative lesion of stomach like non-healing ulcers and gastric outlet obstruction. The yield of endoscopic biopsies is low for granuloma due to submucosal location of the lesion so deeper and repeated biopsies are advisable for making early diagnosis and avoiding surgical interventions. If diagnosed early, it responds very well to standard ATT.

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Section 15

Section Editor: **Sujit Jha**

Endocrinology

CHAPTER

197 Interpretation of Thyroid Function Tests

Dheeraj Kapoor, Ruchi Kapoor, Abhishek Goyal

Abstract

Thyroid disorders have various etiologies and presentations. Pertinent treatment needs a conclusive diagnosis and is influenced by variety of coexisting medical conditions. This chapter delineates how to interpret thyroid hormones, referring to various evidence-based clinical guidelines for the management of thyroid disorders. In depth research of relevant literature and evidence-based approach has been taken to simplify interpretation of thyroid hormone levels. Topics addressed include thyroid hormone assays, thyroid antibodies levels, hyper- and hypothyroidism along with thyroid dysfunction in pregnancy.

Introduction

Thyroid is a small butterfly shaped endocrine organ located anteriorly in the lower part of neck. On an average it weighs around 25–30 g in an adult. It produces the thyroid hormones, which are released into the blood stream and then transported to different tissues in the body. They have an effect on each and every cell and organ of the body. Their main function is to maintain homeostasis in various functions ranging from controlling the metabolic rate, the muscle mass, digestive functions, development of brain, and bone maintenance.

Thyroid gland chiefly synthesizes the hormone thyroxine (T4) and small quantity of triiodothyronine (T3). T3 being the active form with a short half life is converted from T4 with removal of an iodine atom mainly in liver and in small quantities in heart, gut, muscle, and nerves. The gland is controlled by a feedback regulation from the pituitary, which releases thyroid-stimulating hormone (TSH), which in turn is controlled by the thyroid-releasing hormone (TRH) released from the hypothalamus.

Progress in technology over time has improved the sensitivity and specificity of thyroid function test available, and hence permitting an accurate diagnosis of thyroid condition to be made in majority of case. However, analytical inference still stands a major hurdle. The interpretation of thyroid function tests is generally straight forward; through sometimes the reports may seem fairly clear but are in fact misleading. This article aims to address the interpretation of thyroid functions test.

Thyroid-stimulating Hormone

TSH is secreted by anterior pituitary and is central to the negative feedback mechanism for secretion of thyroid hormones. It shows a diurnal variance, presenting a peak soon after midnight and a nadir by late noon, with peak values sometimes even twice the value seen in nadir. TSH may vary in between measurements to the extent of up to 20% without any change in thyroid state.[1,2]

TSH is now considered as the first diagnostic test for assessment of thyroid condition.[3] It presents as a foremost irregularity in case of thyroid disorders when the other test are normal. When TSH is used to confirm patients with suspected thyroid diseases in an Endocrine clinic it carries high sensitivity of up to 98% and a specificity of up to 92%. But in cases of mass screening the sensitivity and

BOX 1 Conditions associated with high risk for thyroid disease in which screening is recommended

- All new borns (neonatal screening)
- Those with strong family history of thyroid disease
- Those having an autoimmune disease, such as type 1 diabetes mellitus
- Genetic conditions (e.g., Down's syndrome, Turner's syndrome)
- Past history of neck irradiation
- Drug therapies such as lithium and amiodarone
- Elderly patients
- Women over age 35
- Pregnant women during the first trimester
- Women at 6 weeks to 6 months postpartum
- Dyslipidemia
- Atrial fibrillation
- Depression
- Reduced bone mineral density

positive predictive value is low due to underlying diseases or health of the individual screened, hence making the interpretation of test result problematic. As a routine now, value of TSH is considered low when less than 0.1 mU/L and high when more than 6.5 mU/L.

Using TSH as an ace standard does help to categorize patients in over 95% cases. But, TSH alone can be used only if the pituitary thyroid axis is intact. In case of pituitary diseases (hyperthyroidism secondary to TSH producing pituitary adenoma), non-thyroidal illness, HAMA antibody, drugs (glucocorticoids, tyrosine kinase inhibitor, octreotide, etc.), lab results can be misleading and difficult to interpret. Aberrant TSH levels may persist for up to few months even after initiation of thyroid treatment.

The American Thyroid Association recommends routine screening for thyroid disorders in all adults by measurement of serum TSH starting from the age of 35 years and then every 5 years, with more frequent screening in high risk or symptomatic person.[4] The American Association of Clinical Endocrinologists recommend routine measurement of serum TSH in all women of child bearing age before they conceive or during the first trimester of pregnancy **(Box 1)**.[5]

Conditions associated with abnormal TSH levels:

- Decreased TSH levels—
  - Primary hyperthyroidism
  - Pituitary or hypothalamic disease—secondary or tertiary hypothyroidism
  - Non-thyroidal illness
  - Drugs, e.g., glucocorticoids, dopamine
- Increased TSH levels—
  - Primary hypothyroidism
  - Pituitary adenoma (TSH producing)—secondary hyperthyroidism
  - Pituitary resistance to thyroid hormone (TSH unreliable)
  - Generalized thyroid hormone resistance
  - Old age
  - Drugs, e.g., amiodarone
  - Recovery phase after severe systemic illness

Thyroid Hormone Assays

Serum Thyroxine

T4 levels are elevated in patients of hyperthyroidism. Hence, in the course of treatment their levels are measured to ascertain the degree of thyroid dysfunction and titration of doses of anti-thyroid medication, because serum TSH values may remain suppressed for a continued duration during the course of therapy.[6]

Serum T4 values are also important in diagnosis of patients suffering from secondary hypothyroidism. Because a case of normal TSH and suppressed T4 should direct the clinical toward a possible diagnosis of secondary hypothyroidism, justifying the assessment of pituitary hormone levels for further investigations.

Serum Triiodothyronine

Evaluation of T3 levels is not suggested routinely because of its short half life and normal levels of it influenced by the endocrine homeostasis. Despite this it is of values in cases of T3 toxicosis, in which patients have low TSH, normal T4, and features of hyperthyroidism. This condition is observed in a small fraction of patients suffering from Graves' disease. A ratio of T3:T4 > 20 ng/mL is indicative of Graves'.[6]

Free Thyroxine and Free Triiodothyronine

Merely a meagre portion of thyroid hormones circulate in free form not bound to protein. These free form of thyroid hormones are physiologically more important. Their quantification is of value in conditions where levels of thyroid-binding globulin (TBG) are altered. Levels of TBG influence the levels of T3 and T4 in direct proportion

TABLE 1 Conditions associated with altered TBG[6]

Increased binding	*Decreased binding*
Oral contraceptives	Nephrotic syndrome
Pregnancy	Active acromegaly
Neonates	Major systemic illness
Acute intermittent porphyria	Genetic factors
Hepatitis, biliary cirrhosis	Asparaginase
HIV infection	Drugs—androgens, large dose glucocorticoids
Drugs—estrogen supplements, tamoxifen	

without any change in hormone activity, more TBG falsely more T3, T4, and low TBG presenting as falsely low T3 and T4 **(Table 1)**.

Free Thyroxine

fT4 is performed for optimizing thyroxine therapy in patients of newly diagnosed hyperthyroidism. It is also prescribed in diagnosis of secondary hypothyroidism and in cases of end organ thyroid hormone resistance.

Conditions associated with decreased fT4:
- Primary hypothyroidism (thyroid hypofunction)
- Secondary hypothyroidism (pituitary hypofunction)
- Tertiary hypothyroidism (hypothalamic hypofunction)

Conditions associated with increased fT4:
- Graves' disease
- Plummer's disease (toxic thyroid adenoma)
- Early phase of subacute thyroiditis
- Struma ovarii
- Thyrotroph hyper function—secondary hyperthyroidism

Free Triiodothyronine

fT3 levels are rarely required.

Conditions associated with decreased fT3:
- Critically ill patients
- Patients on high dose steroids
- Patients on beta blockers
- Severe hypothyroidism

Conditions associated with increased fT3:
- T3 toxicosis
- Hyperthyroidism

Thyroid Antibodies

Estimation of thyroid antibodies is advisable in altered thyroid functions. They help to determine if patient is having an autoimmune thyroid dysfunction. Various antibodies exist against thyroid antigens. The ones of importance include Anti Thyroperoxidase antibody (Anti-TPO Ab), antithyroglobulin antibody and TSH receptor antibody (TSH-RAb).

Anti-thyroperoxidase Antibody (Anti-TPO Ab)

Anti-TPO is also known as thyroid microsomal antibodies. They cause hypothyroidism by two distinctive mechanisms. First by blocking the thyroid peroxidase thereby hindering the synthesis of T3 and T4 and secondly by antibody dependent cell toxicity and inflammation of thyroid gland.[7] Anti-TPO Ab levels facilitate in the diagnosis of subclinical hypothyroidism and helps in evaluation of autoimmune thyroiditis.

TSH Receptor Antibody (TSH-RAb)

TSH-RAb may either stimulate of block the TSH receptor. If they stimulate they cause Grave's disease and associated ophthalmopathy. If they act as blocking anti-antibodies they may lead to hypothyroidism.[7]

Measurement of TSH-RAb is helpful in confirming the cause of hyperthyroidism and radioactive iodine therapy is not an option. This assay if of particular importance in managing pregnant patients with Grave's disease as high concentrations is a fair predictor of fetal and neonatal thyrotoxicosis.[8]

Thyroglobulin

It is a large glycoprotein, secreted along with the thyroid hormone. Raised thyroglobulin levels is not a reliable marker or a screening test for thyroid carcinoma; however, it gains importance as an important marker of remaining or recurrent malignancy in patients who undergo total thyroidectomy or radioactive thyroid ablation for papillary or follicular carcinoma.

Thyroid Function in Pregnancy

During pregnancy there is a paradigm shift in level of thyroid hormones leading to an increase in T4 levels and a reciprocal decrease in level of TSH. The reason for this physiological change is linked to—

- Human chorionic gonadotropin has an alpha subunit similar to TSH, which binds to TSH receptor. This leads to an increased production of T4, which gives a negative feedback to the pituitary resulting in reduction of TSH.[9]
- Estrogen produced by the placenta leads to increased secretion of sex hormone binding globulin (SHBG) by the liver. This SHBG increases secretion of T4 from thyroid.
- Pregnancy being a hypermetabolic state leads to increased glomerular filtration rate; hence, increased secretion of T4 by thyroid due to augmented elimination by the kidneys.

Detecting Thyroid Dysfunction

There exist an inverse log relationship between TSH and T4 levels. Elevated TSH levels indicate hypothyroidism and low TSH indicate hyperthyroidism.[10] Analysis of thyroid function test can be a challenge in case of hypothalamic pituitary disease (low TSH, low T4), systemic illness, starvation (low TSH, low T3).

Hyperthyroidism

An elevated fT4 and low TSH is indicative of thyrotoxicosis. Most of the young age group patients with these levels presents as Grave's disease while the elderly are more prone for nodular thyroid disease.

In cases of subclinical hyperthyroidism TSH levels may be borderline suppressed in the presence of normal fT3 and fT4. Treatment of subclinical hyperthyroidism is warranted in the presence of underlying condition like increased age, cardiac condition like atrial fibrillation, recent history of stroke, and osteoporosis.[7]

Temporary or short lived thyrotoxicosis can be presented in the form of viral thyroiditis. Most patients have a recent history of viral upper respiratory tract infection. This usually responds to anti-inflammatory medication. Prompt diagnosis of the condition stands as a key to treatment.

A small subset of patients may present with low TSH and normal fT4 thereby representing T3 toxicosis. In these cases measurement of T3 levels is of value. If in case fT3 is not raised then fT4 and TSH should be rechecked.

High fT4 with normal or raised TSH depicts a T4 to T3 conversion defect, or an analysis error.

During the course of treatment, TSH may remain suppressed for varied amount of time; in this case fT4 is measured every 6–8 weeks to monitor the treatment.

Hypothyroidism

Elevated TSH levels with low fT4 suggest a diagnosis of primary hypothyroidism, primarily autoimmune in nature but can also be a result of previous surgery or radio iodine ablation of thyroid gland. The prevalence of high TSH with raised antibody levels is more common in elderly women.[7]

Raised TSH in presence of normal fT4 indicates autoimmune thyroid condition. When TSH levels are more than 4 μIU/mL but less than 10 μIU/mL without any clinical sign, it represents subclinical hypothyroidism. Treatment is warranted in this condition in presence of thyroperoxidase antibody, pregnancy, goitre, or dyslipidemia. TSH levels more that 10 μIU/mL require treatment.

Low or normal TSH usually excludes the diagnosis of primary hypothyroidism. However, presence of low TSH and low fT4, low fT3 should indicate toward secondary hypothyroidism, most commonly seen in cases of Sick Euthyroid syndrome.

Thyroxine replacement in hypothyroid patient should be titrated to maintain a TSH of about 2 μIU/mL. Guidelines recommend that test for thyroid function and changes in dose of thyroxine should not be done before 6 weeks unless clinically indicated because it takes this much time for the body to accomplish reliable T4 levels. Patients who are less compliant to medication usually have tendency to replenish the dose before the scheduled visit. This presents as a raised TSH but normal fT4.

Patients suffering with differentiated thyroid cancers are given suppressive doses of thyroxine to maintain TSH levels below 0.1 μIU/mL to prevent flare ups. Those who initially had a high risk disease but are now disease free post-treatment are advised to maintain TSH levels between 0.1 and 0.5 μIU/mL for at least 5–10 years.[7,11]

Sick Euthyroid Syndrome

This is referred as a thyroid-related change that occurs during systemic illness in the absence of an intrinsic thyroid disease. The syndrome is acute, reversible, and occurs commonly after surgery, starvation and in many acute febrile illnesses. These changes may be observed in up to 75% of hospitalized patients. Any abnormality in hormone level is possible, but the most common observed abnormality is low fT3.

TABLE 2 Interpretation of thyroid function test[7]

	TSH	*fT4*	*fT3*	*Thyroid antibodies*
Normal	↔	↔	↔	↔
Primary hypothyroidism	↑	↓	↓	↑
Subclinical hypothyroidism	↑	↔	↔	↑
Hyperthyroidism	↓	↑	↑	↑
Subclinical hyperthyroidism	↓	↔	↔	↔
Pituitary diseases	↓	↓	↓	↔
T3 toxicosis	↔↓	↔	↑	Variable

↔ Normal, ↑ High, ↓ Low

Conclusion

Diseases of thyroid gland are common and initial test to be done for assessment of this condition is serum TSH. fT4 is indicated as a second line test, but the reference range for fT4 and TSH are not universal and reference interval provided by the lab should be acknowledged. Results of thyroid function test are interpreted in light of clinical status of patients: hypothyroid, euthyroid, or hyperthyroid. Subclinical thyroid diseases are commonly encountered and present with an abnormal TSH and normal fT4. Awareness of associated conditions can serve as a guide for further investigations and management. Confounding factors should be excluded before embarking upon further biochemical, radiological, or genetic testing **(Table 2)**.

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CHAPTER

198 Cognitive Aspects of Hypothyroidism

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Abstract

Hypothyroidism is associated with myriad of neuropsychiatric manifestations in clinical practice. Due to its variable and wide clinical presentation it sometimes poses a dilemma for the treating physician and consultation—liaison should be considered when treating patients with neurocognitive symptoms.

Introduction

Disorders of Thyroid are one of the common endocrine problems encountered in clinical practice; the hypothalamic-pituitary-thyroidaxis is needed to maintain the normal functioning of various organs and systems, including the central nervous system.[1]

Thyroid dysfunction affects the nervous system and produces a wide and variable spectrum of clinical presentation due to alterations in cognition and emotions.[2] As early as 1888 Clinical Society of London had described myxoedema and its association with behavior and psychological disturbances.[3]

Pathophysiology

The hypometabolism of brain has been postulated to be associated with cognitive decline.[4] Thyroid hormones exert their influence on the central nervous system through a variety of mechanisms like modulation of gene expression of several groups of proteins and the influence on serotonin and noradrenergic neurotransmission. Antithyroid antibodies are also postulated to play a causativerole.[5] In autoimmune Hashimoto's thyroiditis link with Unipolar and Bipolar Depressive disorders is established; however, the exact pathophysiology, role of inflammatory markers or of second messengers is yet to be established and a direct correlation between the more specific marker of the disease, that is, thyroid peroxidase antibodies (TPOAb) or of thyroglobulin antibodies (TGAb) is still an ongoing research.

Epidemiology

Due to improvements in diagnosis and treatment of the hormonal disorders and universal iodine supplementation of common salt the most severe neuropsychiatric syndromes in endocrine diseases are not as frequent as in the past although psychiatric and subtle cognitive disturbances are still seen.[6] Data shows that 1–4% of patients diagnosed with affective disorders have overt hypothyroidism and 4–40% may have subclinical hypothyroidism (SCH). However, majority of patients diagnosed with major depression have normal thyroid function.[7]

Overt Hypothyroidism

Overt hypothyroidism by definition is an elevation of serum thyroid stimulating hormone (TSH) level with a low-free thyroxine (fT4) level.[2] Autoimmune thyroiditis (Hashimoto's) is the most common cause of

hypothyroidism which is commonly seen in middle age females.[8]

The most common presenting complaints are fatigue and impaired quality of life. Due to advances in interventional and functional imaging the subtle changes in cognition in specific domain like working memory and executive function are now more commonly diagnosed along with the more commonly seen anxiety and depression.

Neurocognitive Effects Seen in Overt Hypothyroidism

Cognition

Cognition is referred to as mental activities involved in the acquisition, storage, retrieval and use of information.

Memory is most commonly affected domain with specific deficits seen in verbal memory. Hypothyroid individuals have also shown deficits in visuospatial and executive functions.

The other cognitive domains affected include general intelligence, complex attention and concentration, language, learning and memory along with perceptual and visuospatial functions. The frontal lobe executive functions like reasoning, problem solving, decision-making may be affected. There are various psychological tests and measures available for evaluation of these individual cognitive domains.[4]

In congenital hypothyroidism irreversible cognitive deficits may happen if hypothyroidism is left untreated or intervention started belatedly after the critical window of brain development.

In adolescents who develop hypothyroidism again cognitive domains are affected and those who were treated with Thyroxine Replacement Therapy (TRT) were found to have improved performance on a battery of cognitive tests including reading performance and block design but the patterns of recovery are not definitive.

In adults with hypothyroidism again vocational and occupational pursuit may be affected whereas specific tests of cognitive domains are often seen to be not significantly impaired.

Dementia

In geriatric population there may be an overlap of symptoms seen in hypothyroidism and due to old age, itself. Hence, the diagnosis of hypothyroidism may be clinically missed.

Traditionally, Myxoedema used to be known as a reversible cause of dementia in the elderly. There occurs progressive neurocognitive decline leading to impaired social and cognitive functioning. Elderly patients tend to have problems with recent memory though remote memory and overall intelligence remains intact other common problems observed are lack of attention and emotional liability with easy fatigability leading also to a lot of family and caregiver burden.

There is decline in auditory acuity which might contribute indirectly to memory impairment due to sensory deprivation and poor registration usually seen in uncontrolled hypothyroidism which can partially be reversed with thyroxine. TSH levels and risk of developing Alzheimer's disease may also show some correlation.[9,12]

Other Neurological Complications[10]

Cerebellar dysfunction and motor coordination like ataxia, intention tremors are usually mild and more commonly seen in children and may result in poor outcomes in motor functions in later childhood if delayed treatment or inadequate hormone replacement is done.

Neuropathy: Hypothyroidism is associated with peripheral nerve demyelination and decreased nerve conduction velocity (NCV).

Entrapment neuropathy, like Carpal tunnel syndrome and polyneuropathy, is also seen but the bilateral and distal sensorimotor neuropathy is the most common.

With thyroxine replacement therapy the symptoms and signs of neuropathy along with changes in NCV usually normalize in adulthood but those who have symptoms of longer duration may show some residual symptoms of peripheral neuropathy.

Myopathy can occur when associated with symptoms or signs of hypothyroidism such as poor linear growth or global developmental delay with pain and muscle weakness along with elevation of creatine phosphokinase.

The delayed acquisition of early motor milestones may be a sign of missed congenital or early acquired hypothyroidism in young children and investigation of thyroid function should be performed in them.

Hashimoto's encephalopathy (HE) is a rare neuro-endocrine disorder to be associated with autoimmune thyroiditis (Hashimoto thyroiditis). Hashimoto's

encephalopathy is frequently seen in women and presents with symptoms of seizures, myoclonus, stroke, and also psychiatric manifestations mainly depressive disorders and even psychosis. These symptoms usually recover with treatment but relapses can also be seen.

Thyroid tests are usually normal. Neuroimaging is often normal. The diagnosis of Hashimoto's encephalopathy is made with classical clinical picture with positivity of antithyroid peroxidase antibodies. Treatment of Hashimoto's encephalopathy is corticosteroids.[11]

Anxiety disorders: These disorders present as restlessness, inability to concentrate, irritability, distraction, increased sweating, muscular tension, and insomnia. The most prevalent anxiety disorders are social anxiety disorder, generalized anxiety and panic disorder, the incidence of which is increased in hyperthyroidism and also in hypothyroidism.[2,7]

Mood disorders: Depression has a prevalence of 10–15% in the general population and may be more common in people with thyroid disorders. The normal circadian secretion of TSH peaks from 11 pm to 4 am. In depressive patients there is a dysregulation of Hypothalamic-Pituitary-Adrenal axis; hence, the nocturnal surge is absent which may point to functional central hypothyroidism in some depressed patients.

It has been seen that self-knowledge of mildly elevated TSH may be associated with poor quality of life or fatigue known as ("labeling effect").

Major depressive disorder can also happen in hyperthyroidism although more common in hypothyroidism, presence of antithyroid antibodies may have an etiopathological role and severity in causing depression. There are further complications as Lithium the gold standard medicine of Bipolar disorders leads to Hypothyroidism on prolonged use.

Depression is characterized with cognitive distortion in form of hopelessness, helplessness, and worthlessness this may lead to suicidal ideation and in few cases lead to self-harm and suicide.

Many cognitive symptoms like poorer memory, in attentiveness, slower thinking and speech, impaired concentration and apathy is seen in both the diseases. The common symptoms of being easily tired, lack of interest, and pleasure along with loss of appetite, decrease libido, and constipation may pose a difficulty in diagnosis though certain symptoms like weight gain, hypersomnolence or insomnia and impoverished quality of life may give a clue toward diagnosis of hypothyroidism but they are also common in mood disorders. An overlap of anxiety and mood disorders can be seen leading to variety of emotional disturbances.[2,7,15]

Psychotic disorders: Severe hypothyroidism in 5–15% may present as melancholic depression with mood congruent psychotic features, rarely frank psychosis, delusions, and hallucinations. These features are often seen in Myxedema madness.

Capgras syndrome a delusional disorder has also been associated with hypothyroidism where psychotic symptoms are preceded by symptoms of hypothyroidism even months to years of diagnosis.

Effects of Thyroxine Replacement Therapy on Hypothyroidism

After supplementation of thyroxine replacement therapy there may occur incomplete normalization of subjective neuropsychiatric symptoms even on reaching euthyroid state. There is no rationale of using combination of Levothyroxine (LT4) and Liothyronine (LT3) treatment for hypothyroidism who still complained of depressive symptoms. In these subsets of individual revaluation of other chronic medical condition and consultation liaison with psychiatrist should be sought.

Subclinical Hypothyroidism

"Subclinical" hypothyroidism (SCH) by definition is an elevation of TSH with a normal $fT4^2$. In young adults and middle age, the symptoms of depression are more frequent along with mild cognitive impairment, difficulty in learning and selective attention. Subclinical hypothyroidism is prevalent in as many as 20% of post-menopausal women and in older patients many of whom already have some cognitive decline.[14] The correction of the subclinical hypothyroid state with neuropsychiatric symptoms still remains elusive.[9]

There have been no improvements in symptoms of Subclinical hypothyroidism on thyroxine replacement therapy diagnosed with depression who are biochemically euthyroid. Various studies have shown no significant clinical improvement with coadministration of Levothyroxine (LT4) and Selective Serotonin Reuptake

Inhibitors (SSRI) in depressed patients when compared with SSRI alone.[9]

Congenital hypothyroidism (CH) is a common and treatable cause of preventable intellectual disability with a prevalence of approximately 1 in 2,000–4,000 new born. Thyroxine is an essential hormone during pregnancy especially during first trimester as it is required for fetal brain development at around 12 weeks postconception. Deficiency of thyroxine may lead to abnormal dendritegenesis and synaptogenesis leading to congenital hypothyroidism in neonates.

Congenital hypothyroidism can impair cognition but also cause arrange of other neurological sequelae including abnormal muscle tone, ataxia and strabismus and motor in coordination the most severe forms of congenital hypothyroidism may include alterations in domains of attention, memory, arithmetic, verbal skills, memory, and behavior.

In severe cases mental retardation, deafness, and spastic diplegia can be seen. There is also presence of other clinical features such as short stature, delayed puberty, and craniofacial abnormalities.

For prevention of neurobehavioral effects of congenital hypothyroidism supplementation of iodine preconceptually may be advised. The immediate goal of thyroxine replacement is to normalize T4 within 2 weeks and TSH within 1 month of birth to ensure growth and neurodevelopmental outcomes as close as possible to their genetic potential.[13]

Hypothyroidism has also been associated with attention deficit hyperactivity disorder (ADHD) and this may persist even in adults.

The preventive measures of congenital hypothyroidism may be early identification and early initiation of treatment, which has shown improvement in tests for formal intelligence. But certain domains of neurocognition may persist in late childhood and adolescence. Some domains like language, motor skills, attention, and visuospatial processing may be affected even after becoming euthyroid.[9,10]

Conclusion

Overt hypothyroidism is associated with myriad of symptoms ranging from fatigue affecting quality of life to mood and behavior changes along with cognition. Among the cognitive impairment seen in hypothyroidism is its effect on memory.

Though these changes may be subtle in patients of SCH and may not show major changes on mood and cognition, SCH have been seen to be associated with mild deficits in working memory and executive function especially in elderly.

The treatment with thyroxine replacement is the cornerstone and is always indicated in overt hypothyroidism. There have been improvements in physical symptoms along with resolution of deficits in mood or cognition though complete recovery may not be seen. The treatment of SCH is elusive and it depends upon the decision of treating physician.

The neuropsychiatric symptoms with mild hypothyroidism should be evaluated and treated as independent diagnosis with consultation liaison.

There appears significant merit in recommending universal thyroid screening for all pregnant females along with testing for any young infant or child with global neurocognitive or neuromuscular dysfunction.

Also, emphasis on thyroid testing for patients presenting with neuropsychiatric disorders and conversely assessment of mental health for all patients diagnosed with thyroid disorders can be instrumental for good clinical management as the timely intervention may improve quality of life among thyroid disorder patients with comorbidities.

Neuroplasticity more often favors infant rather than older individual. Thyroxine replacement therapy remains the main stay of treatment but the extent and duration of recovery especially neurocognitive domains is often incomplete and inconsistent. There is global decline in cognition if thyroxine replacement therapy is delayed or absent. Hence, universal screening of TSH in pregnant women should be emphasized.

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CHAPTER

199 Thyroid Myopathy—An Update

NS Neki

Abstract

Muscular complaints are common symptoms of thyroid disorder: hypothyroidism or hyperthyroidism. About 79% of hypothyroid patients and 67% of hyperthyroid patients develop neuromuscular symptoms. However, muscle stiffness is more common in hyperthyroidism while muscle weakness is observed commonly both in hypothyroidism and hyperthyroidism. The onset of weakness is usually insidious and proximal muscles are predominantly affected in both types of thyroid myopathy. Thyroid myopathy occurs as a result of either deficiency or overproduction of thyroid hormone, i.e., Thyroxine. Skeletal muscle is a major target of thyroid hormone. Patients with untreated or uncontrolled hypothyroidism and hyperthyroidism can develop severe myopathy resulting in severe functional limitations. These symptoms subside completely with proper diagnosis and appropriate treatment.

Introduction

Abnormal thyroid functions/disorder either too increased or too low can result in neuromuscular manifestations including hypothyroid myopathy, hyperthyroid (thyrotoxic) myopathy, thyrotoxic periodic paralysis, and thyroid associated ophthalmopathy because the skeletal muscle is a major target of thyroid hormone. Muscular complaints are common symptoms of thyroid dysfunction, especially muscle stiffness more so in hyperthyroidism and muscle weakness in both hypothyroidism and hyperthyroidism. The prevalence of neuromuscular manifestations varies between 20% and 50%. Most of these studies were retrospective and were done before FT4 and TSH assays were available.[1,2]

Types of Myopathy

Hypothyroid Myopathy

Various manifestations of hypothyroidism are observed in clinical practice. Hypothyroid myopathy (HM) occurs as a complication of uncontrolled or untreated hypothyroidism involving about 79% of patients. It is seen in both congenital and acquired hypothyroidism. Sometimes subclinical hypothyroidism manifests as HM. HM can occur at an age but most common age is 40–70 years and involves both sexes. However, females are predominantly affected than males.[3]

Pathogenesis: The exact pathogenesis of HM is not known. Thyroid hormones markedly influence the cellular metabolism and their deficiency results in cellular functional impairment. Thyroxine (T4) deficiency in hypothyroidism causes:

- Abnormal glycogenolysis
- Reduced mitochondrial oxidation
- Insulin resistant state of the cell

Ultimately this causes selective atrophy of Type 2 muscle fibers (fast twitching type) because these muscle fibers are dependent on glycolysis for energy. Finally, it results in slowing of muscle contraction which may be observed clinically. However, compensatory mechanism

occurs from accumulation of glycosaminoglycans in the muscle further causing muscle hypertrophy. Myopathy symptoms in HM result from low muscle carnitine. Various factors causing muscle involvement in hypothyroidism are due to

- Deposition of glycosaminoglycans
- Low myosin ATPase activity
- Changes in muscle fibers from fast twitching Type 2 to slow twitching Type 1 fibers
- Decrease in ATP turnover in skeletal muscle
- Structural muscle injury. A significant feature is that degree of muscle weakness does not always correlate with the severity of thyroid hormone deficiency. Rise in serum muscle enzymes in the absence of clinical manifestations or structural alterations results from changes in the muscle cell membrane permeability. Thyroid hormone may have a role in regulating gene expression of skeletal muscle proteins like myosin ATPase thus favoring the role of thyroid hormone deficiency in the pathogenesis of TM.[4]

Thyroid myopathy is of four types:

- *Myasthenic syndrome:* It is associated with Ptosis and marked weakness. It is commonly seen in children.
- *Atrophic type:* It is seen in severe muscle atrophy.
- *Kocher-Debre-Semelaigne syndrome:* It is commonly seen in children. Clinical features include myxedema, short stature, cretinism, and generalized muscle hypertrophy.
- *Hoffman syndrome (HS):* It occurs in adults. Clinical features include pseudohypertrophy of muscles, proximal muscle weakness, stiffness, and painful spasms. Commonly involved muscles are tongue, arm, and leg muscles. The pathogenesis of pseudohypertrophy is not exactly known but may be due to deposition of glycosaminoglycans and increased muscle fiber size.[5] Few cases of HS have been reported from India.[6,7] HS was first described by Hoffman in 1897 in an adult who developed muscle stiffness and difficulty in relaxation of muscles after thyroidectomy.[8] Usually the cause of HS is primary hypothyroidism (Hashimoto thyroiditis) but rarely secondary. Muscle biopsy is usually not required to confirm the diagnosis. Muscle MRI may be helpful. Prognosis is good in HS. Muscle enlargement usually regresses over time, but may persist in a few cases.

Clinical features of HM include cramps, muscle weakness, myalgia, stiffness, myxedema, and hyporeflexia. Muscle hypertrophy, wasting, and rhabdomyolysis are unusual features.[9] Rhabdomyolysis is a rare life threatening complication being precipitated by trauma, exercise, alcohol, and electrolyte disturbances. Rarely HM may present as acute compartment syndrome being precipitated by thrombosis, surgery, trauma, or IV drug abuse.

Differential diagnosis of calf muscle (gastrocnemius) hypertrophy include Duchenne and Becker muscular dystrophy, sarcoidosis granuloma, amyloid, and focal myositis.[10]

Myoedema is a classical sign of HM but is uncommon and hence is mostly missed by clinicians. It is demonstrated by percussion or applying pressure stimulus with thumb and index finger on the muscles of arm, especially biceps belly. This causes the muscle to form a visible palpable, nontender, firm, localized swelling around the site of stimulus. The swelling reaches its maximum size after 1–2 seconds and gradually subsides over 5–10 seconds so that the muscle regains its normal contour with no palpable localized hardening. The swelling does not spread elsewhere along the muscle. Myoedema is due to prolonged muscle contraction caused by delayed calcium reuptake by the sarcoplasmic reticulum after the stimulus causes release of local calcium. Differential diagnosis of myoedema is from malnutrition, hypoalbuminemia, hypovitaminosis, and hypothyroidism.[11]

Hyperthyroid Myopathy

Various names are Graves myopathy, thyrotoxic myopathy, Basedow myopathy, or Basedow paraplegia. It was described in early nineteenth century by Graves and Von Basedow documented in severe hyperthyroidism. There are two types of muscle fibers—Type 1 or Slow fibers are required for sustained effort like standing, while Type 2 fibers are fast fibers required for short rapid bursts like sprinting. In hyperthyroidism, there is increased production of ATP and reuptake of calcium. This results in very rapid contraction and relaxation. When this process occurs repeatedly, the structure and mechanics of slow fibers is changed to fast fibers so that muscles lose their endurance, become fatigued, weak, and wasted.

Hyperthyroid (thyrotoxic) myopathy occurs due to overproduction of thyroid hormone, that is, thyroxine.

Etiology includes mostly multinodular goiter and Graves' disease. Clinical features consist of muscle weakness, fatigue and heat intolerance, difficulty in climbing stairs, and proximal myopathy. If untreated, it can lead to marked debilitating condition and rarely death.[12]

Hyperthyroid myopathy can be acute or chronic. Acute hyperthyroid myopathy is rare than chronic hyperthyroid myopathy. It occurs due to rapid degradation of muscle fibers so that patients complain of severe muscle pain, muscle cramps, blurring of vision, and bulging eyes. It may present with more severe proximal and distal weakness and rarely quadriplegia with bulbar and respiratory involvement. Patients develop rhabdomyolysis and severe respiratory failure requiring artificial ventilation.

Chronic hyperthyroid myopathy develops after 6 months of onset so that symptoms appear slowly in the form of increased fatigue and difficulty in performing certain tasks. Some patients in thyrotoxic myopathy may have involvement of upper motor neurons related to pyramidal tract dysfunction as well as lower motor neuron symptoms related to peripheral neuropathy. This may overlap with those of amyotrophic lateral sclerosis (ALS).[13] However, there is no association found between hyperthyroidism and motor neuron disease.

Some patients of hyperthyroid myopathy may present with sensory polyneuropathy, carpal tunnel syndrome, headache, seizures, ischemic cardiovascular disease especially in patients of hyperthyroidism with atrial fibrillation, as well as cerebral venous thrombosis occurring as a result of hypercoagulable state, and auto immune mechanisms. Rarely, Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy have been associated with hyperthyroid patients.

Pathophysiology

Excess of thyroid hormone, that is, thyroxine, causes degradation of muscle fibers, especially at the motor end plates of neuromuscular junction. There occurs low level of acetylcholinesterase (AChE), which breaks down ACh in neuromuscular junction. Decrease in AChE blocks degradation of ACh causing Ach to overstimulate motor end plates of muscle fiber. Ultimately overstimulation of motor end plate leads to more sustained muscle contraction resulting in fatigue, muscle weakness and degradation occurring as a result of overproduction of thyroxine.[14]

Other theory of hyperthyroid myopathy is decrease in protein kinase affinity to cAMP within muscle fibers resulting in increase in cAMP within muscle fibers, which ultimately causes increased release of calcium from muscle fibers' sarcoplasmic reticulum. Finally, it results in more muscle contractions.[15]

Chronic hyperthyroid myopathy can be so severe that the patient may develop winging of scapula. If the myopathy progresses untreated, then patient may have involvement of muscles of face, swallowing, and respiration.

Ocular myopathy: It is also called dysthyroid ophthalmopathy, or exophthalmic ophthalmoplegia. It is more common in females. It may or may not be associated with chronic thyrotoxic myopathy. It may occur even after treatment for hyperthyroidism. In severe cases it may result in blindness and severe residual deficit.

Thyrotoxic periodic paralysis: It is a rare clinical entity mostly occurring in young adult Asian males in age group of 25–30 years. It manifests as sudden episodes of muscle weakness involving muscles of trunk and limbs, developing over a few minutes to hours, and lasting for hours to a few days. It is due to altered muscle membrane excitability secondary to hypokalemia. It reverses spontaneously or requires potassium. Patient may die due to cardiac arrhythmias. Many cases have been reported in the literature.[16]

Diagnosis: Laboratory investigations include CBC, FT3, FT4, TSH, serum sodium, serum potassium, serum calcium, serum phosphorus, blood glucose, blood urea, serum creatinine, serum vitamin B12, serum folic acid, ECG, auto antibodies against thyroid disease, CPK, CPK-MB levels (muscle enzymes), lipid studies, ultrasound of thyroid, hand-held dynamometry, EMG, nerve conduction study, and muscle biopsy, if needed. Normal levels of CPK may reveal early stages of progression while increased levels indicate late stages of progression.

EMG findings of thyroid myopathy include polyphasic action potential with early recruitment full interference pattern. Electromyography (EMG) findings in HM may show low/small amplitude potentials suggesting myopathic changes although it may be normal in half of the patients.

The distal muscles in thyrotoxic patients may show EMG findings of a rather neuropathic process. EMG is used

to diagnose myopathies by comparing muscle contraction responses to electrical stimulus. Response may be normal or myopathic. Muscle biopsy findings in case of HS include muscle fiber hypertrophy, increased nuclei, mucous deposits at places with increased inter fiber ground substance consistent with thyroid myopathy. Muscle biopsy in hyperthyroid myopathy is not specific but may show mild atrophic changes and type 2 fiber predominance. Management of HM consists of thyroid hormone administration and hyperthyroid myopathy treatment consists of antithyroid drugs (propylthiouracil, methimazole), radioactive iodine or surgery in the form of partial or total thyroidectomy. Treatment of thyroid myopathy is carried out by multidisciplinary team consisting of neurologist, endocrinologist, surgeon, ophthalmologist, and physical therapist. Aim in hyperthyroid myopathy is to reduce overproduction of thyroxine from the thyroid gland. While in HM aim is to correct thyroid hormone deficiency by administration of thyroid hormone. Thyroid replacement usually leads to resolution of laboratory abnormalities and symptoms over a few weeks. However, weakness may take months for recovery. Ultimate goal is to restore normal hormone homeostasis.

Conclusion

Neuromuscular symptoms and signs are common in 75% of hypothyroid patients and 67% of hyperthyroid patients because the skeletal muscle is a major target of thyroid hormone.[17] It is uncommon for a patient with hypothyroidism to present with muscle weakness as the chief complaint. Patients of hyperthyroid myopathy usually report after the age of 40 years unlike patients of hypothyroidism. Clinical suspicion supported by laboratory investigations is needed to diagnose patients of both hypo- and hyperthyroid myopathy. Weakness in hyperthyroid myopathy develops early but resolves completely during treatment, thus suggesting a functional muscular disorder.

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CHAPTER

200 Impact of Altered Thyroid Status on Diabetes: Partners in Metabolic Malfunction

Swati Srivastava

Abstract

Diabetes and thyroid dysfunction have impact on each other and mutual interdependence has been a matter of interest since long. The prevalence of thyroid disorder in people with diabetes was found to be higher than in general population. Diabetic patients with hyperthyroidism experience a deterioration of glycemic control. Thyroid hormone excess can sometimes precipitate ketoacidosis in diabetic patients. About half of the patients with Grave's disease exhibit glucose intolerance of variable degree and about 2–3% may develop overt diabetes. Hypothyroidism is the most frequently encountered thyroid disease in patients with diabetes. Studies have found the occurrence of hypothyroidism in 5.7% patients suffering from diabetes. In individuals with T1DM, repetitive events of hypoglycemia hint toward hypothyroidism.

Introduction

The two most often seen endocrine disorders in medical experience are diabetes mellitus and thyroid abnormalities. Thyroid dysfunction is found to occur more frequently in patients with diabetes as compared to the general society.[1,2] Diabetes and thyroid dysfunction have impact on each other and mutual interdependence has been a matter of interest since long. Increasing body of evidence suggests a pattern of multiform combination of biochemical, inherited, and endocrinal defects leading to this pathophysiological interdependence. Epidemiologic data reveal that thyroid dysfunction is seen in 13.4% of diabetic population. Amongst the patients with diabetes, the subgroup having maximum prevalence of thyroid dysfunction were females with type 1 diabetes (31.4%) and minimum were males with type 2 diabetes (6.0%).[1] Thyroid hormones play role in metabolism, energy disbursement as well as insulin sensitivity. Vis-a-vis diabetes impacts TSH responsiveness to thyrotropin releasing hormone and causes low T3. The reciprocal interlinkage between thyroid hormone levels and diabetes mellitus has clinical connotation.

Epidemiological studies have shown similar genetic background for diabetes mellitus and thyroid disorders. However, the common genes identification is presently focused on the autoimmune etiology. The closest connection seen amongst type 1 diabetes and autoimmune thyroid diseases have relation with HLA class II sequences.[3] There is evidence to propose the likelihood of impact of intracellular T3 on insulin sensitivity.[4]

It is said that rectification of abnormal thyroid status in individuals with diabetes will enhance blood glucose levels, diminish cardiac and other complications chances, and improve overall health. However, there is dearth of unanimity concerning timing and periodicity about thyroid assessment to be conducted in standard approach to diabetes management.[5]

Hyperthyroidism and Glucose Metabolism

Thyroid hormones may affect glycemia secondary to their influence on glucose metabolism. Hyperthyroidism is known to increase blood sugar levels.[6]

Increase in thyroid hormones lead to enhanced intestinal absorption of glucose, insulin clearance,

glycogenolysis and gluconeogenesis.[7] The hepatic glucose output is increased with decreased insulin action and increased lipolysis.[7]

Hyperthyroid patients encounter decline in blood sugar control if they are also suffering from diabetes mellitus. Thyroid hormone excess can also sometimes precipitate diabetic ketoacidosis in diabetic patients.[8] Also, the clinical features of hypermetabolic state of thyrotoxicosis and those due to hyperglycemia may be confused among each other leading to missing the diagnosis.

About half the patients of Grave's disease exhibit glucose intolerance of variable degree and about 2–3% may develop overt diabetes.[6]

There is an escalated β-cells reaction to blood sugar levels/catecholamines perhaps secondary to expanded β-cell volume. Patients with elevated thyroid hormones may also have enhanced removal of insulin. Hyperthyroidism leads to increased glucose output from the liver and upregulates glycogenolysis producing glucose intolerance **(Flowchart 1)**.[9,10] It has been advocated that there is hypothalamic sympathetic impact on liver along with enhanced expression of hepatic GLUT 2 transporters with resultant increase of plasma-free fatty acids.[5] This situation accounts for magnification of elevated blood glucose levels in diabetics. Thyrotoxicosis can also result in state of ketoacidosis in patients with diabetes. This is secondary to the accelerated lipolytic activity and escalated liver β-oxidation.[7,11]

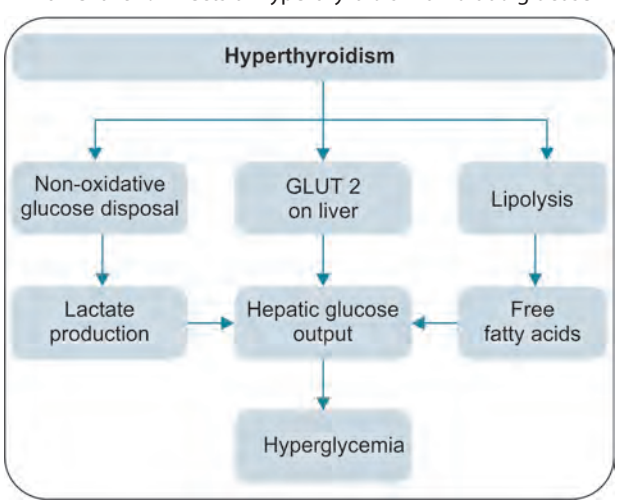
Hypothyroidism and Diabetes Mellitus

The most often thyroid disease that we come across in diabetes is hypothyroidism. Studies have found the occurrence of hypothyroidism in 5.7% patients suffering from diabetes.[1] The most common etiology in iodine sufficient regions being autoimmune thyroiditis.

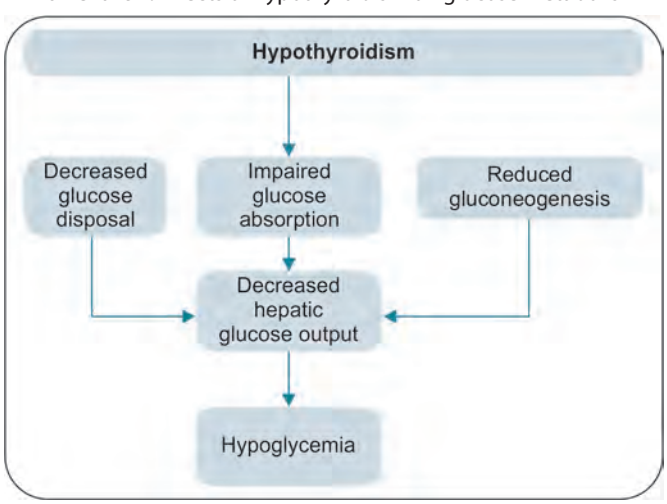
In individuals with T1DM, repetitive events of hypoglycemia hint toward hypothyroidism. It has been shown that treatment with thyroxine lowers the blood glucose variations.[12] It is documented that insulin resistant condition is seen in both overt as well subclinical hypothyroidism.[13]

The impact of reduced levels of thyroid hormone on metabolism in diabetic patients is contrary to that observed in hyperthyroidism.[5] Reduced thyroid hormones lead to reduced glucose absorption from gastrointestinal tract. Extended peripheral glucose accretion, lessened hepatic glucose yield, gluconeogenesis and lower peripheral glucose use is witnessed in hypothyroidism.[5] The insulin stimulated glucose transport and GLUT expression are lowered. Insulin clearance is reduced and less hunger further decreases insulin. A combination of all these metabolic alterations in patients with diabetes and coexistent hypothyroidism lead to reduction in blood sugar with increased frequency of hypoglycemia **(Flowchart 2)**.[14] Studies have also shown reduction and benefit in hypoglycemic episodes following treatment of hypothyroidism.[15] Studies have correlated hypothyroidism with lowered insulin sensitivity.

Flowchart 1: Effects of hyperthyroidism on blood glucose



Flowchart 2: Effects of hypothyroidism on glucose metabolism



Other factors:

- Role of thyroid hormones in lipid metabolism has been studied by many authors.
- They work along with controlling route for energy equilibrium and directly modify insulin equipoise and glucose disbursement by tissues.
- Triggering of melanocortin receptor type 4 (MC4R) brings about lowering of food ingestion and elevation in energy disbursement. Hypothalamic TRH neurons express these receptors which play role in central pathways of energy control.[16]
- Thyroxine relates to adipocytokines and gut hormones disturbing carbohydrate metabolism.
- Ghrelin hormone which impacts insulin sensitivity has been observed to have counter alliance with T3.
- The β-cell activity of insulin secretion mediated by glucose also is reduced in low thyroid hormone status.

Does Diabetes Mellitus Modify Dysfunctional Thyroid Status?

Diabetic patients have dampened diurnal TSH climax occurring at night. Also, there is weakened TSH response to TRH. Low T3 levels are witnessed in individuals with unchecked diabetes mellitus. It is seen that in diabetic individuals with unrestrained blood glucose, there may be blunted T4 to T3 conversion leading to low T3 state, which corrects with normalization of hyperglycemia.

Evidence suggests that reduced insulin sensitivity and hyperinsulinemia may cause multiplicative sequel on thyroid tissue resulting in thyromegaly and nodularity. Presence of concomitant diabetes also changes therapeutic response to thyroxine in hypothyroidism. Patients with Grave's orbitopathy have an increased prevalence of type 1 diabetes mellitus as compared to general population. Dysthyroid optic neuropathy has higher occurrence with patients with diabetes mellitus and Grave's orbitopathy as compared to those without diabetes mellitus.[17]

Does Thyroid Dysfunction Affect Diabetic Complications?

Diabetes is a well established individual predisposing cause for cardiac ailments. Hypothyroidism is known to have independent association with atherosclerotic cardiac diseases.[18] Coexistence of these disorders augment the cardiovascular risk of the patient.

Lipid profile disturbances are recognized in patients with hypothyroidism. Elevated total cholesterol, LDL cholesterol, apolipoprotein B, and decreased HDL are the typical findings.[19] Altered thyroid status has been correlated with dyslipidemia and insulin resistance in several studies. Literature also shows relation of hypothyroidism and obesity. Blood pressure changes in patients with hypothyroidism have also been studied by authors. Increase in systemic vascular resistance leading to high diastolic blood pressure has been documented in hypothyroidism.[20] Studies documenting higher intima media thickness in hypothyroid patients suggest endothelial dysfunction resulting in increased chances of CV risk.

The escalated peripheral vascular resistance and drop in cardiac output witnessed in subclinical and overt hypothyroidism put them to increased susceptibility to nephropathy. The diabetic patients with concurrent low thyroid hormones observed good renal response to therapeutic thyroid correction. Retinopathy seen in patients with diabetes was of greater intensity in subclinical and overt hypothyroid individuals than euthyroid people.[21] The above findings of high renal and eye complications documented in coexisting thyroid dysfunction in patients with type 2 diabetes provides rationale for assessing thyroid dysfunction in patients with type 2 diabetes mellitus.

Effect of Metformin on Thyroid Function

Studies document impact of metformin on thyroid function. Metformin given as therapeutic intervention for diabetes resulted in subduing of TSH in a study.[22] Another study conducted on thyroid nodules revealed a decrease in nodule size with use of metformin in patients with insulin resistance.[23] The studies show the effect to be without any changes in LT4 and LT3. Studies have also shown that following withdrawal of metformin there was some rebound rise in TSH levels.

Do Hypothyroid Individuals have Factitious Spike in HbA1c?

- Rising HbA1c in hypothyroid patients was witnessed in non-diabetic subjects also in a study.[24] The possibility of false spike probably owing to the lower hemoglobin levels in hypothyroid subjects was suggested.

- This questions the validity of using glycosylated hemoglobin for diagnosis of diabetes and management in cases with concomitant thyroid abnormalities.

Summarizing diabetes mellitus and thyroid cross-linking:

- Diabetes + Euthyroid — Reduced T3, reduced responsiveness to TRH
- Diabetes + Hyperthyroid — Glycemic control worsens
- Non-diabetic + Hyperthyroid — Proceeds to glucose intolerance in half cases
- Diabetes + Hypothyroidism — More events of hypoglycemia

Is there any Difference in Diagnosis of Hypothyroidism in Coexistent Diabetes?

- The elucidation of tests of thyroid function in individuals with unrestrained diabetes may be erroneous.
- Typical alterations include a low-serum T3, a low-serum T4 caused by decreased protein binding, and a low-serum TSH level.
- The similar symptoms of pallor, fatigue, edema, and increase in weight being common to renal disease related to diabetes and hypothyroidism may cause overlooking the diagnosis of the other disorder if one is suspected.

When should we screen diabetics for thyroid dysfunction:

- The significant interdependence seen between thyroid function and metabolic status in T1DM patients warrants timely and adequate monitoring of thyroid levels in these subset of patients.
- Regarding T2DM patients, the consensus regarding thyroid testing is less lucid. There are either no clear cut recommendations regarding once a year screening or in opposition to routine annual estimation of thyroid status in these patients.
- More often testing for thyroid abnormalities in diabetic individuals is approved.
- Similarly, some associations endorse analysis of thyroid status in pregnancy with diabetes. They propose TSH estimation along with palpation of the thyroid gland at identification of diabetes, with systematic observation thereof in individuals with positive results.
- On similar grounds, in those with abnormal lipid profile, age more than 50, TSH is proposed.
- A recent analysis by Kadiyala et al. suggested a comprehensible perspective to this matter. An initial TSH and TPO antibody assessment in patients with diabetes was advocated. Accordingly a high-risk group could be identified. This group would be consisting of T1DM patients, those with elevated TSH and those with TPO antibody positive. An annual TFT evaluation in this subset would be more likely to be cost effective and yielding desired results.[4]

Conclusion

There is a multifaceted linkage between thyroid defects and diabetes mellitus. In individuals with normal blood glucose status, high thyroid hormones bring about glucose intolerance whereas amongst those with established diabetes the metabolic control gets disturbed. On the other hand, hypothyroidism increases the susceptibility of hypoglycemic episodes in diabetic individuals. Increased insulin resistance is another important feature associated with hypothyroidism. Obscure thyroid defects would have unfavorable consequence not only on diabetes but also on its complications. Therapeutic interventions of subclinical hypothyroidism in patients with diabetes would be advantageous. A structured and well outlined approach to thyroid testing in diabetic subjects is suitable; nevertheless, there is a paucity of categorical specifications in this direction.

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CHAPTER

201 Thyrotoxicosis: Evaluation and Management

Manoj Saluja

Abstract

Thyrotoxicosis, or inappropriately high circulating thyroid hormone concentration causing surplus action at the tissue level, may present as a constellation of clinical manifestations. Causes vary depending on various factors like iodine intake, age, and geography. Diagnosing the entity begins with detailed history and clinical examination aided by tests like thyroid hormone profile, radio and nuclear imaging, Doppler sonogram, serology for antibodies. While management differs according to cause and patient, the target is to control symptoms (beta blockers, glucocorticoids) and treating the cause (surgery, anti-thyroid drugs, radiotherapy). Latest researches on autoimmunity and molecular targets have opened new horizons in term of diagnosis and management as well.

Introduction

Thyrotoxicosis, characterized by inappropriately high circulating thyroid hormone concentration causing surplus action at the tissue level, may present as a constellation of clinical manifestations.[1,2] Hyperthyroidism, a clinical subset of thyrotoxicosis, indicates inappropriately high synthesis and secretion of hormone(s) by the thyroid.[1,2]

Effective management of the disease demands an intricate knowledge of the etiologies, pathophysiology, and treatment options. A basic understanding of approaching a patient, clinical, and lab parameters is important, as is the knowledge about various therapeutic regimens.

Etiology

A multitude of causes have been identified, differing in frequency—depending on iodine intake (Graves' disease predominates in iodine sufficient regions, nodular thyroid disease in iodine deficient regions), age (toxic nodular goiter increases with age; autoimmune thyrotoxicosis is common in young and middle aged), and geography (painless thyroiditis seen in 0.5% of cases in Denmark, 22% in Wisconsin)[1,2] **(Flowchart 1)**.

Approach to a Patient with Suspected Thyrotoxicosis

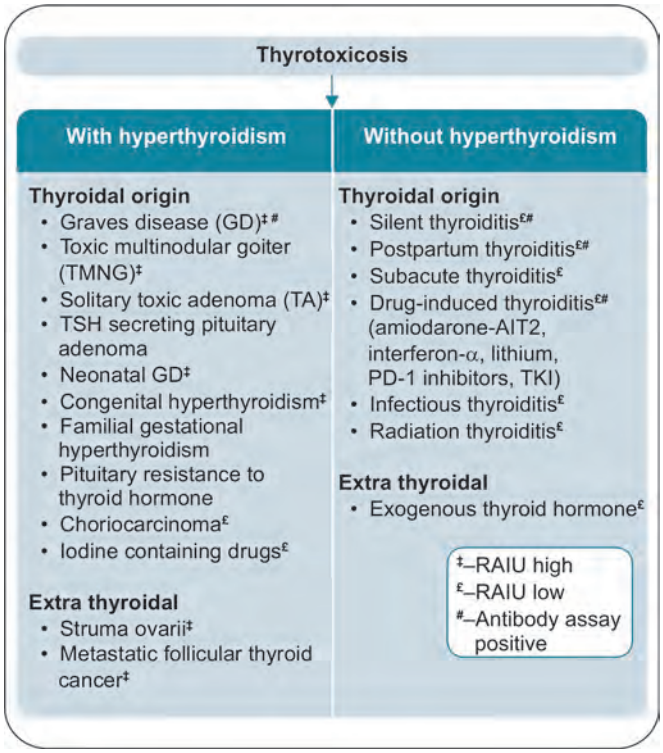
Combined and balanced assessment of history, clinical examination, and investigations guides the physician to diagnosis and management.

History

Clinical presentation, like medical and obstetric history, drug and diet intake, familial clustering of similar disease, is important. This provides an organized approach in less time, money, and resources.

Thyrotoxicosis has specific stigmata **(Flowchart 2)**[5] and may be suspected in presence of given signs and symptoms, concomitant type 1 diabetes/autoimmune diseases, new-onset atrial fibrillation, unexplained anxiety or change in behavior. Thyrotoxicosis typically presents with low thyroid stimulating hormone (TSH),

Flowchart 1: Causes of thyrotoxicosis[2-4]



AIT2, amiodarone-induced thyroiditis type 2; PD-1, programmed cell death 1; TKI, tyrosine kinase inhibitor; TSH, thyrotropin; TSHR, TSH receptor.

with (overt) or without (subclinical thyrotoxicosis) raised fT3 and fT4.

The **Flowchart 3** shows the approach to a patient with suspected thyrotoxicosis.[3]

Laboratory Investigations/Imaging

While thyroid profile (TSH, fT3, and fT4) is done to detect the disease, further workup assists in determining the underlying cause.

Radioactive iodine uptake (RAIU) using ^{123}I has become mainstay in diagnosing GD (diffuse uptake of radioactive iodine by the gland) and nodular thyroid disease (focal increased and decreased uptake in TMNG; uptake only in the nodule in TA). Anti-thyroid drugs (ATD) is given only in patients showing increased dye uptake, implying hyperthyroid state **(Fig. 1)**.

Color Flow Doppler Study (CFDS) is safe and efficient, particularly useful when RAIU is contraindicated (pregnancy/breastfeeding). It distinguishes between thyroid hyperactivity (increased flow) from destructive thyroiditis and between the two types of amiodarone-induced thyroiditis (AIT).[1]

Measurement of TRAb, especially in thyrotoxicosis without nodular signs/orbitopathy, distinguishes between GD and other etiologies. Young age, pre-existing autoimmune diseases, a positive family history are indications for antibody assays. Reduced cost and faster diagnosis have been proven in some studies when compared to RAIU.[1]

^{99m}Tc pertechnetate scan is used in nodular thyroid. Ratio of total T3 to T4 is useful in assessing hyperthyroidism. A hyperactive gland produces more T3 than T4, elevating T3 above the upper limit of normal more than T4. Vice versa is true in thyroiditis[1] and thyrotoxicosis factitia (exogenous levothyroxine). Acute phase reactants indicate active inflammation, as in subacute and infectious thyroiditis.

Management

We will discuss management of some of the common etiologies with a protocol for follow-up **(Flowchart 4)**.

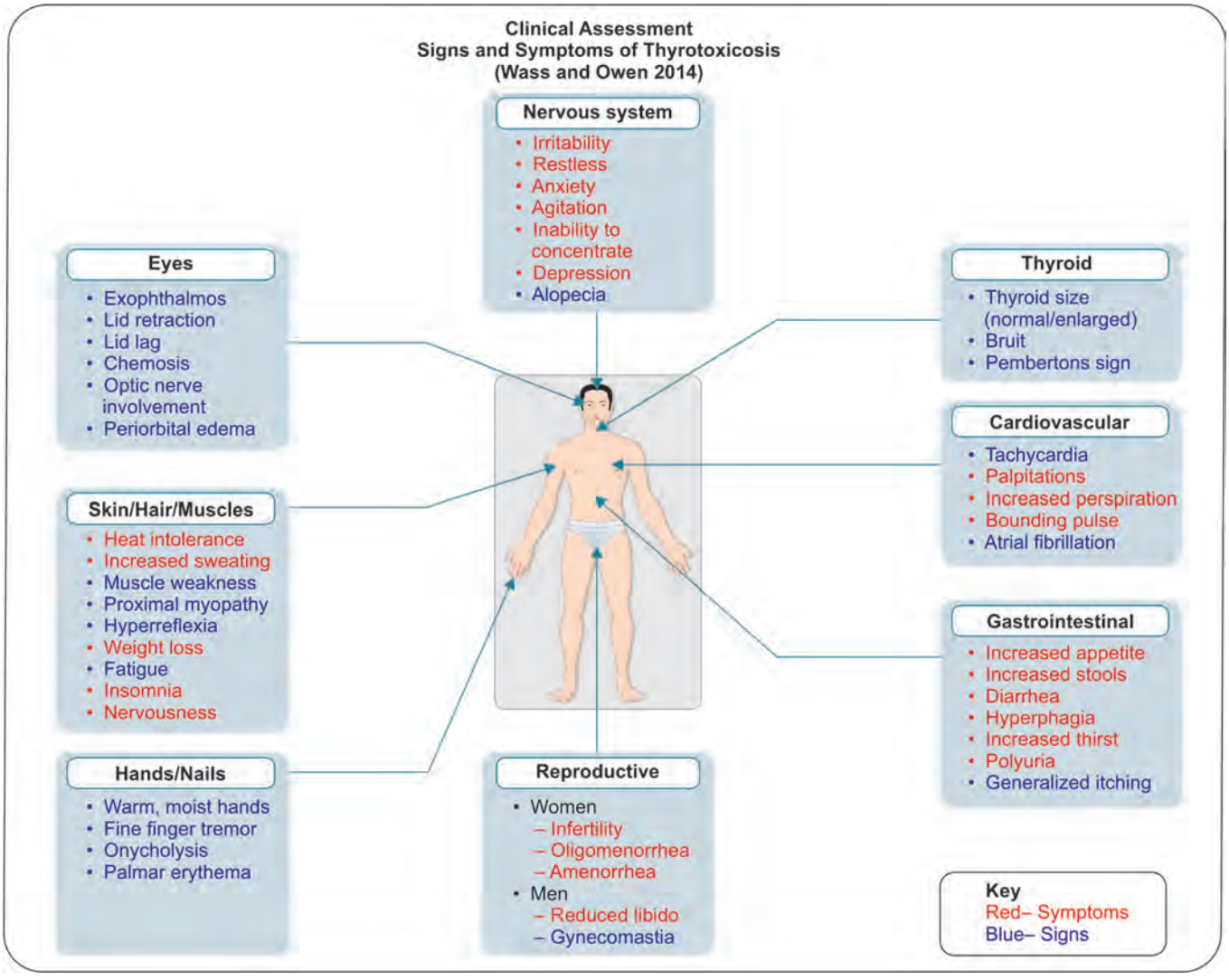
Graves' Disease

Follow two steps—one, symptom control and second, treat the underlying illness. Beta-blockers are used to abate symptoms (caused by overstimulation of beta adrenergic receptors). Propranolol (non-selective) additionally inhibits peripheral conversion of T4 to T3.[2] Glucocorticoids may be used in thyroid storm. For the underlying illness, radioactive iodine (RAI), ATD, and thyroidectomy are potential options. ATDs should be stopped 12–18 months after initiation to look for remission—defined as no recurrence of GD after 12 months without treatment **(Table 1)**.[2]

GD may be associated with ophthalmopathy, but only 5% develop severe symptoms (diplopia, visual field defects, and blurred vision). Mild symptoms like photophobia, irritation, and tearing can be solved using tight fitting sunglasses, saline drops/gel, and application of paper tape (at night) to avoid exposure keratitis. In case of corneal abrasion due to the tape, goggles are recommended. Medical emergency may ensue if orbital edema causes optic nerve compression. In such cases, high dose glucocorticoids and orbital decompression surgery are considered.

Dermopathy-nonpitting erythematous edema on anterior shin is due to glycosaminoglycan accumulation in dermis. High potency local steroid cream with nightly occlusive plastic wraps may be advised.[6]

Flowchart 2: Signs and symptoms (hyperthyroidism)



Young females may benefit from RAI and surgery more than ATD (better remission rates of former, high teratogenicity of latter), but comorbid condition/pregnancy or refusal to undergo RAI/surgery are indications to initiate ATDs.[2]

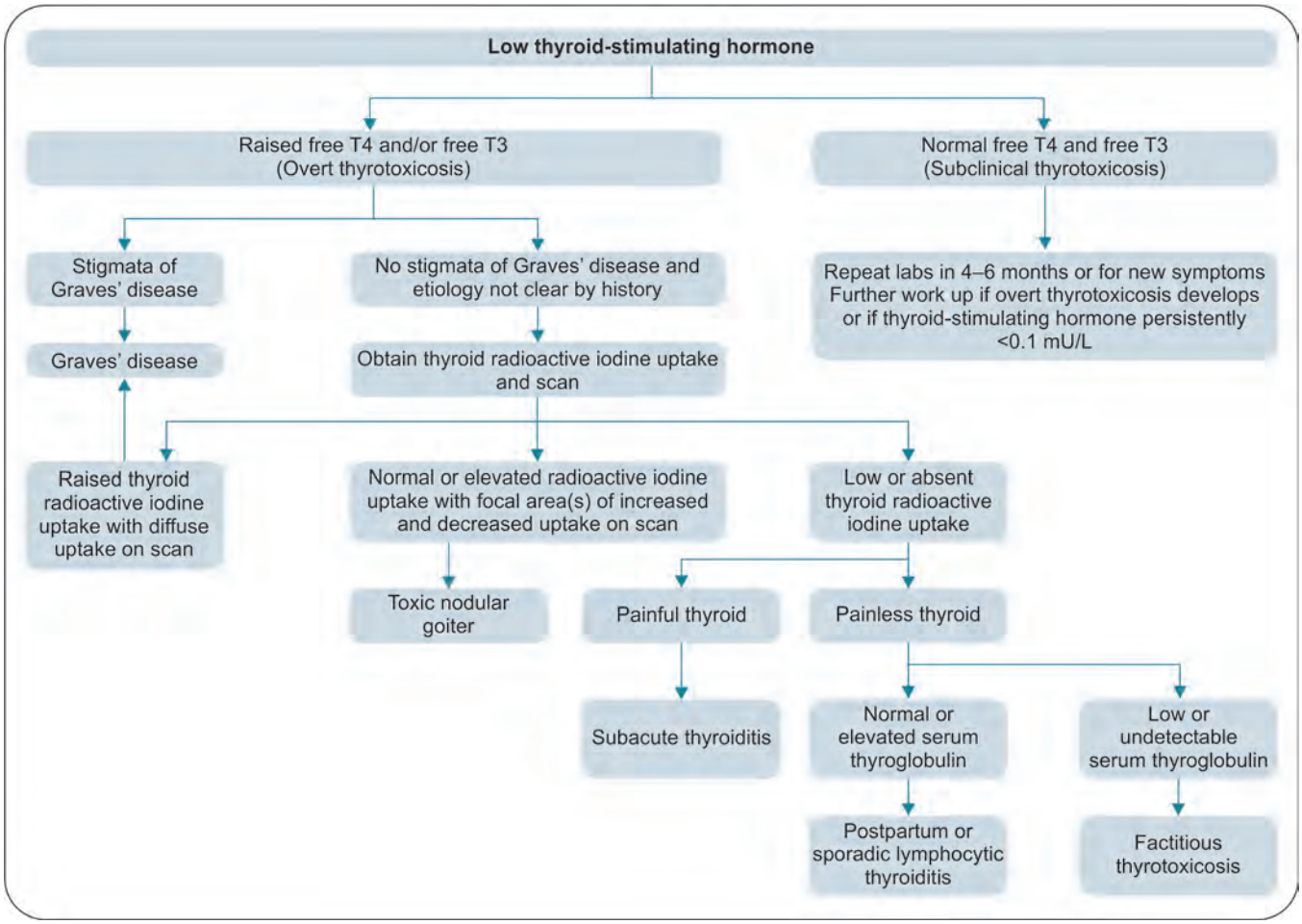
Toxic Adenoma and Toxic Multinodular Goiter

Toxic adenoma (TA) (benign monoclonal thyroid tumor) secretes excess thyroid hormones due to activating mutation in TSH receptor gene (increasing adenylyl cyclase independent of TSH). TMNG or Plummer's disease manifests as multiple autonomous nodules. Owing to this pathophysiology, ATDs show less satisfactory results and no remission despite long-term use. RAI and thyroidectomy are feasible and better management options. Selective uptake of the radioactive dye, as opposed to diffuse destruction as seen in GD, makes RAI first-line therapy unless contraindicated.[2] Risk of persistent hyperthyroidism is 11–20% with RAI and <1% with near-total/total thyroidectomy, but hypothyroidism at 5 years occurs in 16% and100%, respectively.[2]

Miscellaneous

Amiodarone-induced thyroiditis, caused by direct toxicity of amiodarone and its iodine content, is treated with

Flowchart 3: Approach to patient with thyrotoxicosis



long-term high dose ATDs and potassium perchlorate (type-1) or high dose prednisone (40–60 mg/day) for 1–3 months then tapered (type 2). Thyrotropin secreting pituitary adenoma is suspected if raised TSH with high T3, T4 is noted. Pituitary imaging (MRI) confirms the diagnosis. Apart from radiotherapy and/or radiosurgery, several new pharmacotherapies are being explored. Somatostatin receptors 2 and 5 on tumor cells have advocated somatostatin analogues as a possible cure or at least as a preoperative adjunct.[2,7] They also express dopamine receptors, but agonists have produced variable results.[2]

Hydatidiform mole, choriocarcinoma, testicular germ cell tumor, metastatic follicular thyroid cancer primarily require symptom control and multimodal approach to eradicate the root cause via surgery, radiation, or RAI. Detailed discussion is beyond the scope of this article.

Thyrotoxicosis without Hyperthyroidism

Subacute thyroiditis, seen post-viral infections due to antigenic mimicry, is painful but resolves spontaneously over a span of 2–3 months. It undergoes phases of hormonal changes: initially thyrotoxicosis caused by preformed hormone release followed by hypothyroidism due to the lack of new hormone synthesis during the disease period. Painless thyroiditis (seen in iodine sufficient areas), postpartum thyroiditis (seen after delivery/miscarriage) share an autoimmune etiology with a positive family history found more often than not. Supportive treatment is indicated beta-blockers, NSAIDs, and prednisone (for pain relief). During the latter part of disease, levothyroxine should be supplemented and tapered gradually while monitoring the hormone levels every 3–4 weeks. Selenium therapy has been tried in some

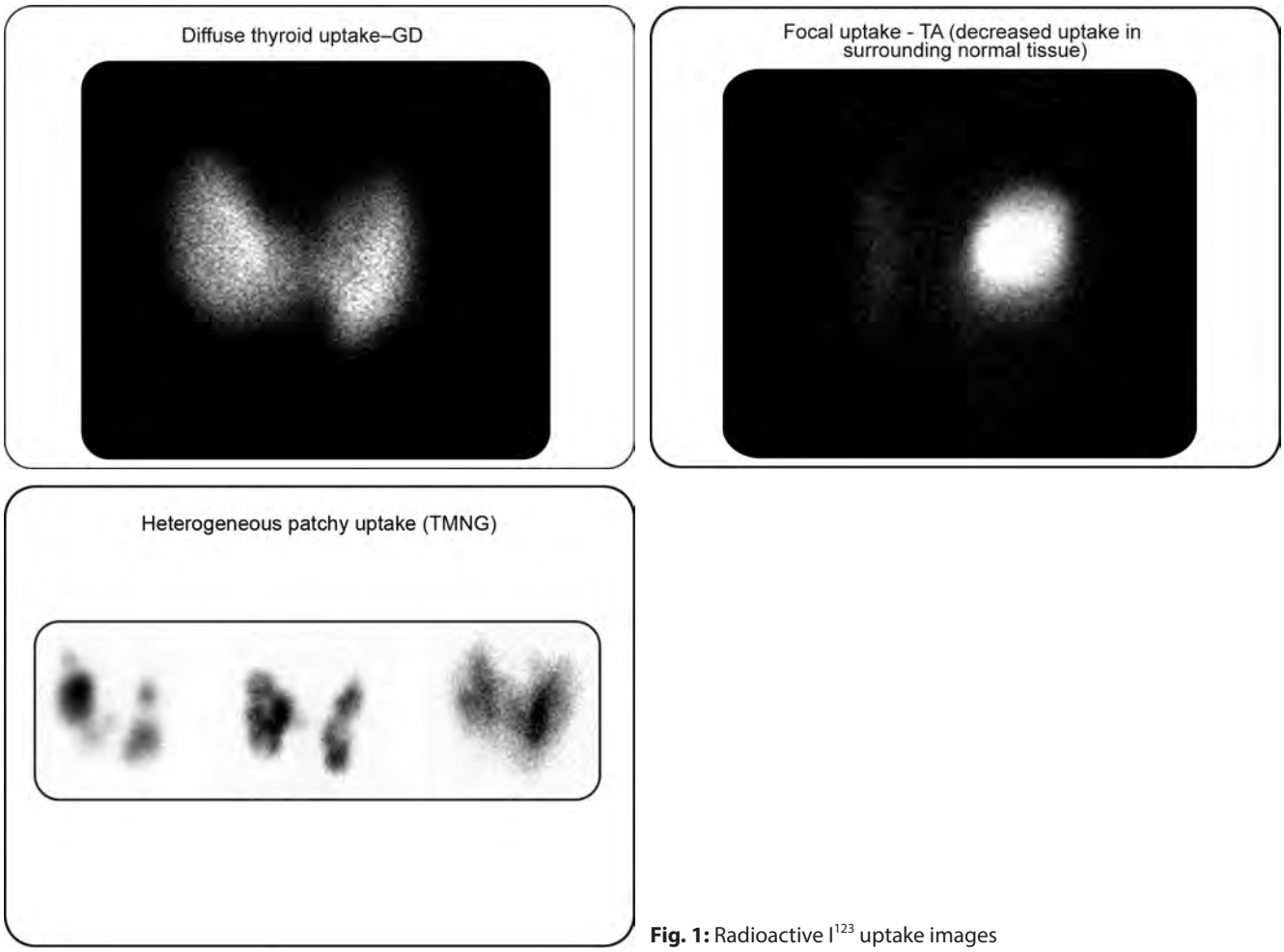


Fig. 1: Radioactive I^{123} uptake images

cases with inconsistent results.[2,8] Drug induced thyroiditis (sunitinib, sorafenib, ipilimumab, and pembrolizumab)[2,9] demands removal of offending agent and beta-blockers.

Exogenous Thyrotoxicosis

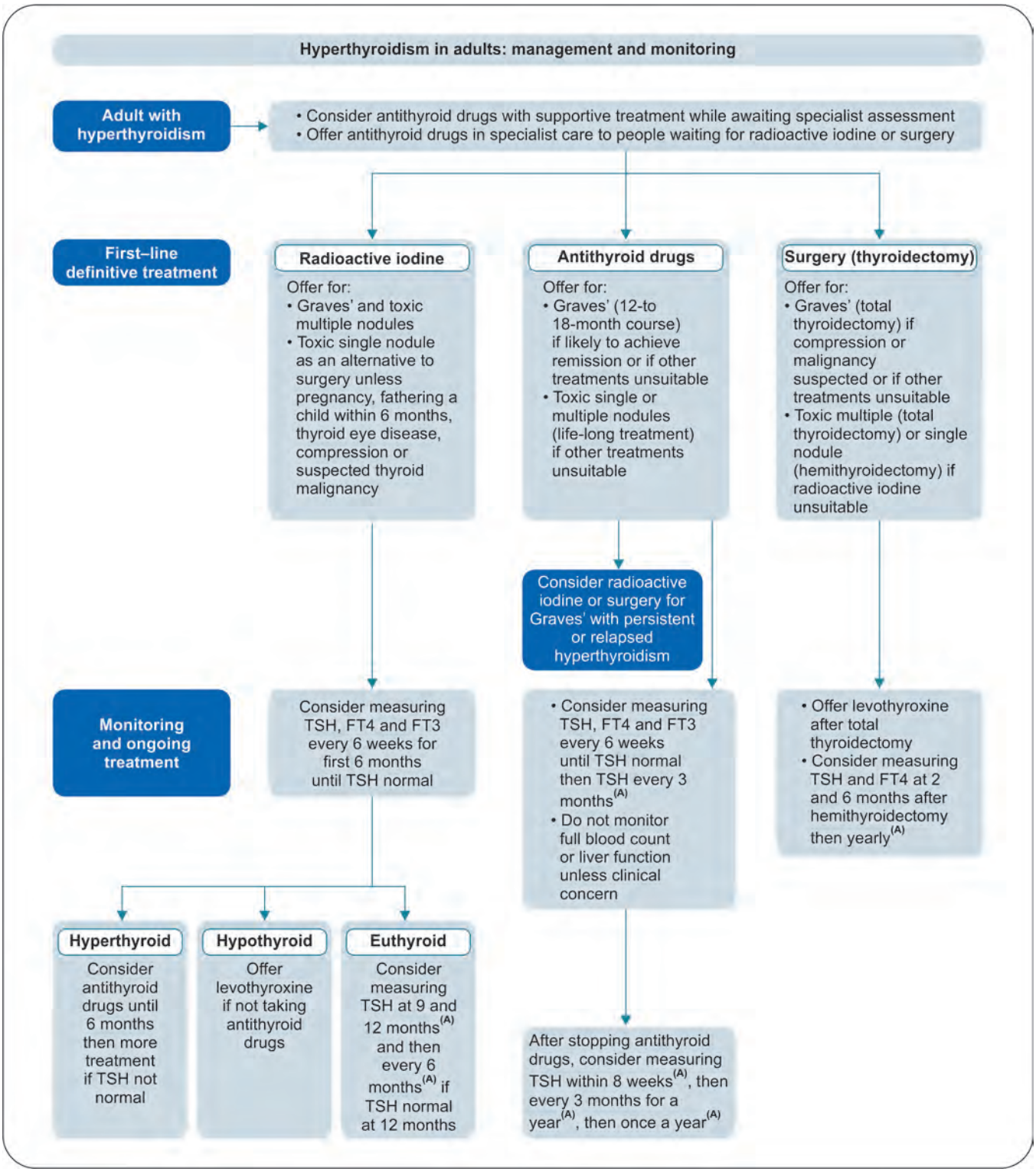
This may be accidental or intentional (thyrotoxicosis factitia). Intentional overdose needs appropriate counseling[2] along with beta-blockers, iopanoic acid and cholestyramine. In extreme cases, plasmapheresis may be required.[2,10]

Antithyroid Pharmacotherapy

ATD (methimazole, carbimazole, and propylthiouracil) inhibit formation of iodotyrosines in thyroglobulin (takes 2–8 weeks). PTU remains drug of choice in thyroid storm (due to its peripheral inhibition of T4 to T3) and in first trimester pregnancy. Methimazole and carbimazole have longer duration of action with once daily dosing, ensuring better compliance. Owing to teratogenicity (cutis aplasia), they are less preferred in first trimester of pregnancy, but may be restarted post 12 weeks gestation.[1,2,6]

ATDs should be titrated every 4 weeks. Adverse reactions are mild—include fever, rash, urticarial and arthralgia, usually seen within first week of treatment. Grave side effects include agranulocytosis, aplastic anemia, hepatic failure, lupus like vasculitis. Except agranulocytosis, all are more common with PTU. Granulocyte colony-stimulating factor (G-CSF) appears to accelerate recovery in patients with agranulocytosis. Dipping prevalence of these side effects from 30/1,000 to 1/1,000 at the end of 30 and 180 days, respectively, establishes safety in long-term therapy, especially in GD.[1,2]

Flowchart 4: Management and follow-up of thyrotoxicosis[4]



(A)With cascading--measuring FT4 in the same sample if TSH above reference range, and FT4 and FT3 in the same sample if TSH below reference range

TABLE 1 Treatment of Graves' disease

Treatment	*Mechanism*	*Dosing*	*Remission rate (%)*	*Adverse effects*	*Pregnancy*
ATDs[a] • MMI • PTU[b]	Block TPO	Initial dose proportional to degree of elevation of thyroid hormones, symptoms, and goiter size	30–60	Dose and duration dependent Rash, elevated liver enzymes, agranulocytosis (0.3%), vasculitis (<0.1%)	*MMI* ↑ Risk of congenital abnormalities; recommended in 2nd and 3rd trimester. *PTU* Lower teratogenic risk, ↑ risk of hepatotoxicity; recommended in 1st trimester All ATDs ↑ Risk of fetal hypothyroidism
Radioactive iodine I^{131}	Thyroid follicular cell necrosis	Fixed or calculated dose based on goiter size and uptake	80–90	Worsening thyrotoxicosis/ orbitopathy, Thyroiditis	Contraindicated
Thyroid surgery	Removal of thyroid tissue	Total thyroidectomy	100	Hypoparathyroidism, laryngeal nerve injury	Done in 2nd trimester

a ATDs, anti-thyroid drugs; MMI, methimazole; PTU, propylthiouracil; TPO, thyroid peroxidase; T3, triiodothyronine; T4, thyroxine; ↑, increased.
b Blocks TPO and peripheral T4 to T3 conversion.

Monitoring of liver function and explaining the possible reactions to the patients are quintessential. Up to 750 mg/day of PTU or 20 mg/day of methimazole in lactating mothers does not affect infants' thyroid function.[11]

Severe thyrotoxicosis calls for use of additive therapy with saturated solution of potassium iodide (SSKI) at a dosage of 10 drops twice daily, iopanoic acid at 1 g/day, cholestyramine (enhances enterohepatic clearance of thyroid hormone) up to 12 gm in three divided doses (for 4 weeks).[1,2]

Radioactive Iodine Therapy

RAI is effective, safe, avoids hospitalization with higher cure and lower recurrence rates. It causes thyroid specific fibrosis of the gland over weeks to months.[2] ^{131}I is administered at 75–200 μCi/g of estimated thyroid tissue divided by percent of ^{123}I uptake in 24 hours.[1]

It is absolutely contraindicated in children (<5 years), pregnancy (as it causes fetal hypothyroidism) and in lactating mothers. Patients are counseled to avoid conception for 3–6 months post RAI therapy. Severe ophthalmopathy could be exacerbated, so is either avoided or given with concomitant glucocorticoid therapy (prednisone 0.4 mg/kg for 1 month with subsequent taper).[2] To diminish the risk of worsened thyrotoxicosis, pretreatment with ATD (methimazole than PTU) may be considered for 3–5 days.

Thyroidectomy

Subtotal, near-total, total thyroidectomies are various options available. Severe hyperthyroidism in children, pregnant females noncompliant or intolerant to ATDs, patients with large goiters, severe ophthalmopathy, suspicious nodules, refractory AIT, and patients with unstable cardiac conditions are common indications.[6]

Prior to the surgery, euthyroid state should be achieved using beta-blockers (target heart rate <80/minute), ATDs (4–8 weeks) and stable (cold) iodine treatment. SSKI (1–2 drops twice daily for 10–14 days) is administered after ATDs and before the procedure. It reduces hormone secretion and decreasing gland vascularity (moderates intraoperative blood loss). Preoperative single dose dexamethasone (8 mg) is suggested avoid post-procedure nausea, vomiting, and pain.[1,2,6] Laryngeal nerve injury and hypoparathyroidism are possible complications. Hormone levels are checked every 4–8 weeks and T4 is titrated accordingly (started at 50–75 μg/day).

Endoscopic technique is a novel approach with better cosmetic satisfaction, lesser complications, and reduced time. Any surgical procedure, open, or endoscopic, yields better result if performed by a high-volume thyroid surgeon (>25 surgeries/year)[2,6,12]

Pitfalls, Controversies, and Unanswered Questions

Biotin has proven to cause spurious diagnosis of GD, especially at a dose of more than 10 mg/day, hence should be avoided for at least 12 hours prior to testing.[13] Second common pitfall is misdiagnosing iodine deficiency for thyrotoxicosis under the setting of increased radioiodine uptake by the gland. Amplified uptake but normal T3/T4/TSH implies iodine deficiency than endogenous hyperthyroidism.

Treatment of subclinical thyrotoxicosis has been a matter of debate for long. Current guidelines recommend treatment in case TSH is persistently <0.1 Mu/L.[12] Risk reduction of atrial fibrillation and low bone density in postmenopausal women is seen.

Questions concerning optimum dose and duration of ATD in GD, use of ATDs before and after RAI therapy, risk benefit ratio of block replacement regimen during RAI therapy, role of rituximab, lanreotide remain largely unanswered. Immunomodulatory therapy is being tested for GD.

Conclusion

The evaluation for cause should begin from the clinical picture itself to be supported by biochemical tests, nuclear medicine, and ultrasound imaging. Increased gland function remains an important aspect for therapy selection. GD and MNG remain the common causes. Long-term ATDs have replaced RAI and surgery for managing GD, except in special circumstances, while nodular goiter fare less well with ATDs. Thyroiditis constitutes major cause of thyrotoxicosis in absence of a hyperfunctioning gland. Thyroid autoimmunity has huge scope for developing novel therapies, particularly GD by addressing the pathophysiology itself. From redressal of less effective therapies to identifying newer targets at a molecular level, we have definitely come a long way with even better prospects in near future.

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CHAPTER

202 Evaluation of Non-Diabetic Polyuria

Indira Maisnam, Soumita Mandal

Abstract

Polyuria is defined as urinary output more than 50 mL/kg/day or 3–3.5 L/day. It should be differentiated from increased urinary frequency by proper history and documentation of increased urinary volume. Polyuria can be due to solute diuresis or water diuresis. In most cases of solute diuresis the etiology is evident from history, physical examination and baseline laboratory investigations. For water diuresis a detailed history and physical examination and a number of tests consisting of serum sodium and other electrolytes, paired plasma and urine osmolality, water deprivation test, hypertonic saline infusion, and plasma copeptin levels help establish the diagnosis.

Introduction

Polyuria is defined as urinary output more than 50 mL/kg/day or 3–3.5 L/day.[1] It should be differentiated from increased urinary frequency. Polyuria can interrupt daily activities, disturb sleep, and cause bed-wetting in children. The two major types of polyuria are solute and water diuresis.

Water Homoeostasis

Extracellular fluid balance is under control of two factors: Antidiuretic hormone (ADH) also known as arginine vasopressin (AVP) and thirst. A rise in serum osmolality (most sensitive to serum sodium) and hypovolemia sensed by baroreceptors stimulate ADH secretion and thirst. ADH (V2) receptors are located at the luminal side of collecting duct of the kidney. On receptor binding, ADH leads to cAMP production with translocation of aquaporin 2 channels to luminal membrane, allowing reabsorption of water from lumen forming concentrated urine. Water moves out of the tubule along the concentration gradient created and maintained by reabsorption of solutes in thick ascending loop of Henle thereby producing hypertonic renal medullary interstitium. The sensation of thirst and ADH secretion is suppressed upon normalization of ECF volume and serum osmolality (280–295 mOsm/kg).

Determinants of Daily Urine Output

The daily urine output is dependent on solute load and concentrating ability of the nephron. Polyuria can therefore be solute diuresis, water dieresis, or both.

Solute diuresis due to excess saline/hypertonic saline infusion, protein excess with urea generation, glucose, and mannitol produces concentrated urine. Water diuresis (polyuria-polydipsia syndrome) producing dilute urine is of two types: diabetes insipidus (DI) and primary polydipsia (PP). In central diabetes insipidus (CDI), there is partial or complete ADH deficiency; in nephrogenic DI (NDI), there is resistance ADH action. Excessive water intake in absence of physiological stimulus, often in the background of psychiatric disorders is seen in PP. Sometimes solute and water diuresis coexist, for example, ADH deficiency/resistance with solute diuresis. Chronic

TABLE 1 Causes of polyuria

Osmotic diuresis	*Water diuresis (polyuria-polydipsia syndrome)*		
	Central diabetes insipidus (CDI)	*Nephrogenic diabetes insipidus (NDI)*	*Primary polydipsia (PP)*
Glucosuria **Urea diuresis** • Resolving phase of acute kidney injury • High protein diet • Glucocorticoid excess → protein breakdown → urea generation **Sodium diuresis** • Large volume of saline/ hypertonic saline • Post release of bilateral urinary tract obstruction **Mannitol**	**Tumors** • Craniopharyngioma • Pituitary tumor with suprasellar extension • Germinoma • Metastasis **Trauma** • Traumatic brain injury • Pituitary surgery • Pituitary apoplexy **Infiltrative/Autoimmune** • Lymphocytic hypophysitis • Langerhans cell histiocytosis • Sarcoidosis • IGF4 mediated • Immune check point inhibitors **Congenital/Genetic** • Familial CDI • Septo-optic dysplasia • Congenital hypopituitarism • Wolfram syndrome **Idiopathic** **Hypoxic encephalopathy**	**Congenital** • V2 receptor mutation • AQ2 channel mutation **Drugs** • Lithium • Amphotericin • Cidofovir • Foscarnet **Electrolyte imbalance** • Hypercalcemia • Hypokalemia **Renal disease** • Medullary cystic kidney • Adult polycystic kidney disease (ADPKD) **Obstructive uropathy** **Systemic diseases** • Sjogren's syndrome • Renal amyloidosis • Sickle cell disease	**Psychogenic** **Psychiatric illness** **Antipsychotics** • Causing dry mouth

renal failure, infiltrative renal parenchymal disease and relief of longstanding urinary obstruction sometimes have a mixed solute and water diuresis. Sometimes DI is seen in pregnancy due to placental vasopressinase increasing ADH breakdown and transient ADH resistance in second half of pregnancy **(Table 1)**.

Approach to a Patient with Polyuria

History

A detailed history regarding age and mode of onset, progression, and duration of polyuria and family history should be taken. Polyuria should be differentiated from increased urinary frequency. Hereditary NDI typically has a neonatal presentation; most craniopharyngiomas present in childhood and adolescence; infiltration, tumors, and metastasis present in any age. Polyuria with weight loss with family/personal history of diabetes mellitus suggests diabetes mellitus/uncontrolled hyperglycemia; polyuria after recent acute kidney injury, high protein diet/ supplement and after release of urinary tract obstruction suggests urea-induced diuresis. In glucocorticoid excess states, polyuria occurs due to hyperglycemia and protein breakdown with urea generation. A detailed medication history, history of head injury, or central nervous system surgery is important. Mannitol and hypertonic saline cause solute diuresis; many drugs cause NDI. Patients with DI prefer cold water; in CDI symptoms develop almost suddenly (as urine concentrating capacity is maintained until ADH synthesis decreases to 10–15% of normal); in PP symptoms develop gradually. Patients with PP may have coexisting psychiatric illness. These are not precise discriminating criteria and overlap exists in clinical features of CDI, NDI, and PP. The etiology of DI may be evident at presentation. Polyuria in a non-diabetic patient with breast cancer could be due to metastasis to posterior pituitary or hypercalcemia of malignancy. Metastasis to posterior pituitary is more common than to anterior pituitary as the systemic circulation supplies the posterior pituitary whereas the hypophyseal portal system supplies the anterior pituitary. DI due to craniopharyngioma may present with growth retardation and visual impairment.

Often the etiology is not obvious on presentation and unfolds as investigations progress, for example, infiltrative disorders, tumors, hypercalcemia, hypokalemia in Bartter syndrome, etc.

In most patients with DI, presence of intact thirst mechanism ensures that sodium levels are within normal. However, DI may present with hypernatremia in patients with limited access to water or unable to express thirst, for example, elderly people living alone, patients admitted in intensive care, infants, and in adipsic (impaired thirst) hypernatremia. Typically, patients with DI visiting a physician in out-patient setting complaining of polyuria have normal sodium levels; whereas those in intensive care setting, infants and elderly living alone may have hypernatremia.

Physical Examination

Clinical examination is unremarkable in most cases; however, one should look for wasting (diabetes, malignancy), evidence of glucocorticoid excess, and enlarged kidneys on abdominal palpation. Anthropometric evaluation in a child and confrontation perimetry is to be done when history or physical examination suggests sellar or suprasellar mass. Hypernatremic patients may have irritability, disorientation, unconsciousness, seizures, and focal neurologic deficits.

Investigations

Confirm Polyuria

While evaluating any case of polyuria, one must confirm it by advising patients to maintain a home fluid intake and output record. A 24-hour urine output and creatinine measurements help confirm polyuria and adequacy of urine collection, respectively.

Baseline Investigations

Baseline investigation include plasma glucose, HbA1c, urea, creatinine, complete hemogram, thyroid function tests, sodium, potassium, calcium, potassium, plasma and urine osmolality, urine routine examination including specific gravity (normal 1.010–1.025; low in DI); and other tests as history and physical examination suggest.

Paired Serum and Urine Osmolality

Baseline paired serum and urine osmolality gives valuable information. The hallmark of DI is production of large volume of dilute urine. Urine osmolality less than 300 mOsm/kg with normal, or slightly elevated serum, osmolality suggests DI. To ascertain DI type; confirmatory tests like water deprivation test and hypertonic saline infusion test are required. The water deprivation test is labor intensive and both tests entail some risk in susceptible individuals. Fortunately, the water deprivation and hypertonic saline tests are not indicated in every patient with polyuria.

Polyuria in Hypernatremic Patients

Hypernatremic patients with polyuria, with urine osmolality less than 300 mosmol/kg, have DI and water deprivation test is not required as ADH is already stimulated to maximally concentrate urine. The next step is differentiation between NDI and CDI by evaluating response to desmopressin **(Box 1)**.

Hypernatremic polyuric patients with urine osmolality more than 600 mosmol/kg have solute diuresis; however, mixed osmotic and water diuresis may be present. If on giving hypotonic fluids despite normalization of serum sodium, urine osmolality remains more than 600 msomol/kg, diagnosis is solute diuresis. If on giving hypotonic fluids, urine osmolality falls to 300–600 msomol/kg before sodium comes down to less than 145 mEq/L, diagnosis is mixed osmotic and water diuresis. If on giving hypotonic fluids, urine osmolality falls to less than 300 msomol/kg before sodium comes down

BOX 1 Assessing desmopressin response to differentiate between CDI, NDI, and PP

- Desmopressin is given at a dose of 10 µg by nasal insufflation or 2–4 µg subcutaneously or intravenously. Urine osmolality is measured every 30 minutes for the next 2 hours.
- **Complete NDI:** Urine osmolality rises <15% to a value <300 mOsmol/kg
- **Partial NDI:** Urine osmolality rises 15–45% to a value <300 mOsmol/kg
- **Complete CDI:** Urine osmolality rises >100% to a value >300 mOsmol/kg
- **Partial CDI:** Urine osmolality rises to 15–100% to a value >300 mOsmol/kg
- **Non-diagnostic:** Minimal or no rise in urine osmolality to a value >300 mOsmol/kg. In most cases non-diagnostic results are seen in partial CDI and PP
- **A baseline (without desmopressin) plasma copeptin >21.4 pmol/L suggest NDI**

to less than 145 mEq/L, diagnosis is DI. Desmopressin response will determine DI type **(Box 1)**.

Hypernatremic polyuric patients with urine osmolality 300–600 mosmol/kg may have solute or water diuresis. A total daily osmolar output (urinary osmolality × 24-hour urine output in litres) more than 1,000 mosmol indicates solute diuresis and less than 900 mosmol suggests water diuresis (DI). Desmopressin response will determine the DI type **(Box 1)**.

Polyuria in Normonatremic Patients

Normonatremic patients with urine osmolality more than 600 mosmol/kg have osmotic diuresis. The diagnosis is frequently obvious from history and laboratory investigations.

Normonatremic patients with urine osmolality 300–600 mosmol/kg may have solute diuresis, DI, or PP. A total daily osmolar output more than 1,000 mosmol indicates solute diuresis and lesser suggest water dieresis.

Normonatremic patients with urine osmolality of less than 300 mosmol/kg suggest water diuresis.

Determining the Cause of Water Diuresis in Normonatremic Patients

The next step in water diuresis is to determine the cause namely CDI, NDI, and PP.

If history and investigations suggest NDI, for example, bilateral urinary tract obstruction, hypercalcemia, long-term lithium use, and presenting in infancy with family history of DI; water deprivation test may not be done. A baseline plasma copeptin level or desmopressin response may be directly evaluated to confirm NDI **(Box 1)**.

In other cases of normonatremic polyuria [urine osmolality <300 mosmol/kg (and where NDI is not the obvious etiology) and total daily osmolar output <1,000 mosmol)]; water deprivation or thirsting test is done to raise the serum sodium more than 145 mEq/L and plasma osmolality more than 295 mosmol/kg to stimulate ADH to maximally concentrate urine.

The adequacy of ADH secretion and/or action can be assessed indirectly or directly. In indirect testing, at end water deprivation or hypertonic saline infusion, the urine osmolar response to exogenous AVP or desmopressin is assessed to classify the diuresis as CDI, NDI, and PP. In direct test, direct measurement of AVP or copeptin is done upon osmotic stimulation. Plasma AVP below, above, and at normal is diagnosed as CDI, NDI, and PP, respectively. However, AVP measurement provided a correct diagnosis in only 38% cases and was especially weak in differentiating partial CDI from PP.[2] AVP limitations include its platelets binding, instability in isolated plasma even at –20°C and insensitivity of commercially available assays.[3] Copeptin a 39-amino acid peptide is the C-terminal glycoprotein moiety of AVP prohormone pre-pro-vasopressin. It is cosecreted in equimolar amounts with AVP and neurophysin II. Copeptin is a surrogate marker for AVP secretion because of long half-life, insignificant diurnal variation, and absence of extraction step or pre-analytical procedures for testing.[4]

Water Deprivation Test

Before subjecting patient to the test, moderate fluid restriction for few days re-establishes medullary hypertonicity, which might have been lost (medullary washout) due to excessive water intake in psychogenic causes. This could have led to persistent serum hypoosmolality with wash out of solutes from medulla; hindering ADH mediated water reabsorption.

All fluids are withheld during the test to induce dehydration to stimulate maximal ADH secretion. It is important to ensure patients have no access to drinking water during the test (to avoid surreptitious drinking); avoid cigarette and caffeine in preceding 24 hours; and are free from non-osmotic stimuli for ADH release (e.g., nausea and vomiting). In patients with severe symptoms (e.g., complete forms of DI), few hours of fluid restriction cause sufficient dehydration. Thus, the test can be started in the morning. In mild disorders (e.g., PP), it can take several hours for sufficient dehydration, the test may need to begin the previous night. Duration of fluid deprivation may range 4–18 hours.

At the beginning of test, patient is asked to void urine and initial body weight measured. Hourly monitoring of body weight, serum sodium, urine volume, and urine osmolality is done. The test is terminated when dehydration is sufficient enough determined by body weight reduction of 3%, serum sodium more than 145 mEq/L or no further increase in urine osmolality (three consecutive urine samples with osmolality <30 mOsm/kg variability).[5] At test, termination plasma sodium, osmolality, and AVP/copeptin are measured. The patient is administered AVP or desmopressin and response

assessed. Giving exogenous AVP (or desmopressin) before serum sodium is more than 145 mEq/L cannot distinguish CDI from PP, since in both cases ADH levels are submaximal and will anyway respond to exogenous AVP or desmopressin. Therefore, maximum endogenous ADH secretion should be ensured by increasing serum sodium (>145 mEq/L) and osmolality (>295 mosmol/kg) before response to AVP or desmopressin is assessed.

Hypertonic Saline Infusion Test

Hypertonic saline infusion maybe used in place of water deprivation or may be used to supplement the water deprivation when it is insufficient to raise the serum osmolality to more than 295 mOsmol/kg and serum sodium more than 145 mEq/L (often in primary polydipsia or partial DI). 3% NaCl is infused @ 0.1 mL/kg/minute for 1–2 hours till serum osmolality and sodium are more than 295 mOsm/kg and more than 145 mEq/L, respectively. Hypertonic saline infusion should be avoided in high-risk individuals.

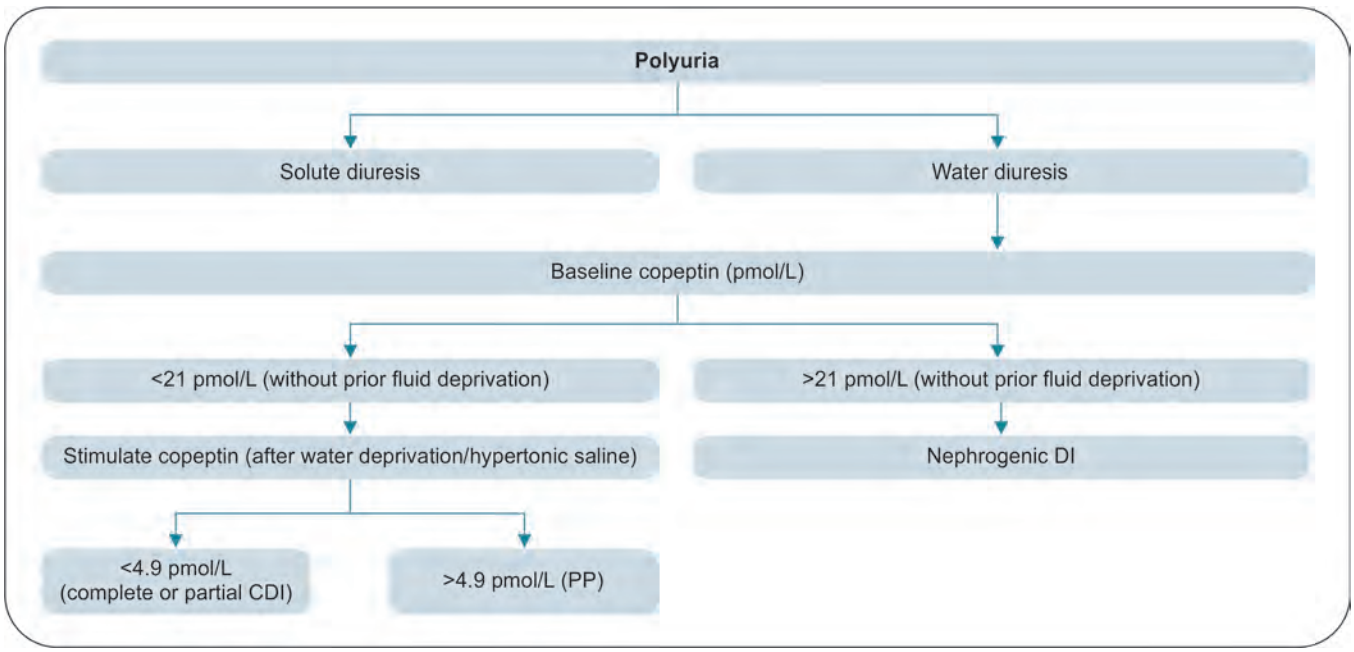
Interpretation[6,7]

- If at the end of water deprivation and/or hypertonic saline infusion test the urine osmolality more than 700 mosmol/kg, diagnosis is PP. If the urine osmolality less than 700 mosmol/kg it can be CDI, NDI, or PP.
- Assess desmopressin response, if urine osmolality of less than 700 mosmol/kg to differentiate CDI, NDI, or PP **(Box 1)**.
- Plasma copeptin more than 4.9 pmol/L at end of the test (when serum sodium was >145 mEq/L) suggests PP and lower value suggests partial CDI.
- Therapeutic trial of desmopressin help differentiates PP from partial CDI. Desmopressin 10 µg/day is given intranasally for 3 days. Patients are advised to limit fluid intake to 1.5–2 liters/day. Thirst and polyuria are assessed; and urine osmolality and plasma sodium measured twice daily. In partial CDI, there is resolution of symptoms of thirst and polyuria; whereas persistent thirst, non-adherence to fluid restriction, and development of hyponatremia suggest PP.

Polyuria in Hyponatremic Patients

Hyponatremia, low urine osmolality (less than half of plasma osmolality) in polyuric patients, suggests water overload due to PP. Hyponatremia, polyuria, and high urine osmolality suggests osmotic (solute) diuresis.

Flowchart 1: A simplified approach to polyuria



A Simplified Approach to Polyuria

Patients with polyuria should initially be classified as solute or water diuresis. In solute diuresis the cause is often obvious from history, physical examination, and baseline investigations. To further classify water diuresis, more tests are needed. Due to limitations of the indirect tests and increasing availability and reliability of copeptin measurements, a simplified approach to water diuresis is suggested **(Flowchart 1)**.[6]

Additional Testing

The polyuria type will determine additional testing. If history, physical examination, and laboratory evaluation suggest osmotic diuresis; the differential diagnosis are narrowed to diabetes mellitus, urea, saline/hypertonic saline, and mannitol. If evaluation suggests partial or central DI, MRI focusing on the hypothalamus and pituitary is required. It may show mass lesions; and loss of posterior pituitary bright spot in CDI. The bright spot results from T1-shortening effects of AVP stored in the neurosecretory granules. In PP the bright spot is usually seen. However, sometimes in NDI the bright spot maybe absent due to prolonged stimulus for vasopressin release. If evaluation suggest NDI; offending drugs, anatomic lesions of kidney and other systemic illness should be looked for. In PP no further testing other than counseling is required.

Conclusion

The diagnosis of polyuria can be challenging and needs to be differentiated from increased urinary frequency. A systematic approach, including detailed history, physical examination, and appropriate laboratory testing, helps in diagnosis in most cases.

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CHAPTER

203 Postgraduate Clinic on Non-Thyroidal Illness Syndrome

Pankaj Kumar Agarwal

Abstract

Abnormalities in thyroid function test in a hospitalized patient are not always carried forward from the past; some do develop during the course of current systemic illness as well. Such abnormalities, where thyroid gland by itself is not at fault, are categorized under the heading, non-thyroidal illness syndrome. The commonest amongst such abnormalities is lowering of serum T3. Sometimes, serum T4 and TSH may also be reduced. These may develop because of alteration in synthesis, transportation, metabolism, or regulation of these hormones at different levels of hypothalamus-pituitary-thyroid axis. Most of these changes gradually return back to normal but the extent of correction and its exact course can't yet been defined very well. Therapeutic interventions in these cases have been found to be largely futile in most cases though T3 supplementation has been shown to be of partial help in some cardiac patients.

Introduction of the Clinical Case

Abnormalities in thyroid hormone tests (TFT) are a frequent finding in patients admitted in ICU or wards because of various systemic illnesses. Many of them have had normal TFT in the past and some are found with normal TFT in follow-up as well. This poses a question upon the genesis of these abnormalities in patients suffering from systemic illnesses. Today, in this Postgraduate Clinic, we will discuss about a similar patient and will try to understand the disorder in a thorough manner.

A 63-year-old female was admitted in near ICU for altered sensorium and right hemiplegia, two days back. Her TFT revealed low serum T3, low normal serum T4 and mid normal serum TSH. Her family members informed that her TFT was absolutely within normal limits, just 2 months back.

Question: Given this scenario, how would you interpret current low T3?

Answer: Normal TFT, and also normal T3, 2 months back suggests that the lady was not carrying any thyroid disorder in the past. Low T3 observed during cerebrovascular event can therefore suggest that it might have been produced by the effect of systemic non-thyroidal illness (NTI) on the thyroid hormones (TH) rather than being produced because of any organic disorder of the thyroid gland itself. Such abnormalities in TFT, which arise after any NTI and are not produced by the disorder of thyroid gland itself, are called non-thyroidal illness syndrome (NTIS). Considering TFT to be normal before and after the NTI, such abnormalities in the past were also known as *sick euthyroid syndrome*. The nomenclature has now been discarded because normalcy cannot be assured in future, always.[1,2]

Question: Name some disorders which can make a person prone for NTIS.

Answer: NTIS can be observed in as high as 70% patients admitted in the ICU.[3] Some common disorders associated with NTIS are as follows:

- *Severe critical illnesses*: Such as pneumonia, septicemia, MI, CHF, respiratory failure, IBD, cirrhosis, CRF, DKA, and malignancies.
- *Trauma and major surgeries:* Such as CABG
- *Deprivation of calories:* Such as starvation and anorexia nervosa[4]

Question: Does NTIS affect serum T3 only or it has any other clinical characteristics as well?
Answer: Clinical characteristics observed in NTIS are actually that of NTI and not because of abnormalities in TFT. Even total deficiency of TH may take as long as 2–3 weeks in producing its effects. So, even with the given abnormality of TFT, most patients appear to be clinically euthyroid. In the absence of any discernible clinical finding specific for the thryoid, NTIS is classified according to its laboratory characteristics only.

Low T3 syndrome—This is the commonest presentation of NTIS, which is seen in nearly 70% (40–100%) cases. It is often associated with elevated serum reverse T3 levels. Serum T4 and TSH levels are usually normal in the beginning.[3-5]

Low T4 syndrome—With the progression of systemic illness, serum T4 level also starts declining along with serum T3.[1]

Low TSH—Acute incident events such as major trauma, MI, or surgery are immediately associated with transient TSH elevation but progression of systemic illness may lead to fall in serum TSH levels in nearly 10% of such cases.[1]

Question: What could be the pathophysiology of abnormalities in TFTs in NTIS?
Answer: NTI may affect every aspect of TH including its secretion, peripheral metabolism, and action.

Low T3 syndrome (downregulation of T3 content in target tissues)—Low serum T3 is the initial feature of NTIS, which is associated with fall in tissue T3 concentration and its effects. It can be produced because of following factors.

Inhibition of conversion of T4 into T3—Approximately 80% of circulatory T3 is derived from the deionization of T4 by 5'-deiodinase type 1 (D1). NTIS leads to downregulation of D1 leading to reduced T4 to T3 conversion and therefore low serum T3.[6]

Inactivation of T3 and production of reverse T3—Another enzyme, 5'-deiodinase type 3 (D3), converts T4 into reverse T3. This is upregulated in NTIS leading to increased synthesis of reverse T3. In addition to converting T4 into T3, D1 is also responsible for metabolism of reverse T3. Downregulation of D1 in NTIS reduces its metabolism as well which is the main reason behind rise in reverse T3 in NTIS.[7] T4 metabolism in NTIS, thus is diverted toward the formation of bio-inactive reverse T3 in place of bioactive T3.

Inhibition of TH uptake into the cell and binding of T3 with its nuclear receptor—Numerous cytokines can be produced during systemic illnesses such as IFN-gamma and Nonesterified fatty acids (NEFA). These may interfere with the entry of TH into the target cell and their interaction with TH receptor. It creates a situation of tissue hypothyroidism in NTIS.[8]

Low T4 syndrome (downregulation of T4 content in circulation)—Fall in serum T4 is an indicator of rising severity of NTIS. This can be produced because of two main reasons.

Increased metabolism of T4—Systemic illnesses are often associated with fall in tissue perfusion. This may be associated with expression of D3 which converts T4 into reverse T3.[7] This leads to rise in serum reverse T3 level and fall in serum T4 level.

Inhibition of binding of T4 to TH binding proteins—Not only the metabolism, but the circulatory transportation of T4 is also affected in NTIS. As an acute phase reactant, serum albumin concentration falls in any acute illness. NEFA, which is otherwise bound to this albumin; therefore, increases in circulation. It displaces TH from TBG, which leads to fall in total T4 (and total T3) concentrations.[5] Free T4 and T3 hormone concentrations largely remain unaffected.[8,9]

Low TSH (central downregulation of hypothalamic TRH and pituitary TSH release)—NTIS may be associated with reduction in sensitivity of thyrotrophs toward TRH leading to fall in TSH secretion. This too may arise out of two reasons.

Cytokines induced direct suppression of TSH—Cytokines, especially interleukins (mainly IL6), tumor necrosis factor (TNF alpha) and interferons (IFN beta), can directly suppress thyrotrophs to reduce TSH secretion.[5]

Reduced stimulation of TSH secretion—Thyrotrophs possesses a different set of enzyme, deiodinase type 2 (D2), which converts intra-pituitary T4 into T3. T3 thus produced within the thyrotrophs is responsible for negative feedback and suppression of TSH secretion. This D2 is up regulated in NTIS, leading to rise in intra-pituittary T3 and suppression of TSH secretion.[6] NTIS,

thus is associated with exactly opposite effects on tissue T3 concentrations. Tissue T3 concentration falls in peripheral tissues but rises in thyrotrophs.

Reduced T3 concentration in target tissues and its reduced binding with TH receptors favors the hypothesis that NTIS is not merely an adaptive response to the systemic illness but is an actual state of "tissue hypothyroidism." Initial changes could be the compensatory responses toward a systemic illness but prolongation of this adaptation definitely becomes harmful in the long term.[8]

Question: What are the differential diagnoses for various abnormalities found in TFT in NTIS?
Answer: In fact, abnormalities in TFT, seen in NTIS, may mimic any organic disorder of the thyroid gland.

Low or low normal serum T3, T4, and elevated serum TSH level, sometimes found in the initial course of the disease may mimic Hashimoto thyroiditis and subclinical or overt hypothyroidism.

Midnormal or low normal serum T3, T4, and low TSH level, often seen in advanced NTIS may mimic subclinical thyrotoxicosis or central hypothyroidism.

NTIS may not only produce new changes in TFT, which may mimic organic disorders of thyroid gland, but may also interfere with the detection of its preexisting organic disorders as well. Chronic severe NTIS and use of dopamine or glucocorticoid therapy may lead to marked suppression of TSH secretion. This may interfere with the diagnosis of untreated or partially treated thyroprivic hypothyroidism. Similarly, low serum T3 in NTIS will change the reflection of T3+T4 thyrotoxicosis into T4 toxicosis alone.[1,8]

Raised serum T3, low serum reverse T3, markedly disturbed serum TSH (>20 mIU/L or <0.1 mIU/L) and presence of antithyroid antibodies may be the indicators of organic thyroid disorders along with systemic illnesses.[5,8]

Above mentioned facts preclude the policy of routine screening of critically ill patients for thyroid dysfunctions. In fact, during any critical systemic illness, only those patients should be screened for thyroid dysfunctions in whom there is a high degree of clinical suspicion of any organic disorder of thyroid gland.

Question: Does NTIS carry any prognostic significance as well?
Answer: Serum T3 levels have been found to be inversely proportional to the severity of NTI. Low serum T3 levels observed during coronary angiography are not only associated with significant morbidities but have been found to carry 1.8× higher risk of total mortality and 2.5× higher risk of cardiac mortality as well.[10]

Low T4 level with NTI actually points toward a much grave prognosis. Serum T4 <4 mcg/dL may increase mortality by 50% and level <2 mcg/dL may increase it up to 80%.[1,5,8,10-13]

Question: If low T3, T4, and TSH are so clearly linked with poorer clinical outcomes then should these patients be offered TH supplementation?
Answer: NTIS was earlier thought to be just compensatory adaptation of acute systemic illnesses only but the view is gradually changing. Now we know that this adaptation is not always beneficial for the patient. Many clinical studies have been performed in recent past to look for the effects of TH supplementation in such cases.

Intravenous T4 therapy—Intravenous T4 therapy (1.5 mcg/kg/d IV) has been tried in some critically ill patients with low serum T4 concentration. Contrary to the presumptions, it could not reduce total mortality rate.[14,15] Inability to normalize serum T3 level was opined to be the reason for its inefficacy.[8]

T3 Therapy—In an attempt to normalize serum T3 levels, T3 supplementation was also tried but this too could not reduce mortality.[16]

Till date, clinical benefits of TH supplementation have been observed in cardiac patients only.[17] Its hypothesized that IV T3 supplementation should at least be tried in patients with NTIS in whom serum T4 level is less than 4 mcg/dL. With clinical recovery in NTI, it can be switched to oral T4 supplementation.[8]

TRH therapy—Knowing that the hypothalamo-pituitary set point is low in patients with NTIS, TRH therapy has also been tried in it. It could successfully normalize serum TSH, T4, T3, and reverse T3 levels. Considering the catabolic state of these ill patients, addition of growth hormone to TRH has been found to be more effective in raising anabolic activities in these patients.[13,18]

Conclusion

It can clearly be understood that systemic illnesses can affect TFT in variety of manners. Many of these affections have been recognized well and there pathogenesis have also been deciphered up to some extent. Yet, there are still many unseen facets of this disorder which are restricting us from offering any meaningful therapy to our patients.

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CHAPTER

204 Common Mistakes in Thyroid Disorders

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Abstract

The knowledge on practical management of thyroid disorders with precision is ever expanding as a huge number of cases are detected because of easy availability of investigation facility. However, all the cases with abnormal results of thyroid function do not require treatment immediately, or nor ever. In this chapter, brief analysis of relevant investigation and modalities of treatment on such entities of thyroid disorders is presented.

Introduction

For long time, the diagnosis of hypothyroidism was only clinical. It used to be suspected only after manifestation of myxedema (spotters in undergraduate examination) and hyperthyroidism on development of features of Graves or hypermetabolic state. Later indirect tests like effective thyroxine ratio was available, but not within reach. Hence, clinical parameters were only the guidance to manage the cases until availability of triiodo thyroxine (T3), tetraiodo thyroxine (T4), and thyroid stimulating hormone (TSH).[1]

Ever since direct hormone assay (T3, T4, TSH) is widely available for past three decades, there is great leap in detection of number of thyroid disorders and management precision. In the last decade, diagnosis of thyroid disorders clinically has become a rarity and physician is encountered with abnormal reports of thyroid function tests for opinion. This is because the thyroid function tests are done as routine in non-thyroid illness and sometimes on self motivation. Potentially misleading reports may result in mistakes of management. In such a scenario, physician is expected to guide the patient for further appropriate investigations, final diagnosis, plan of long-term treatment, and management. This article focuses on discussed issues of thyroid functional disorders to guide the physician approach.

Common Mistakes

- Proceeding further without recheck of the laboratory results
- Not ordering further investigations
- Starting on medicines on certain thyroid disorders, which spontaneously remit
- Use and abuse of iodine
- Under utilization of radioisotope scanning of thyroid
- Hurry to start on medicines in subclinical hypo- and hyperthyroidism
- Monitoring of treatment of hyperthyroidism by TSH levels
- Selection of modalities of treatment (anti-thyroid drugs, radioiodine ablation, surgery) in hyperthyroidism
- Pregnancy versus thyroid disorders
- Diet restriction

Common Abnormalities in Thyroid Function Test (TFT)

- Increased TSH, normal/abnormal T3, T4
- Decreased TSH, normal/abnormal T3, T4
- Goiter or swelling of thyroid with normal TSH, T3, T4

Further investigations:

- Confirm the abnormality by repeating first line investigation TFT, since the treatment is prolonged and/or destructive
- Estimation of thyroid antibodies
  - Thyroid peroxidase antibodies (TPO)
  - Thyroglobulin antibodies (Tg-Ab)
  - TSH receptor antibodies (Tr-Ab), assay form of thyroid receptor stimulating immunoglobulin (TSI) used to predict neonatal thyrotoxicosis[2]

The above antibodies tests are neither 100% sensitive nor specific.[2,3] TPO assay is commonly done to assess the immune status of the disease, rest of the tests are not routinely done and expensive. TPO and Tg-Ab present in normal population, auto immune hypothyroidism, Grave's disease, multinodular goiter (MNG), transient thyroiditis. Where as Tr-b is absent in normal population, MNG, transient thyroiditis, and present in Grave, autoimmune hypothyroidism. Goiter and TPO-Ab are absent in secondary hypothyroidism.

- Ultrasound neck—It is done to know the size of thyroid, nodules in the thyroid gland, and for the presence of increased vascularity seen in Grave's disease.
- Fine needle aspiration cytology (FNAC) usually ultrasound guided is done to differentiate benign and malignant lesions and also to note lymphocytic infiltration suggestive of autoimmune thyroiditis.
- Radioisotope scanning of thyroid—It is very specific investigation in differentiation of hyperthyroidism etiologically. Transient thyroiditis like sub-acute, viral, postpartum thyroiditis shows low uptake of tracer because of follicular damage. In Grave's disease, gland is enlarged with homogenous increased uptake of tracer. Toxic adenoma shows focal areas of increased uptake of tracer and suppressed uptake in the remainder of the gland. Toxic multi-nodular gland is enlarged with increased and decreased uptake of tracer. Cold nodule (absence of uptake of tracer) suggestive of neoplastic lesion.[2]

Disorders with Increased TSH, Normal/Abnormal T3, and T4

- Hashimoto's/autoimmune thyroiditis, atrophic thyroiditis (end stage). It can present as hyper/hypothyroidism/normal. Investigations—TPO antibodies positive, Ultrasound, FNAC-lymphocytic infiltration suggestive of autoimmune thyroiditis.
- Iodine deficiency/endemic goiter—Not seen nowadays, diagnosed epidemiologically. Urine iodine levels are less than 50 ng/L. Treat by iodine supplementation. Iodine has complex effects on thyroid. Chronic administration of iodine causes hypothyroidism due to increased iodine content in thyroid. Paradoxically it can also precipitate thyrotoxicosis.[2,3] Hence, there is hardly any necessity to recommend iodine for healthy persons.
- Goitrogens—Intake of cassava root, cabbage, cauliflower—due to presence of thiocyanate, causes hypothyroidism, diagnosed epidemiologically.[3] Treat by thyroxine supplementation. There is no evidence based study to recommend routine restriction of cabbage, cauliflower, in all cases of hypothyroidism.
- Miscallaneous causes are—Iaotrogenic, infiltrative disorders like amyloidosis, sarcoidosis.

Disorders with Low/Undetectable TSH, Normal/Abnormal T3, and T4

- Subacute thyroiditis/De quervain's—due to viral etiology. There is release of stored hormones due to inflammation.[3] Spontaneous remission in 6 weeks. If thyroid antibodies are positive, suggests risk of ultimate progression to hypothyroidism. When prolonged abnormal levels of TFT, isotope scan—a low uptake confirms transient thyroiditis. Symptomatic treatment with NSAID/prednisolone.
- Silent/postpartum thyroiditis—Presence of TPO antibodies follow for autoimmune thyroiditis. Isotope scanning—negligible uptake. No role for glucocorticoids. Recovery is rule. Sometimes, pregnancy may be masking autoimmune thyroiditis. No role for anti-thyroid drugs. Symptomatic treatment with propranolol.[3]
- Grave's disease—Autoimmune disorder. Monitoring for life long. Ultrasound—increased vascularity. Thyroid antibodies—TPO, Tr-Ab, Tg-Ab all are positive.

Isotope scanning—homogenous and diffuse high uptake confirms the diagnosis. Ideal management by anti-thyroid drugs, sometimes with remission after 12–18 months of treatment.[2-4]

- Toxic adenoma/solitary nodule—Ultrasound and FNAC to confirm the nodule. Isotope scan is the choice of investigation—focal uptake with hyper-functioning nodule and diminished uptake in the rest of the gland. Treatment of choice is radioiodine ablation.[2,4]
- Toxic multinodular goiter—Ultrasound and FNAC, isotope scanning ideal investigation—heterogenous uptake with multiple regions of increased and decreased uptake of tracer. Radioiodine ablation is the treatment of choice. Alternate treatment is surgical if compressive symptoms are present.

Goiter or Swelling of Thyroid with Normal TSH, T3, and T4

- Simple goiter—unknown stimulus[2]
- Juvenile goiter—teenagers[3]
- Non-toxic adenoma
- Non-toxic multinodular goiter

If ultrasound, FNAC, and thyroid antibodies are negative, these conditions require follow-up with monitoring of TFT periodically. No medical treatment is necessary. Surgical treatment if compressive signs develop.

Sick Euthyroidism or Non-thyroid Illness or Low T3 Syndrome

Thyroid gland is normal, Abnormal TFT (Low T3, Low or normal T4, Low or normal TSH) due to acute systemic illness, causing failure of peripheral conversation of T4 to T3. Needs to be re-evaluated after recovery from acute illness for thyroid disorder.[3]

Subclinical Thyroid Disease

Subclinical hypothyroidism with high TSH, normal T3, T4, and Subclinical hyperthyroidism with low TSH, normal T3, and T4 are milder forms of the disease. No universally accepted guidelines for treatment and case to be managed depending on symptoms, age, and comorbidities. Excessive treatment to be avoided.[3,5]

Monitoring of Therapy

Treatment of hypothyroidism is monitored based on the levels of TSH. Treatment of hyperthyroidism is monitored based on the levels of T4, since TSH levels take longer time to reach normal.

Pregnancy—Thyroid Disorders

There is altered metabolism of thyroid hormones and thyroid–pituitary axis stability. Hence trimester specific normal ranges of TSH, T3, and T4, to be followed.[2,6]

Case Reports—Author's Own Experience

Case 1

- Female 35 years; Engineer in Govt. Service
- Incidental finding of low TSH, high T4, and normal T3
- Ultra sound neck FNAC—Cystic colloid nodule
- One month later—Persistent low TSH, TPO positive
- Isotope scanning of thyroid showed normal uptake of tracer. Not started on any treatment because of normal uptake of tracer. Two months later repeat TFT showed raised TSH—26.02 μIU/mL.
- Started on thyroxine. What started as hyperthyroidism turned to be autoimmune hypothyroidism over a period of 2 months.

Case 2

- Male 40 years general check-up before leaving for Gulf. Decrease TSH and increased T4 and T3.
- Ultrasound neck diffuse enlargement of both lobes, increased vascularity. FNAC suggestive of autoimmune thyroid. TPO positive. Isotope scanning—intense homogenous uptake of tracer 11.28% (normal is 0.5–4%).
- Diagnosis—Graves disease under management with antithyroid drugs.

Case 3

- Male 58 years presented with increased appetite, palpitations, tremors.
- Decreased TSH and increased T4 and T3.
- Ultrasound small colloid cyst left lobe of thyroid. Isotope scanning—diffuse increased tracer uptake—28.1%. Diagnosis Graves disease.
- Clinically this case suggestive of hyperthyroidism, ultrasound showed colloid cyst but isotope scanning is in favor of Graves disease. For the above three cases of hyperthyroidism isotope scanning is the clinching investigation.

Conclusion

It is obvious TFT reports suggestive of hypothyroidism irrespective of etiology, the treatment is thyroxine replacement except in iodine deficiency hypothyroidism. Whereas TFT reports suggestive of hyperthyroidism, the treatment differs.

Transient thyroiditis—No treatment, spontaneous recovery mostly.

Grave's disease—Antithyroid drugs or Radioiodine ablation.

Toxic adenoma/solitary nodule and Toxic multinodular goiter—Radioiodine ablation is the treatment of choice. To differentiate above disorders of hyperthyroidism, isotope scan is the investigation of choice.

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CHAPTER

205 Glucocorticoids-induced Osteoporosis

Saurabh Jain

Abstract

Prolonged use of Glucocorticoids is associated with several adverse effects including Osteoporosis. High daily dose of GC (>7.5 mg), cumulative dose >5 gm both lead to increased risk of fractures. Vertebral fractures are most common. Often asymptomatic, these are found as incidental findings on routine chest X-rays. The fracture risk assessment tool – FRAX considers several risk factors for osteoporosis (including GC use) with the bone mineral density and gives us an estimate of the 10-year risk of major osteoporotic fracture and hip fracture in patients who are more than 40 years old. Prevention of GC-induced fractures requires identifying the high risk patient, and initiating them on preventive strategies like weight-bearing exercises, maintenance of normal weight, smoking cessation, and limitation of alcohol consumption. Bisphosphonates are considered as first-line agents for the management of Glucocorticoid induced osteoporosis. Treatment with an anabolic agent such as teriparatide or abaloparatide and Denosumab (human IgG2 monoclonal antibody specific to RANKL) should be followed by an antiresorptive agent. Patients experiencing treatment failure or having contraindications to conventional medications are considered of third line agents like raloxifene or with calcitonin. Raloxifene (a selective estrogen-receptor modulator) is approved by the FDA for the prevention and treatment of GC-induced osteoporosis in postmenopausal women. Pharmacologic treatment to prevent fractures are not recommended in pregnant ladies.

Introduction

Glucocorticoids (GC) are used in many inflammatory and autoimmune conditions. While being used to treat an underlying disease, GC are associated with appreciable risk of bone loss and increase the risk of fractures, which is actually more pronounced during the initial few months of use.

Epidemiology

The association of GC and osteoporosis was first described 80 years ago. The US data suggests that approximately 3% of adults older than 50 years and almost 1% of all adults receive GC either for allergic conditions or various inflammatory or neoplastic conditions.[1] GC use over long term is associated with various adverse effects. Amongst them fracture is the most common preventable side effect which is often serious.[2-4] Increase in the dose and duration of GC increases the risk of fracture.[5-7]

Risk Factors for Fractures

Related to Glucocorticoid Use

- High daily dose of GC (e.g., >7.5 mg of prednisone daily)
- Cumulative dose of GC >5 g
- Current or recent (<3 month) use of GC
- GC-associated myopathy (increases the risk of falls)
- GC-induced hypogonadism

Related to Underlying Condition

Rheumatoid arthritis, ankylosing spondylitis, etc. are independent risk factors.

Related to Risk of Osteoporosis

Advance age; white race; female sex; menopause; smoking; alcohol use (>2 units per day); bone mineral density T-score less than –1.5; previous fracture.

Vertebral fractures are the most common GC induced fractures and are often asymptomatic. These are diagnosed as incidental finding on chest or abdominal radiograph. In patients who have asymptomatic vertebral fracture there is often no history of preceding trauma. The typical symptomatic patient presents with acute back pain after sudden bending, coughing, or lifting. The risk of vertebral fracture increases within 3 months of starting the treatment and is maximum at 12 months.[7,8]

Studies, having a follow-up of 6 months to 10 years, have shown that with high dose of GC, risk of vertebral fractures is increased significantly. But, high doses if used intermittently (total cumulative dose of ≤1 g) had less fracture risk.[8] High-dose inhaled GC (dose equivalent to ≥1 mg fluticasone) when used for more than 4 years showed a marginal increase in the risk of fracture.[9]

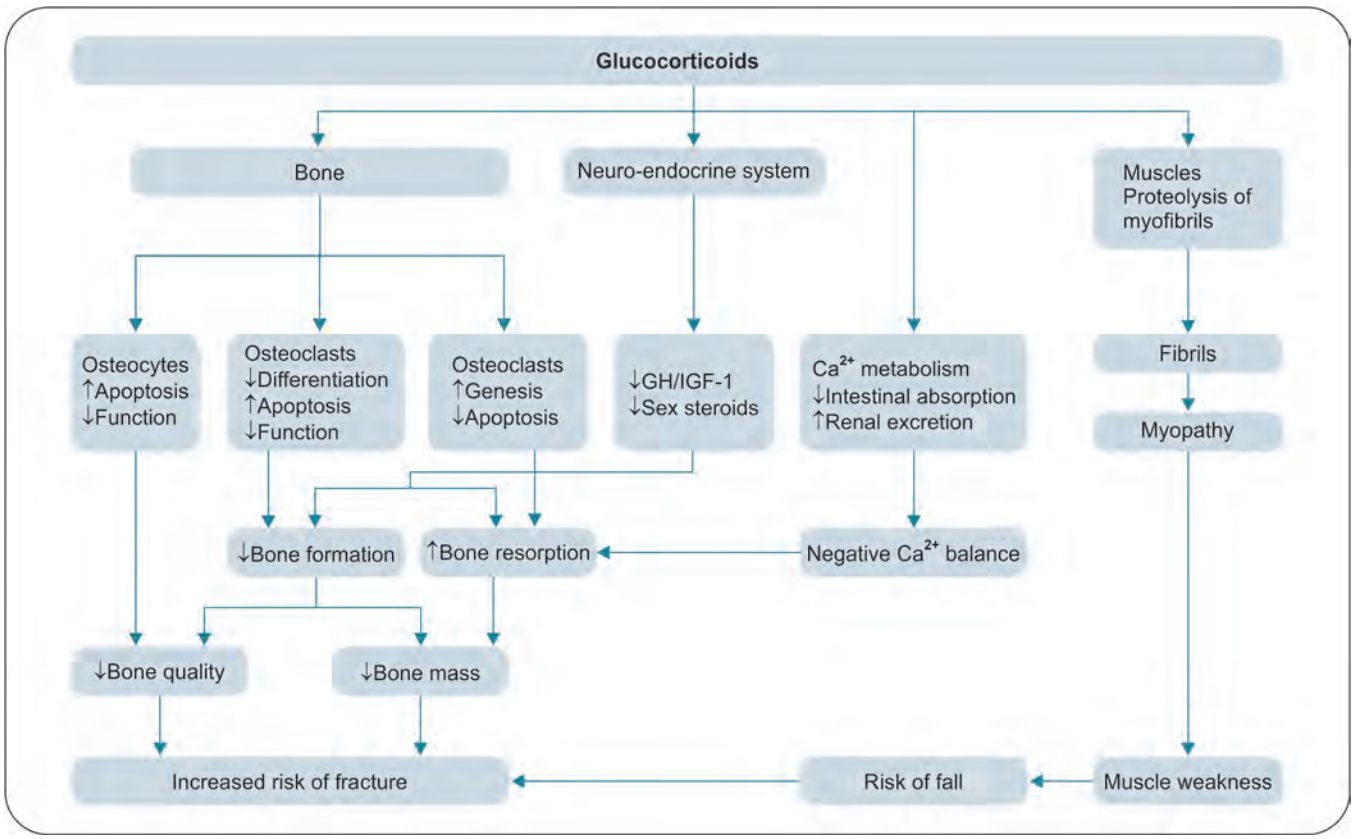
Also worth remembering is that GC can cause avascular necrosis.

Pathophysiology (Flowchart 1)

Specifically related to bone, GC receptors are found on all cells except osteoclast. GC use sends negative feedback effect on the hypothalamus and pituitary gland. It acts as an exogenous cortisol, so elevated GC levels reduce the secretion of ACTH, along with FSH and LH. Reduction in ACTH results in reduced endogenous steroid hormone production from the adrenal glands including cortisol and androgens.

Low FSH and LH reduce production of androgens and estrogen from the gonads. Low androgens and estrogens increase the risk of osteoporosis.

Flowchart 1: Pathophysiology of glucocorticoid-induced osteoporosis



Bones contain three main types of cells. Osteocytes—the mature bone cells formed by osteoblasts, Osteoblasts—the bone building cells, and Osteoclasts—bone eating cells. And in our case, immature osteoclast termed pre-osteoclasts. GC stimulates osteocyte apoptosis, with long-term use. The predominant effect of GC on the skeleton is actually reduction in bone formation. The decline in bone formation is mediated by direct inhibition of osteoblast proliferation and differentiation, and by an increase in the apoptotic rate of mature osteoblasts and osteocytes. High GC levels stimulate RANKL synthesis by osteoblasts thus supporting osteoclast differentiation and net bone resorption. In normal condition there is this molecule called osteoprotegerin, which regulates this osteoblast-osteoclast interaction, by binding to the RANKL and preventing osteoclast stimulation. However, GC increases osteoclastic activity by suppressing synthesis of osteoprotegerin and also by increasing production of RANKL, which is required for osteoclastogenesis. So RANKL binds onto osteoclasts stimulating osteoclastic activity, it becomes active osteoclast, which will breakdown bone minerals and this is termed bone resumption. In addition GC increases bone resorption by decreasing secretion of androgens and estrogens. The net bone resorption by osteoclast reduces bone mineral density and bone remodeling, thereby increasing the risk of fractures. Bone resorption leads to an increase in serum calcium and phosphate levels due to the breakdown of bone minerals. Now when you have a high serum calcium the body does not want to keep it. High serum calcium reduces intestinal absorption of calcium and also increases urinary calcium excretion because you want to get rid of all the calcium in your body, now this will cause hypocalcemia. Hypocalcemia stimulates the parathyroid gland to release parathyroid hormone. Parathyroid hormone works by binding onto parathyroid hormone receptors on osteoblasts, which stimulates expression of RANKL, which will further promote osteoclastgenesis and so increase bone resorption further. Indirect GC effects that also predispose patients to an increased risk of fractures include reduced muscle mass and weakness, both leading to an increase in the risk of fall.

After discontinuation of GC treatment, the risk of fracture also downtrends. It was also reaffirmed in a prospective study where within 6 months after discontinuation of GC, lumbar spine showed significant recovery in bone mineral density.[10]

Clinical Evaluation

The fracture risk assessment tool—FRAX considers several risk factors for osteoporosis (including GC use) with the bone mineral density and gives us an estimate of the 10-year risk of major osteoporotic fracture and hip fracture in patients who are more than 40 years old.[11]

One of the limitation of the FRAX score calculation is that it uses bone mineral density at the hip joint, which can give false values as GC have the greatest detrimental effect on the vertebrae. Also in patients, receiving very high doses of prednisone may underestimate the risk of fracture.

Treatment

Prevention of GC-induced fractures requires identifying the high-risk patient, and initiating them on preventive strategies.

Nonpharmacologic Options

- Weight-bearing exercise
- Maintenance of normal weight
- Smoking cessation
- Limitation of alcohol consumption
- Assessment and management of fall risks
- Minimizing GC use

Calcium and Vitamin D

Because GC increases the excretion of urinary calcium, dietary intake of calcium (1,000 mg per day) and vitamin D (600–800 IU) is commonly suggested to patients receiving GC.

A Cochrane meta-analysis suggested that the bone mineral density at the lumbar spine was significantly better in patients receiving calcium and vitamin D supplementation in comparison with the placebo group.[12]

Pharmacologic Treatment

Bisphosphonates

Multiple randomized trials have suggested that in patients receiving GC, the use of bisphosphonates is associated with an increase in the bone mineral density.[13] A 2016 Cochrane review involving 12 RCTs showed that in the group receiving bisphosphonates the risk of new vertebral fractures was lower by 43% in comparison to those who received either calcium or vitamin D, or both. In patients

receiving bisphosphonate treatment over a period of 3–5 years, there was less incidence of serious adverse events (like osteonecrosis of the jaw and atypical femoral fractures).[14] Due to their good safety profile and affordable cost, oral bisphosphonates are recommended as first-line agents to prevent GC induced fractures unless they are contraindicated or have undesirable adverse effects.

Patients who are not able to tolerate the oral formulation, or who for some reasons are not adherent to oral bisphosphonate regime, are offered intravenous bisphosphonates.

Other Recommended Agents

Teriparatide and abaloparatide are anabolic molecules and increases bone formation.[15] In a study of 428 patients on GC, receiving either teriparatide or alendronate were followed for 36 months. Patients receiving teriparatide showed better improvement in bone mineral density at the spine, than alendronate. They also had lesser rate of radiographic vertebral fractures. However, no significant difference was noted in the rates of nonvertebral fracture in the two groups.[16] In the teriparatide group, 21% of patients had hypercalcemia, as compared to 7% in the alendronate group. In a smaller study, effects of teriparatide and risedronate were noted on middle-aged men receiving GC. Teriparatide group showed higher bone mineral density and lower rate of fractures.[17] However, after discontinuation of teriparatide, bone loss and fractures occurred at a rapid rate. Hence, after discontinuation of teriparatide, it is prudent to initiate an antiresorptive agent such as bisphosphonate or denosumab. In severe osteoporosis where bone mineral density T score is less than –2.5 in patients with a past history of fracture, initial treatment with an anabolic agent such as teriparatide or abaloparatide should be followed by an antiresorptive agent.

Denosumab is human IgG2 monoclonal antibody specific to RANKL. By binding to RANKL, it suppresses the development of osteoclasts. In a trial involving patients on GC, denosumab was compared with risedronate. Denosumab group showed superiority with respect to increase in spinal bone mineral density at 12 months and noninferiority in terms of rates of fracture.[18] Few studies have reported higher risk of infection with denosumab in comparison to bisphosphonates which may be attributed to its immunomodulatory effects.[19] Hence in patients on immunosuppressive medicines or biologicals, denosumab is generally not recommended. Denosumab, in dosages that is used to treat osteoporosis, is associated with minimal risk of osteonecrosis of the jaw and atypical fractures.[13] However, similar to anabolic agents, after its discontinuation there is a rapid increase in the rates of vertebral fracture, especially in patients with a previous history of vertebral fracture. Here also an alternative antiresorptive therapy should be initiated after its discontinuation.[19]

Third-line Agents

Patients experiencing treatment failure or having contraindications to conventional medications are considered of third-line agents like raloxifene or with calcitonin. Raloxifene (a selective estrogen-receptor modulator) is approved by the FDA for the prevention and treatment of GC-induced osteoporosis in postmenopausal women. A study done in postmenopausal women receiving GC showed that raloxifene significantly increased absolute bone mineral density at the lumbar spine by 1.3%, in comparison to Calcium and Vit D supplementation.[20] However, no difference in bone mineral density was noted at the femoral neck between the treatment groups. Studies have shown that raloxifene use is associated with decreased risk of estrogen-receptor–positive breast cancer;[21] however, it can cause serious complications like venous thromboembolism, and fatal stroke.[22]

Calcitonin-Salmon is a man-made form of the hormone. A meta-analysis of nine trials with 500 patients on GC, compared the effects of calcitonin with calcium and Vit D supplementation, concluded that calcitonin improved the bone mineral density at the lumbar spine (but not hip); however, there was no difference in the risk of vertebral fracture in both the groups.[23] Calcitonin is available as injectables which can be administered subcutaneously and also as a nasal spray. Hypocalcemia and Vit D deficiency must be corrected before initiating the treatment. In clinical trials among calcitonin treated patients, overall incidence of malignancies are reported to be higher in comparison with placebo.

Treatment in Women of Childbearing Age

Pharmacologic treatment to prevent fractures is not recommended in pregnant ladies. A summary of case study involving 65 women receiving bisphosphonate

before or in the first trimester of pregnancy showed no clinically significant adverse effects in the fetus.[24] However, there is a reluctance to treat women in child bearing age with bisphosphonates as it may cause long-term retention of these agents in bone and may have affect on the fetal skeleton later when these ladies conceive. If treatment has to be offered owing to their risks, agents having a shorter half-life and lesser retention in bone are generally recommended such as risedronate and teriparatide. Animal's studies have shown that denosumab has teratogenic effects and should be used with caution in women of childbearing age.[25]

Guidelines/Recommendations

The 2017 Guidelines of the American College of Rheumatology[26] recommend the following:

Which patient requires intervention?

- All adults taking ≥2.5 mg of prednisone daily for >3 months

Whom to test and monitor for changes in BMD?

- All adults ≥40 years of age and adults <40 years with a history of fragility fracture or other risk factors;
- Test within 6 months after initiation of GC;
- Repeat testing every 2–3 years and every 1–3 years in adults ≥40 years receiving GC without treatment for osteoporosis.

Correction used with the FRAX tool to adjust risk estimate for prednisone dose >7.5 mg:

- Risk of major osteoporotic fracture is increased by 15% and risk of hip fracture is increased by 20%

Calcium and Vit D supplementation:

- 800–1,000 mg of calcium daily and 600–800 IU of vitamin D daily

Threshold for pharmacologic treatment:

- All adults with a previous fragility fracture
- Adults ≥40 years with BMD T score of –2.5 or less or FRAX risk ≥20% for major osteoporotic fracture or ≥3% for hip fracture
- Consider in adults ≥40 years with FRAX risk 10–19% for major osteoporotic fracture or >1–2.9% for hip fracture
- Adults <40 years with BMD T score below –3 and >7.5 mg of prednisone daily
- Adults with >10%/year bone loss at hip or spine
- Adults ≥30 years taking very-high-dose GC (≥30 mg daily)
- High cumulative use (>5 g in 1 year)

Pharmacologic interventions:

- First-line therapy: oral bisphosphonates
- Second-line therapies (in order of preference): intravenous bisphosphonates, teriparatide, denosumab, raloxifene (only in postmenopausal women when other listed second-line medications are not appropriate)

Duration of pharmacologic intervention:

- If continuing to receive GC >5 years, continue treatment if having moderate to high risk
- If GC is discontinued before 5 years, continue treatment for osteoporosis for 5 years if moderate to high risk
- Discontinue treatment for osteoporosis when GC are discontinued if low risk.

Conclusion

Long-term use of Glucocorticoids is known to cause many adverse effects and it is essential to identify the high risk individuals. After lifestyle change and correction of calcium and vitamin D, initiation of appropriate anti-resorptive medicines can prevent long-term debilitation and morbidity associated with osteoporosis.

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Section 16

Section Editor: G Narsimulu

Rheumatology and CTD

CHAPTER

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Refractory Rheumatoid Arthritis

Rohini Handa

Abstract

A sizeable number of patients with rheumatoid arthritis (RA) are unable to attain low disease activity or remission despite treatment. These difficult to treat (D2T) patients are labeled as refractory RA. The troika of D2T RA, as outlined by the European League against Rheumatism, comprises of treatment failure history, presence of active/symptomatic disease, and clinical perception. The approach to refractory RA is evolving.

Introduction

Rheumatoid arthritis (RA) is the commonest inflammatory polyarthritis seen in clinical practice. Current management paradigms use a "treat to target" stratagem to achieve tight disease control. The conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) led by methotrexate form the initial treatment. A better understanding of the disease, pathobiology has led to the development of several targeted treatments, which are broadly divided into two categories: biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Despite tremendous advances in disease assessment, and an ever expanding treatment armamentarium, a significant proportion of patients are unable to achieve optimal disease control. This group of "refractory" patients poses a challenge to the immunologists from a mechanistic angle, to rheumatologists from the perspective of disease definition, and to all clinicians from a treatment viewpoint. This chapter outlines the approach to refractory RA from a clinical standpoint.

Definition of Refractory RA

The definition of refractory RA is imprecise as different authors, in absence of a consensus, have defined it differently. The analogy that I often use is "pyrexia or fever of unknown origin" (PUO/FUO) that was initially defined as a condition in which the core body temperature is >38.3°C for a period of three weeks or more, with no diagnosis reached after 1 week of "*inpatient investigation*." The quantum and extent of investigations were not spelt out. Also, modern day health care has moved away from hospitalization for investigations. The revised definition of PUO-"persistent fever that remains undiagnosed despite 1 week of hospital evaluation or three outpatient visits" also suffers from lack of specificity. Much in the same way, the definition of refractory RA continues to elude consensus.

Simply put, refractory RA is disease that continues to be active despite adequate treatment for sufficient time. The lack of uniformity stems from the fact that refractory RA has three dimensions: disease activity, adequacy of treatment, and time. The concept of disease activity is a quantitative target with reasonably well defined variables. Validated indices like simplified disease activity index (SDAI) and clinical disease activity index (CDAI) are available and widely used in rheumatology clinics. Their use is overtaking the use of DAS 28 (disease activity score 28). A detailed exposition of various disease activity measures is beyond the scope of this chapter. Briefly, SDAI

TABLE 1 Instruments to measure disease activity in RA

	Score range	*Remission*	*Low*	*Moderate*	*High*
DAS28	0–9.4	≤2.6	≤3.2	>3.2 and ≤5.1	>5.1
SDAI	0.1–86	≤3.3	≤11	>11 and ≤26	>26
CDAI	0–76	≤2.8	≤10	>10 and ≤22	>22

CDAI, clinical disease activity index; DAS, disease activity score; SDAI, simplified disease activity index

TABLE 2 American College of Rheumatology/European League Against Rheumatism definitions of remission in RA

For clinical trials	*For clinical practice*
Boolean-based definition At any time point, patient must satisfy all of the following: • Tender joint count ≤1 • Swollen joint count ≤1 • C reactive protein ≤1 mg/dL • Patient global assessment ≤1 (on a 0–10 scale)	*Boolean-based definition* At any time point, patient must satisfy all of the following: • Tender joint count ≤1 • Swollen joint count ≤1 • Patient global assessment ≤1 (on a 0–10 scale)
Index-based definition At any time point, patient must have a Simplified Disease Activity Index score of ≤3.3	*Index-based definition* At any time point, patient must have a Clinical Disease Activity Index score of ≤2.8

is simple numerical summation of swollen joint count (SJC)-28 joints, tender joint count (TJC)-28 joints, CRP in mg/dL (range 0.1–10), patient's global disease activity on a 10-cm visual analogue scale (VAS) and physician's global assessment on a 10-cm VAS. The CDAI excludes CRP. DAS 28 requires four simple inputs: 28 TJC, 28 SJC, ESR, and general health (GH) assessment by the patient on a VAS from 0 to 100. The formula used is: DAS 28 = $0.56\sqrt{TJC} + 0.28\sqrt{SJC} + 0.7 \ln ESR + 0.014$ GH. Online calculators and apps are available for calculation. The cut offs are mentioned in **Table 1**. The goal of treatment is remission **(Table 2)**,[1] failing which low disease activity (LDA) is an acceptable alternative.

The second operational component—time taken to achieve LDA/remission—has undergone a sea change. Older publications talk about early disease as a disease duration of 2 years. Current recommendations like European League against Rheumatism (EULAR) and American College of Rheumatology talk about early RA as a disease duration less than 6 months.[2,3] They also emphasize that clinicians should aim for clinical remission (ACR-EULAR criteria) or at least low disease activity within 6 months (of which about 80% improvement of disease activity should be within 3 months of starting treatment).[4] It is recommended that if there is no improvement by at most 3 months after the start of treatment, or the target has not been reached by 6 months, therapy should be adjusted.

It is the third component of the definition—adequate treatment—that is a matter of debate. Recent clinical trials define refractory RA as "moderately to severely active RA (≥6 tender joints of 68 joints examined, ≥6 swollen joints of 66 joints examined, and a serum CRP level ≥3 mg per liter) and patients must have previously received one or more TNF inhibitors and discontinued treatment because of an insufficient response after 3 months or more or because of unacceptable side effects."[5] Other authors define refractory RA as patients who have experienced three treatment courses (with at least one biological) over a minimum of 18 months since diagnosis without reaching the treatment goal of low disease activity or remission.[6]

To make matters complex, some authors have proposed that non-responders be classified into "primary" and "secondary" non-responders. The latter, after the initial response to the drug, stop responding after a variable period of time. In some of these, anti-drug antibodies (ADA) to the biologics may be responsible for the secondary non-response. This has been termed "pharmacokinetic refractoriness" to differentiate it from intrinsic refractoriness in the primary non-responders.[7]

It is to be noted that not all secondary non-response are due to ADA. Also, ADA are seen with biologics, which are foreign proteins and not with csDMARDs or tsDMARDs like JAK inhibitors. This group proposes that refractory RA be defined by resistance to multiple therapeutic drugs with different structures and mechanisms of action—inefficacy of optimal dose methotrexate and at least two biologics with different mechanism of action.[7] They suggest that multiple within-class bDMARD resistance (as with TNFi cycling) be excluded from the ambit of refractory RA and a patient failing MTX and one TNFi needs to fail another non-TNF before being labeled as refractory.[7] The time period of 6 months incorporated in most guidelines for achieving LDA with treatment would translate into a period of at least 18–24 months for a patient to fail a minimum of two classes of bDMARDs.[7] It is pertinent to point out that *not* incorporated in this working definition is the place of JAKi.

Can the Same Definition of Refractory RA be Applied to Low Resource Settings?

The uptake of targeted treatments in resource constrained countries is very low. This is especially true of bDMARDs. With little insurance or government support, the bulk of treatment cost is borne by the patients themselves. The average duration of biologic use is less than a year.[8] The indirect implication of this is that definitions of refractory RA, as applicable in the west, cannot be extrapolated to countries like India. Biologic use, to begin with, is quite less and switching or swapping of biologics even lesser. From a practical standpoint, refractory RA in India can be defined as patients who continue to have active disease despite a combination of csDMARDs plus low dose steroids (prednisolone <7.5 mg daily). Implicit in this statement is optimal dosing of drugs: subcutaneous methotrexate (15–25 mg weekly) along with hydroxychloroquine (200–400 mg daily) and leflunomide (20 mg daily). In clinical settings like women of child bearing age, sulfasalazine (2–3 gm daily) can be used in place of leflunomide.

The availability of low cost, generic JAK inhibitors in the near future is likely to change the whole equation. Biologic DMARDs and biosimilars are expensive, given the complexities of manufacture. However, tsDMARDs like tofacitinib and baricitinib are not as difficult or expensive to produce. Their availability would necessitate a change in the definition of refractory RA in India.

How Common is Refractory RA?

Biologics, contrary to the popular perception of many internists, do not work for all patients. As many as one-third of patients treated with TNF inhibitors exhibits inadequate response or intolerance. In general, the efficacy of biologics in patients failing methotrexate is given by the broad thumb rule of ACR-20/-50/-70 of 60/40/20%. That is, ACR 20 response is seen in 60% of such patients, ACR 50 response in 40% patients while ACR 70 response is seen in 20% patients. In patients failing anti-TNFs, the ACR-20/-50/-70 drop further to 50/25/12% respectively.

The prevalence estimates of refractory RA vary between 6% and 21% depending on threshold and study population.[9] Obviously, referral centers would be expected to encounter more refractory patients. Risk factors for refractory RA include treatment delay, baseline disease activity and function, female gender, smoking, obesity, and lower socioeconomic status.[9]

How should Overdiagnosis of Refractory RA be Avoided?

A label of refractory RA should be applied after careful consideration **(Fig. 1)**. Overclassification and misclassification may result in inappropriate therapy escalation. Coexistence of fibromyalgia may lead to disproportionate increase in patient reported symptoms and distort disease assessment. Secondary damage and osteoarthritis can also lead to higher disease activity scores and apparent refractoriness.

Treatment of Refractory RA

The treatment of refractory RA revolves around the use of targeted treatments—bDMARDs or tsDMARDs. Patients failing one drug are switched to another agent. Switching to an alternate agent with same MOA (intra-class switching) has been called "cycling" and switching to agents with a different MOA has been termed "swapping."[10] These terms are by no means universally accepted. There is no consensus on sequence of switching. Physician familiarity, patient preference, and drug characteristics like availability, cost, safety, and efficacy are some of the factors to be considered. Of the ten bDMARDs available worldwide, six are available in India **(Table 3)**. The tsDMARDs in RA are the JAK inhibitors. Two of the four JAKi are available for use in India **(Table 4)**.

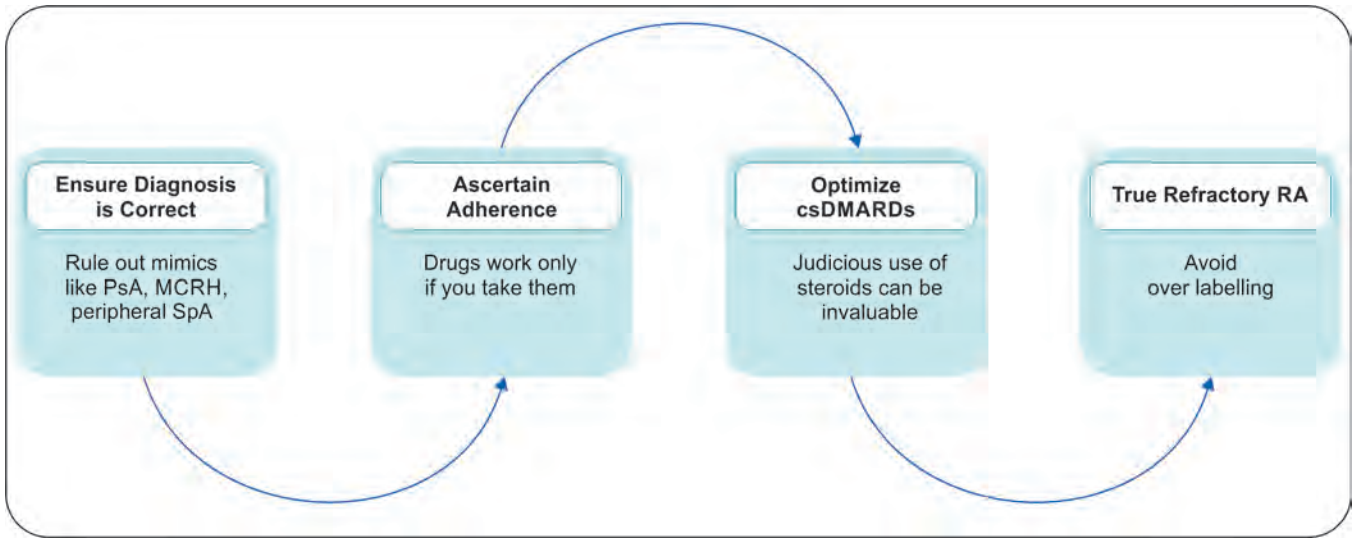


Fig. 1: Pathway to labeling refractory RA
csDMARDS, conventional synthetic DMARDs like methotrexate, hydroxychloroquine, leflunomide and sulfasalazine; MCRH, multicentric reticulohistiocytosis; PsA, psoriatic arthritis; SpA, spondyloarthritis

TABLE 3 Biologics available in India

Biologic	*Target*	*Route of administration*	*Usual adult dose*
Infliximab	TNF	Intravenous	In conjunction with methotrexate, 3 mg/kg at 0, 2, and 6 weeks, then every 8 weeks
Etanercept	TNF	Subcutaneous	50 mg weekly
Adalimumab	TNF	Subcutaneous	40 mg every other week
Golimumab	TNF	Subcutaneous	50 mg once a month
Tocilizumab	IL-6R	Intravenous and subcutaneous	Intravenous: Recommended starting dose is 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. Subcutaneous: 162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Rituximab	CD 20 on B cells	Intravenous	The dose for RA in combination with methotrexate is two-1,000 mg intravenous infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks

IL-6R, interleukin 6 receptor; TNF, tumor necrosis factor
N.B.: Abatacept, Anakinra, Sarilumab, and Certolizumab are not available in India.

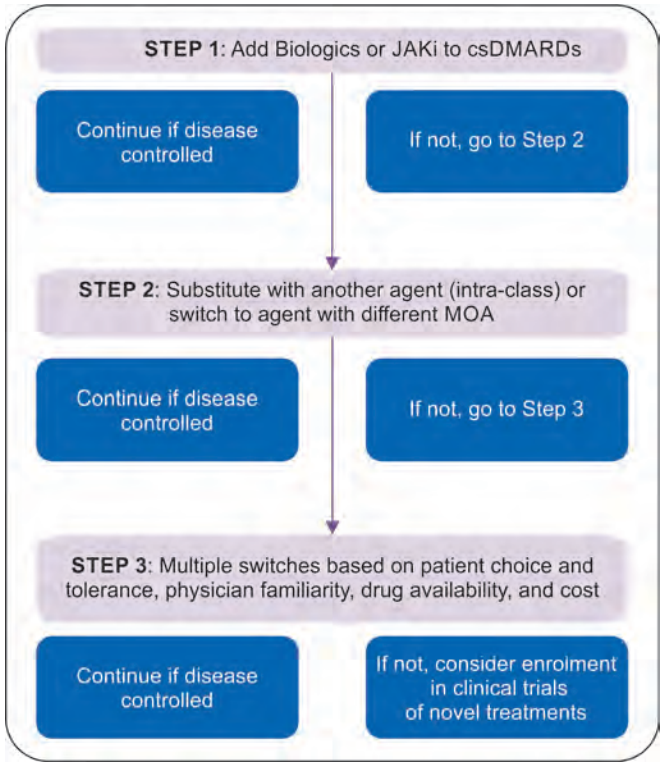
TABLE 4 Targeted synthetic (ts) DMARDs available in India

Agent	*JAKs targeted*	*Oral dose*
Tofacitinib	JAK1, JAK2, JAK3	5 mg BD
Baricitinib	JAK1, JAK2	2–4 mg OD

JAK, Janus kinas
N.B.: Upadacitinib and Peficitinib are not available in India

Recommendations from professional bodies like APLAR and EULAR do not spell out any particular sequence to follow.[2,11] It is to be pointed out that csDMARDs can be combined. However, combinations of biologics or JAKi or biologic-JAKi combination are not recommended for fear of intense immunosuppression **(Flowchart 1)**.

Flowchart 1: Treatment of refractory RA



Conclusion

Refractory RA represents an area of unmet need in the arena of rheumatology. The definition itself continues to evolve with the expansion of DMARD classes—from csDMARDs through bDMARDs to, now, tsDMARDs. Ensuring adherence to treatment and excluding the contribution of damage/degeneration to disease activity assessment are important to avoid misclassification as refractory RA. Biologics and tsDMARDs are used to treat refractory disease. In absence of biomarkers, the sequencing of bDMARDs and tsDMARDs at present is empirical. Hopefully, the advent of precision medicine in future would permit clinicians to move away from "generic" protocols to "individualized" protocols in the disease segment that is refractory RA!

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CHAPTER

207 Difficulties in Rheumatoid Arthritis

Rajan Kumar

Abstract

Rheumatoid arthritis is not an uncommon arthritis. There is overlap in the markers and clinical features. One should try to decipher the diagnosis with their markers and this will help in deciding treatment. By identifying the signs of flare ups and treatment failure we can plan treatment with algorithm.

Introduction

Rheumatoid arthritis marked by synovitis in small joints, acute phase reactants, and biomarkers. Sometimes biomarkers are absent but small joints and acute phase reactants are present diagnosis depend on clinical judgment and wait for others markers to evolve but if treated early, then long-term complications of join deformities and disabilities can be decreased. In presence of other biomarkers along with specific for Rheumatoid arthritis, subtle judgment will help in classifying disease syndrome. It is also pertinent to identify flare ups of disease and failure of treatment so that we can achieve remission. Finally treat to target will help in prolonging life.

Rheumatoid arthritis is one of the most common arthritis. Every clinician might have got an opportunity to treat it. They might have encountered some difficulties in the management, particularly in:

- Diagnosis
- Treatment

To diagnose rheumatoid arthritis when all clinical sings and markers are present is not a difficult task. Patients classically come with the complains of pain and early morning stiffness lasting for more than an hour and for more than 6 weeks with systemic symptoms or no systemic symptoms. There is an involvement of smaller joints in hand symmetrically, particularly involving proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints with positive squeeze sign and loss of guttering in between MCP joints, wrist, elbow, shoulder, knee, and feet with small joints. You can diagnose it easily if there is more than three symmetrical joints involvement in hand of PIP, MCP along acute phase reactants and autoimmune markers in the form of rheumatoid factor (RF) and anti-cyclic citrullinated (ACC) antibodies. When this is the situation, things are very easy. But the problem starts when:

- You have autoimmune markers but no clinical features or synovitis or joint pain.
- Clinical features of synovitis and evidence of symmetrical small joint arthritis with no autoimmune markers.

How to predict the diagnosis of rheumatoid arthritis in these two conditions.

Firstly, with autoimmune markers without evidence of synovitis:

- RF only
- Both RF and anti-cyclic citrullinated protein (ACCP) antibody

TABLE 1 There different studies which shows the predictive value

Nielen et al (2004)	RF-IgM, anti-CCP2	PPV of up to 100% for RA diagnosis within 5 years
Deane et al. (2010)	RF isotypes, anti-CCP2	Anti-CCP and/or two or RF isotypes positive with >96% PPV for RA compared to two control groups
Ramos-Remus et al. (2015)	RF, anti-CCP2	RF and anti-CCP positivity at baseline with PPV 64% for RA within 5 years; anti-CCP alone with PPV of 58%
Sokolove et al. (2012)	RF, ACPA array, variety of cytokines and chemokines	A set of ACPAs and cytokines was 58% sensitive and 87% specific for identifying a sample ≤2 years before diagnosis

ACPA, anti-citrullinated protein antibody; CCP, cyclic citrullinated protein/peptide; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor.

We have to take the account that genetic factors (e.g., the shared epitopes) are environmental factors (smoking and high body mass index) and RF isotypes particularly high-titter IgM-RF and IgA-RF presence will favor the future development of rheumatoid arthritis.

ACCP are of three types on the basis of method of antigen used anti-CCP1 (ELISA), anti-CCP2 (tested with synthetic peptides), anti-CCP3 (tested with synthetic peptides), of theses, presence of anti-CCP2 has more predictive value for the future development of RA.

With only presence of autoimmune markers, it takes 3–5 years to develop from the stage of autoimmunity to autoimmune disease. But it depends on:

- Levels of autoantibodies
- Number of ACCPAs
- Presence of both ACCPAs and RF
- Additional biomarkers such as cytokines and chemokines
- Other factors such as environmental exposures and symptoms

There different studies which show the predictive values have been discussed in the **Table 1**.

We need to develop an effective tools to measure the response of successful preventive interventions in preclinical RA (window of opportunity), when challenged with disease-modifying anti-rheumatic drug (DMARD) or other effective treatment in this window of opportunity.

Rituximab and other pharmacologic agents, including hydroxychloroquine, abatacept, and atorvastatin were tried in various trials for prevention in various trials without much success.

The best time to treat is when patients having arthralgia and synovitis. Treatment within first 3 months of onset of the disease can lead to long-term remission, the so-called window of opportunity period.

Now second situation is that when there is a synovitis with typical joint involvement but no autoimmune markers, then how we can diagnose RA. We need;

History of more than 6 weeks of morning stiffness, symmetric arthritis involving PIP, MCP joints, subcutaneous nodules, and the deformities characteristic of RA.

There are other disorders but having similar presentation but with presence of rashes, dry mouth and dry eyes, Raynaud's phenomenon, myositis, or nephritis, involvement typical organs and by various autoantibodies not seen in RA may clinch the diagnosis, for example. Systemic lupus erythematosus (SLE), Sjögren's syndrome, Dermatomyositis (DM), Sarcoidosis, Psoriatic arthritis, Overlap syndromes such as mixed connective tissue disease.

Some of inflammatory arthritis (IA) which do not fit in any of the classical syndrome, then we mark them as unclassified arthritis. Now even in these situations we can work up diagnosis in the favor of RA with anti-CCP presence, unconventional serologic findings (e.g., IgA type rheumatoid factor, pyridinoline), and MRI-proven early joint damage, synovial thickening, marrow edema, and erosions.

There are situations in which inflammatory arthritis is present with:

- RF with ANA (anti-nuclear antibodies) with erosions, the diagnosis goes the favors RA.
- Without erosions and clinical features suggestive of SLE or but with ANA and ACCP antibody clinch the diagnosis of rheumatoid arthritis.
- But patients having features of both RA and SLE with presence of RF and ANA will favor the diagnosis of overlap syndrome.

- With RF, ANA, and Un RNP and IA, the diagnosis will go in favor of mixed connective tissue disease.

Two of clinical variants of RA poses some difficulty. The first one is the presentation with monoarthritis.

Mono arthritis with involvement a large joint, such as the wrist, knee, shoulder, hip, or ankle, may be the sole manifestation of RA, but how to predict RA in these patients. One should investigate the patients, for the presence of the RF and ACCP antibodies.

If they are there, then wait for typical disease features to evolve. Usually it takes days to several weeks to develop polyarthritis from monoarthritis till then we should treat them as monoarthritis with NSAIDs and local steroid injection if required.

To rule out that monoarthritis of large joints are due to spondyloarthritis, MRI will help to find out more destructive change (synovial thickening, marrow edema, and erosions) in the patients with RA and but enthesopathy in the patients with spondyloarthropathy than in the patients with undifferentiated arthritis.

Second one is the presentation with *Palindromic rheumatism* in this condition, episodes of joint inflammation sequentially affecting one to several joint areas for hours to days, with the symptom-free periods that may last from days to months. Patients with anti-CCP antibodies appear more likely to progress to definite RA later on. It has to be differentiated from the migratory arthritis.

So the key points for predicting RA we will need to focus on sex, age, morning stiffness, localization of symptoms, tender and swollen joint counts, C-reactive protein, rheumatoid factor positivity, and presence of ACCP antibodies. There are scoring systems to predict the development of RA.

We face some difficulties in treatment also.

Firstly, in the choice of treatment, secondly detecting the failure of DMARD and lastly managing the flare ups.

We usually start treating with NSAIDs (nonsteroidal anti-inflammatory drugs), steroid and CsDMARDs (conventional synthetic DMARD). But sometimes it does not give the desired results. Treat to the target is the rule of thumb.

Failure can be defined as:

- Not able to remission with the target achievement within 3–6 months of continuous use of DMARDS irrespective of nonbiologic (conventional synthetic [cs]), biologic (b), or targeted synthetic (ts) DMARD in maximally tolerated doses within the usual therapeutic range.
- Continued erosion despite patient on treatment even with no pain.
- Requirement of 5–7.5 mg prednisone or larger doses to maintain achievement after 3 months of DMARD use.
- Multiple courses of treatment with glucocorticoids for the treatment of recurrent disease flares in patients whose DMARD doses have been increased to the maximally tolerated.

Flares may be with:

- Single or few affected joints treated them with NSAIDs for few days and local steroid injection in joint if required.
- Widespread flares with multiple joints with need low doses of steroid.
- Severe flares, particularly those associated with systemic manifestations and life-threatening conditions, such as rheumatoid vasculitis will need intravenous pulse methylprednisolone in high doses with long use of steroid.
- Flaring frequently or severely will need escalation of doses of continued DMARD and/or addition of another DMARD of same group of different groups.

DMARDS are selected in step ladder approach:

- MTX (methotrexate)
- HCQ/SSZ (hydroxychloroquine/sulfasalazine)
- HCQ + SSZ + MTX, i.e., triple therapy

  Patients resistant to triple therapy can be treated with MTX plus leflunomide (LEF) please note that this may require closer monitoring (e.g., monthly with aminotransferase testing) for hepatotoxicity, given the increased risk of hepatotoxicity in some but not in the most studies, including reports of fatal liver failure.
- MTX + TNF blocker (tumor necrosis factor) ETN (Etanercept) or ADA (Adalimumab)
- Methotrexate plus Rituximab equivalent to TNF blocker combination
- Rituximab is effective alone in the patient intolerant with MTX
- MTX + tsDMARD (tofacitinib)
- LEF (leflunomide) alternative to MTX
- In pregnancy TNF blocker can be used alone
- LEF if there is moderate renal dysfunction/nontolerant to MTX

- MTX + Abatacept
- MTX + IL 6 inhibitors tocilizumab and sarilumab

Patient needs months and years of continued therapy for adequate response.

Downregulating the DMARDs only after 1 year of sustained response otherwise flare ups are very much common.

Some patients remain in remission on reduced doses but decision to discontinue treat remain debatable and controversial.

The best candidates for achieving a drug-free remission appear to be the patients who have a short duration of symptoms when treatment is started, are of the male sex, have an absence of RF and ACPAs, have received early intensive therapy, and have achieved a deep remission based upon composite scores of disease activity.

Conclusion

Autoimmune biomarker testing and clinical features allow us to rightly interpret the diagnosis. And knowing the failure, remission, and flare up sign and symptoms will lead to proper use of different demands in algorithm.

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CHAPTER

208 Monoarthritis—A Clinical Dilemma to Internists

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Abstract

The monoarthritis can either be acute or chronic, and may be either inflammatory or non-inflammatory. A detailed history and meticulous physical examination are essential in determining the etiology of arthritis. Diagnosis of monoarthritis is always a challenge to the internist. The common causes of acute monoarthritis are gout (crystal-induced arthritis), trauma, and infection, while that of chronic monoarthritis are osteoarthritis, tuberculous arthritis, gout, or spondyloarthropathy. So-called polyarticular diseases like systemic lupus erythematosus, rheumatoid arthritis may start as monoarthritis. If one investigation has to be done, it is synovial fluid examination, while synovial biopsy specimen is often examined for etiological agents in Lyme disease, gonococci, tuberculosis, or chlamydia infection. Light microscopy may identify gout crystals, but polarized microscopy is always preferred. Review of systemic diseases like sarcoidosis, malignancy, etc. is important because they may be complicated by monoarthritis.

Introduction

Monoarthritis is defined as inflammation of one joint at a time, while acute monoarthritis is acute inflammation of a single previously healthy joint, typically developing within a few days. Chronic monoarthritis is the inflammatory arthritis of a single joint that persists for more than 6 weeks. Acute monoarthritis may be the initial manifestation of many of the rheumatological disorders or systemic connective tissue diseases. *The most common causes of acute monoarthritis are crystal arthropathy (i.e., gout and pseudogout), trauma, and infection.*[1] The patient of monoarthritis should undergo careful and meticulous history, rational physical examination, and selected laboratory tests. Acute monoarthritis (red-hot joint) represents a rheumatologic emergency and requires rapid assessment, diagnosis, and aggressive treatment, since an untreated septic arthritis may lead to irreversible joint damage and resultant disability. In spite of the intensive investigations, at times, no clear diagnosis can be made. Complete blood count, bleeding and clotting time, ESR, C-reactive protein (CRP), serum uric acid, rheumatoid factor and antinuclear factor, urine analysis, and blood or urine culture should be performed, as and when necessary. Blood culture should be done if clinical suspicion of septic arthritis is very high. Many a time, examination of joint fluid is essential in making a definitive diagnosis. Leukocyte counts may vary widely in septic and sterile synovial fluids, and should be interpreted cautiously in an open mind. The joints, such as hip or sacroiliac joints, are difficult to aspirate and very often computed tomography or ultrasound-guided arthrocentesis helps to draw synovial fluid from these types of deep-seated joints. When an infection is suspected, culture and Gram staining of the synovial fluid should be performed and antibiotics should be started empirically. Light microscopy may identify gout crystals, but polarized microscopy is always preferred. If, however, the diagnosis is yet to be reached, radiographic studies (such as technetium bone scan,

computed tomographic scanning or magnetic resonance imaging) are performed in selected cases (such as internal derangement or osteonecrosis), and even, invasive procedures such as arthroscopy and synovial biopsy may be necessary to clinch the final diagnosis in undiagnosed chronic monoarthritis. The other systems should be evaluated because, many a time, thalassemia, sarcoidosis, sickle cell anemia, or hemophilia may be a cause for monoarthritis.

Monoarthritis: An Overview

Monoarthritis represents a diagnostic challenge to every physician. The doctor first decides the anatomical basis of pain (i.e., articular vs. non-articular). Joint pain can be the result of abnormalities in the joint itself, adjacent bone, surrounding ligaments, tendons, bursa, or soft tissues. Articular structures consist of synovium, synovial fluid, articular cartilage, joint capsule and juxta-articular bone. Non-articular (periarticular) structures include ligaments, bone, tendons, bursa, muscle, fascia, nerve, and overlying skin. "Arthritis" results in stiffness, reduced range of motion, and pain of the involved joint during normal use, which is most noticeable in the morning, improves with motion, and may be associated with systemic symptoms (i.e., malaise or fever). Joint pain due to mechanical factors (non-articular) usually improves with rest, deteriorates with activities and is not associated with systemic symptoms. In differential diagnosis (D/D) of musculoskeletal pain diffuse bone diseases like multiple myeloma, metabolic bone disease or multifocal osteomyelitis should be considered.

Possible causes of acute and chronic monoarthritis have been elaborated in **Table 1**.[2,3] Arthritis may be monoarthritis (single joint), oligo- or pauciarthritis (2–4

TABLE 1 Etiology of monoarthritis[2,3]

Common causes	• Trauma • Crystals—monosodium urate (MSU), calcium pyrophosphate dehydrate (CPPD), hydroxyapatite, calcium oxalate • Septic arthritis (non-gonococcal, gonococcal) • Hemarthrosis (trauma and/or coagulation disorder) • Avascular necrosis of bone (i.e., osteonecrosis) • Internal derangement (e.g., meniscus tear, cartilage debris) • Osteoarthritis • Osteomyelitis • Overuse (e.g., in a pre-existing osteoarthritic joint) • Monoarticular flare of oligoarthritis or polyarthritis
Less frequent causes	• Malignancy of bone • Hemoglobinopathies (i.e., sickle cell anemia) • Enteropathic arthritis (e.g., Crohn's disease, ulcerative colitis) • Sarcoidosis • Loose bodies within joint • Infections—mycobacteria, fungi • Leukemia • Rheumatoid arthritis (RA—palindromic), reactive arthritis (ReA), psoriatic arthropathy (PsA), juvenile idiopathic arthritis (JIA) • Vasculitis
Rare causes	• Hypertrophic pulmonary osteoarthropathy (developing from bronchogenic carcinoma) • Foreign body (e.g., plant thorn) • Pigmented villonodular synovitis • Amyloidosis • Lyme disease • Familial Mediterranean fever • Relapsing polychondritis • Charcot joint • Behçet's syndrome • Synovial chondromatosis/sarcoma/synovial metastasis

TABLE 2 Working classification according to onset and duration[2,3]

Acute (duration <6 weeks)	*Chronic (duration >6 weeks)*
• Infection (bacterial, mycobacterial, fungal, or viral; Lyme disease)	• Infection (tuberculosis, brucellosis, fungal)
• Crystals (MSU, CPPD, calcium hydroxyapatite, calcium oxalate)	• Crystals (MSU, CPPD, etc.)
• Trauma (fracture or internal derangement)	• Osteoarthritis (commonly knee joint)
• Monoarticular presentation of a polyarticular disease (i.e., immunoinflammatory—RA, SpA, PsA, IBD, or SLE)	• Sarcoidosis (e.g., ankle joint)
• Osteoarthritis (knee, hip, or 1st MCP)	• Seronegative SpA and chronic ReA
• Hemarthrosis (trauma, coagulation abnormality)	• Pigmented villonodular synovitis (PVNS)
• Ischemic (avascular) necrosis—of hip from SLE or corticosteroid therapy	• Synovial chondromatosis/sarcoma
• Tumor (metastasis, PVNS)	• Foreign body (plant thorn) synovitis
• Foreign body synovitis (wood fragments, plant thorn)	• Charcot (neuropathic) joint (e.g., leprosy, syringomyelia)
• Systemic diseases presenting as monoarthritis (e.g., acromegaly producing pseudogout)	• Monoarticular presentation of a polyarticular disease (i.e., RA, SpA, PsA)
Summary of working classification: Acute monoarthritis—Septic, crystals, traumatic, SpA (especially, ReA) Chronic monoarthritis—Osteoarthritis, crystals, SpA (especially chronic ReA), tuberculous	

IBD, inflammatory bowel disease; MCP, metacarpophalangeal; PsA, psoriatic arthropathy; RA, rheumatoid arthritis; ReA, reactive arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthropathy

joints) and polyarthritis (≥5 joints). Monoarthritis can either be acute (duration <6 weeks) or chronic (duration >6 weeks), and may be either inflammatory or non-inflammatory **(Table 2)**.[2,3]

Approach to Evaluation of Monoarthritis

The first and most important steps in evaluation are thorough *history taking*. Onset of symptoms, history of fever, recent travel, IV drug or alcohol abuse, sexual exposure, tick or insect bite, diarrhea, urinary tract infection, trauma, gardening (e.g., plant thorn synovitis), or pre-existing systemic disease should be enquired. History of drug therapy (e.g., diuretics in gout), skin rash, oral or genital ulcers, and prolonged bleeding should be taken into account **(Table 3)**. Next task is to start thorough *physical examination* where a physician has to differentiate articular from non-articular disease (see previous paragraph). Deep-seated joints like hip and sacroiliac joints are difficult to evaluate. Consider the D/D of single "red-hot joint" **(Table 4)**.

Clue for initial clinical observation (ideal examples):

- Middle-aged male with red, hot, tender, and swollen 1st metatarsophalangeal joint points toward gout.
- Elderly diabetic lady having knee replacement 1 year back where the knee is presently acutely swollen, hot, tender with high pyrexia, and toxicity indicates septic arthritis.
- Young male with acute knee pain, plus history of neck and back pain will have a probable diagnosis of ankylosing spondylitis (SpA).

Investigations—If one investigation has to be done, it is synovial fluid examination, and the fluid should be examined for

- Gram stain
- Routine culture
- Total and differential WBC count
- Crystals under polarized light microscope.

It is simple, safe, and a very easy bedside procedure without any complication, if performed aseptically. Synovial biopsy is done in selective cases (e.g., tuberculous synovitis) by needle aspiration or arthroscopy. Recently, by polymerase chain reaction and immunoelectron microscopy, synovial biopsy specimen is examined for etiological agents in Lyme disease, gonococci, or chlamydia infection. Other common tests done are blood for total and differential count, blood and urine culture,

TABLE 3 Clinical clues in the history and physical examination

History and clinical findings	*Probable diagnosis*
Sudden onset of pain developing within seconds or minutes	Trauma, fracture, internal derangement
Onset of pain arising over several hours or within days	Infection, crystal arthropathy, any inflammatory arthritis
Onset of pain developing over days to weeks	Indolent infection, osteoarthritis, infiltrative disease, tumor (synovium/bone)
Young adult with history of promiscuous sex and migratory arthritis	Gonococcal arthritis
History of diabetes mellitus, immunosuppression, bacterial endocarditis, or IV drug abusers	Septic arthritis
Previous history of acute attack in the joint with spontaneous resolution	Gout, any inflammatory arthritis
History of sustained bleeding (coagulopathy) or use of anticoagulants	Hemarthrosis
Positive family history	Gout, IBD-induced spondyloarthropathy, psoriasis, ankylosing spondylitis, osteoarthritis
Prolonged use of corticosteroid in the recent past	Infection, avascular necrosis
Urethritis (chlamydiae), conjunctivitis, skin or penile rash, diarrhea (campylobacter, salmonella, shigella)	Reactive arthritis (ReA)
Arthritis precipitated after binge alcohol intake or consumption of diuretics	Gout
Low back pain, uveitis (red eye), heel pain, or Achilles tendonitis	Ankylosing spondylitis
Hilar adenopathy, erythema nodosum (Lofgren syndrome)	Sarcoidosis
Bedside clinics: • Oral ulcers • Pyrexia • Lymphadenopathy • Tophi over olecranon process, or helix • Erythematous rash in face • Bronzing (darkening) of skin • Pyoderma gangrenosum • Erythema nodosum • Psoriatic skin patches or pitting nails • Circinate balanitis or keratoderma blenorrhagicum	 • Behçet's disease, SLE, ReA • Infection, crystals, immunoinflammatory • Tuberculosis, malignancy • Gout • SLE (butterfly-like), lupus pernio (sarcoidosis) • Pseudogout (hemochromatosis) • IBD, RA • IBD, SLE, sarcoidosis, tuberculosis • Psoriatic arthritis • ReA

TABLE 4 Acute monoarthritis presenting as 'red-hot joint'[4]

Infectious	Bacterial (Staphylococci, Streptococci, Gonococci, gram-negative organisms), viral
Crystal-induced	Gout, pseudogout (i.e., from hemochromatosis, acromegaly, hypoparathyroidism)
Acute exacerbation of:	RA, ReA, PsA, palindromic rheumatism

serum uric acid, and rheumatoid factor. Radiology is not much helpful except in sacroiliitis, osteoarthritis, and chondrocalcinosis (e.g., pseudogout). MRI may be helpful in deep-seated arthritis.

Pitfalls and Reality in Monoarthritis (Table 5)

Management

Management of acute monoarthritis depends on the actual diagnosis though the general principles of management include rest to the joint, application of ice, and physiotherapy to help maintain range of motion in joints and minimize subsequent muscle atrophy. Specific therapy includes antibacterial agents for septic arthritis, non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular corticosteroid injections for non-infectious inflammatory monoarthritis; arthroscopy is performed for internal derangement. *Presence of infection*

TABLE 5 Pitfalls versus reality in diagnosing monoarthritis[5]

Pitfalls	*Reality*
A normal serum uric acid level excludes gout	Serum uric acid may be normal or low up to 30% cases of gout as stress-induced liberation of ACTH and TNF-α may act uricosuric. Moreover, there may be unrelated asymptomatic hyperuricemia associated with other monoarticular arthritis
Presence of fever distinguishes infective from non-infective arthritis	Presence of fever is not a reliable indicator of septic arthritis, and moreover acute attack of gout or pseudogout may be associated with pyrexia. Similarly, absence of leukocytosis, raised ESR, raised CRP, or absence of organisms does not exclude septic arthritis
Presence of crystals (MSU or CPPD) in the joint fluid rules out infection	Crystal may be present in septic arthritis
The problem is always in the 'joint' as the patient complains of joint pain	Many a time, soft tissue rheumatism due to adjacent soft tissue inflammation (such as olecranon bursitis of the elbow) may be the source of pain
Diseases manifested as polyarthritis cannot have monoarthritis-like presentation	Monoarticular flare of rheumatoid arthritis or reactive arthritis is not uncommon
A negative Gram staining and culture of synovial fluid virtually excludes infection	Results of culture may be negative in early infection, and thus culture of blood/urine should be performed repeatedly in strong clinical suspicion of infection
In synovial fluid analysis, presence of WBC >2,000/mm^3 clinches the diagnosis of septic arthritis	Synovial fluid WBC >2,000/mm^3 is very often found in RA, SpA, SLE, or gout

should always be ruled out before giving intra-articular corticosteroid injection. Acute gout should be treated with colchicine, NSAIDs, or prednisolone. Joint aspiration is necessary in hemarthrosis. Osteoarthritis patients are advised to save their cartilage by practical demonstration, and treated with intra-articular corticosteroid and/or hyaluron injection. Pain in reactive arthritis is relieved by NSAIDs and ultimately the patients are advised to take disease-modifying anti-rheumatic drugs (DMARDs).

If the clinical suspicion of septic arthritis is very strong, empiric antibiotic therapy should be started, pending the reports of synovial fluid analysis. Modifications of antibiotics and its dosage may be done as soon as Gram staining and culture reports of synovial fluid are available. Septic arthritis should be treated in a hospital under the supervision of an orthopedic surgeon. Many a time, surgical drainage of a septic arthritis is required.

Practical Recommendations for Acute Monoarthritis[1,6]

- Acute monoarthritis is a medical emergency. With a short history of red-hot swollen joint, one should always suspect infection and unless otherwise indicated, it should be treated as septic arthritis. Other D/D are acute gout, trauma, and acute onset of inflammatory polyarthritis.
- The most significant point of clinical examination is to differentiate true synovitis (i.e., arthritis) from periarticular disease (e.g., cellulitis, bursitis, etc.).
- Septic arthritis can destroy a joint very rapidly, if not treated promptly. Septic arthritis is often superimposed on gout or pseudogout. Gonococcal arthritis is commonly a disease of sexually active young women.
- RA, ReA, IBD-associated arthritis, SLE, PsA, Behçet's disease can begin as acute monoarthritis, while systemic diseases like sarcoidosis, sickle cell anemia, or hemophilia may be complicated by monoarthritis. Tuberculosis and other indolent infections should be considered in chronic monoarthritis, and synovial biopsy may be needed to pin-point the diagnosis.
- The synovial fluid should be aspirated and sent for Gram staining and cultures (apart from total analysis) in acute and chronic monoarthritis. Synovial fluid analysis is the most important investigation.
- Absence of leukocytosis/high ESR/high CRP, negative Gram stain, or negative synovial fluid cultures does not exclude infection.

- In gout, synovial fluid samples must be sent for polarized microcopy for demonstration of intracellular MSU crystals as serum uric acid may be normal in acute attack of gout; in its absence, ordinary microscopy often gives a clue for crystals.
- Plain X-ray of the affected joint is usually of no benefit.
- In septic arthritis, start relevant antibiotics as early as possible pending culture reports. Usual pathogens are *Staphylococcus aureus* or streptococci but Gram-negative organisms are commoner in the elderly and immunocompromised patients. Conventionally, IV antibiotics are given for 2 weeks, followed by oral antibiotics for 4 weeks or more till local/systemic manifestations resolve and acute phase reactants (e.g., CRP) return to normal.
- Septic arthritis should be treated by orthopedic surgeon, crystal arthropathy, and inflammatory arthritis by rheumatologist, and osteoarthritis by orthopedic surgeon and physiatrist jointly.

Conclusion

Acute monoarthritis is a rheumatologic emergency and demands prompt diagnosis. So far as diagnosis and treatment of chronic monoarthritis are concerned, it needs patience, sound clinical background, and experience. Prompt diagnosis of joint infection is crucial as it rapidly results in joint destruction. Before putting the needle within a joint to inject corticosteroid, it is the duty of orthopedic surgeon or rheumatologist to exclude infective arthritis. The diagnostic and therapeutic dilemma in monoarticular arthropathy can be solved easily if the attending doctor examines the patient meticulously, and analyze the clinical findings and investigation reports logically.

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CHAPTER

209 Oral Targeted Treatments in RA—Update 2021

Ramakrishna Rao Uppuluri, Sripurna Deepti Challa

Abstract

The current concept in the management of rheumatoid arthritis (RA) and other immune-inflammatory arthritis is "treat to target", the target being low disease activity or remission. The standard of care in RA involves pharmacotherapy initiating conventional synthetic disease modifying anti-rheumatoid drugs. However, some patients do not respond to the conventional therapy. Advanced target therapy for RA involves biologic agents or oral small molecules. JAK inhibitors, a form of oral targeted treatment, are convenient, orally administered which do not produce drug antibodies. Robust clinical trials demonstrated their efficacy and safety.

Introduction

Among the inflammatory polyarthritis, rheumatoid arthritis (RA) is the most common. Over the past few decades, significant advances were made in understanding the pathogenesis of RA. The role of several important proinflammatory cytokines, such as tumor necrosis factors (TNF), interleukins (e.g., IL-6), and cell-associated targets (e.g., CD20) have been validated by the use of targeted biologic therapies in last two decades. Standard of care in RA involves initiation of the treatment with conventional synthetic disease modifying anti-rheumatoid drugs (csDMARDs) such as methotrexate (MTX). Biologic therapies (bDMARDs) have led to further reduction of the signs and symptoms of RA resulting in low disease activity (LDA) or remission of the disease. However, they have limitations—they have to be given parenterally and stored at lower temperatures. They can induce immunogenicity developing tolerance. Small molecules with low molecular mass that inhibit intracellular inflammatory signaling pathways are developed during the last decade. They are an important alternative to biologics for RA. These are called oral targeting treatments of RA.

Advances in the Treatment of RA

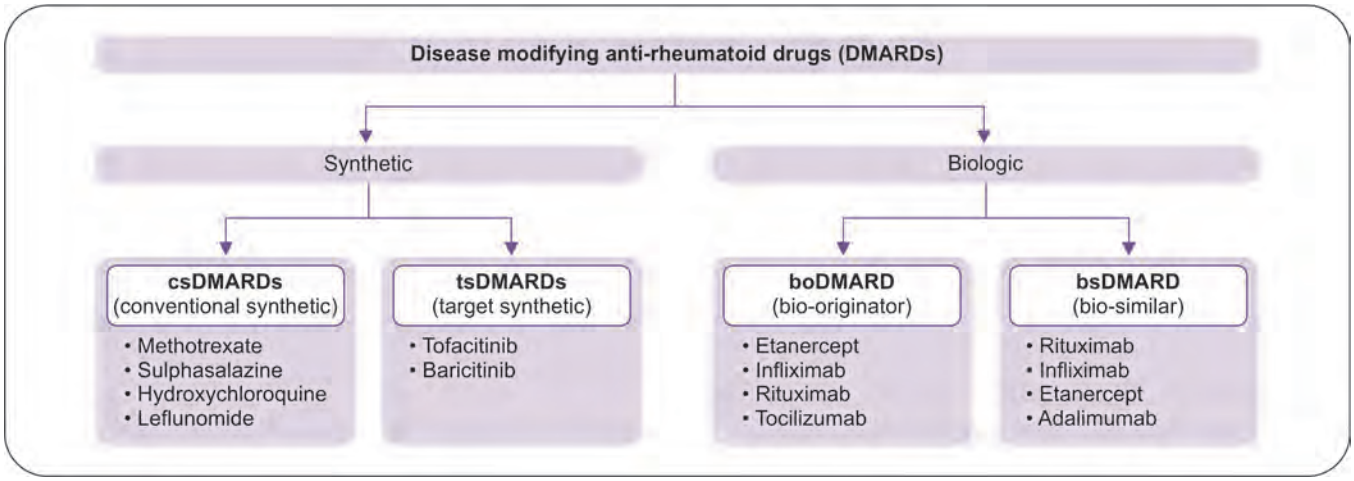
In the treatment of RA, csDMARDs occupy a central role **(Flowchart 1)**. MTX is still a baseline therapy unless contraindicated. Most of the rheumatologists use combination therapy with csDMARDs.[1]

However, significant number of the patients of RA do continue to progress with erosive arthritis. Biologic era in the past few years had seen remarkable advancement in the therapy of RA. In view of persistent unmet needs in the management of RA, oral targeted therapy inhibiting intracellular signaling pathways is developed in the last decade **(Fig. 1)**.[2]

Oral Targeted Therapy: Janus Kinase Inhibitors

Intracellular signaling pathways involved in signal transduction from the cell surface to the nucleus after ligand receptor binding have been identified. Small molecular therapies target these intracellular pathways. Protein kinases that phosphorylate intracellular proteins are major players in signal transduction. Tyrosine kinases,

Flowchart 1: Classification of DMARDs



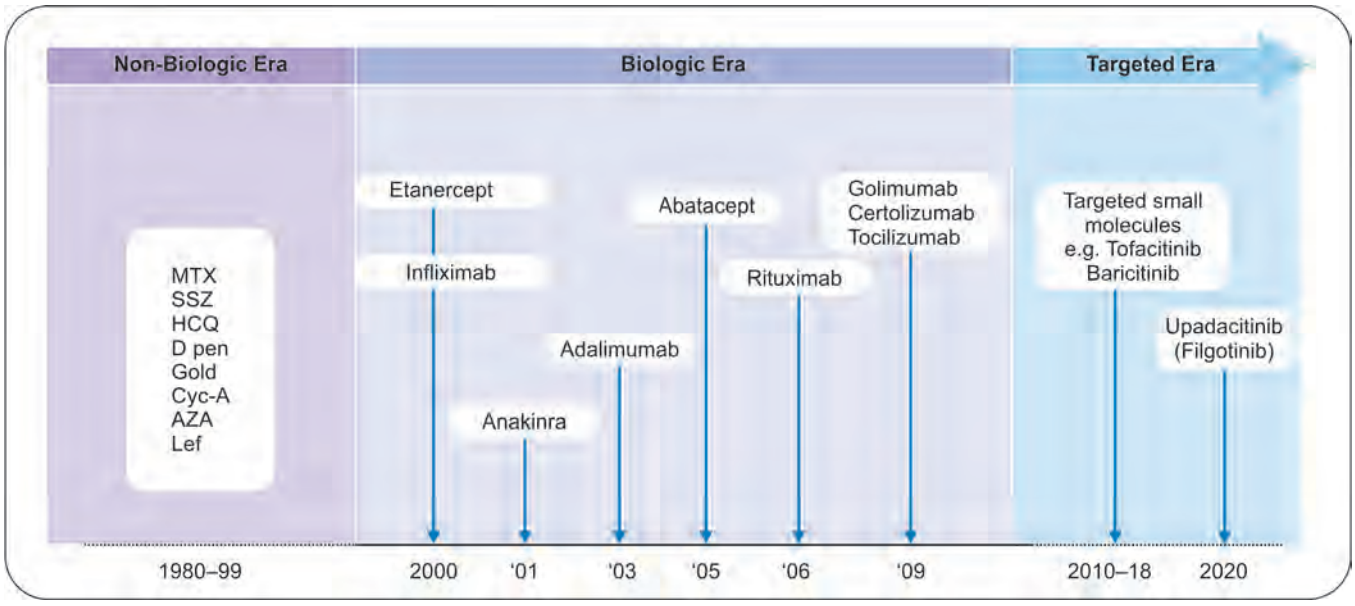


Fig. 1: Timeline in RA therapy (FDA approvals)
Arrival of oral targeted treatment—JAKinibs

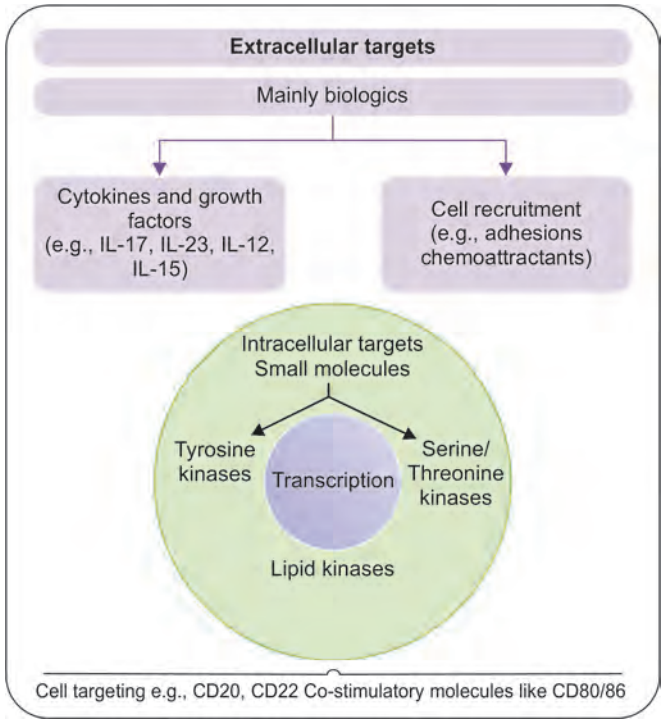
Janus kinases (JAKs), and Serine kinases are some of the protein kinases **(Flowchart 2)**.

Receptor polymerization and activation of associated JAKs occur once the cytokine binds to its cell surface receptor. JAKs, named after the two-faced Roman God Janus, consist of four types—JAK1, JAK2, JAK3, and TYK2. Phosphorylation of the receptors activated by JAKs dock the STATs (Signal Transduction Activator Transcription) **(Figs. 2A and B)**. They dimerize, translocate to the nucleus, and activate new gene transcription generating further cytokines **(Figs. 2C and D)**.[3]

JAK inhibitors (Jakinibs) have been successfully developed as oral targeted therapy in RA. Autophosphorylation and further activation of JAKs is inhibited by Jakinibs, for example, Tofacitinib. JAKs cannot phosphorylate the receptors and cannot dock the STATs. Phosphorylation of STATs, dimerization, and translocation are inhibited. Hence, gene transcription and further

production of cytokines do not take place **(Fig. 3)**. There are seven STATs: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Different cytokines have the ability to preferentially recruit different STATs by virtue of selective binding to cytokine receptors.[4] The JAK/STAT pathways exert their function through type I and type II receptors. Type I receptors are used by several interleukins (ILs), colony-stimulating factors, and hormones, while type II receptors are used by interferons (IFNs) and IL-10 related cytokines **(Fig. 4)**.[5]

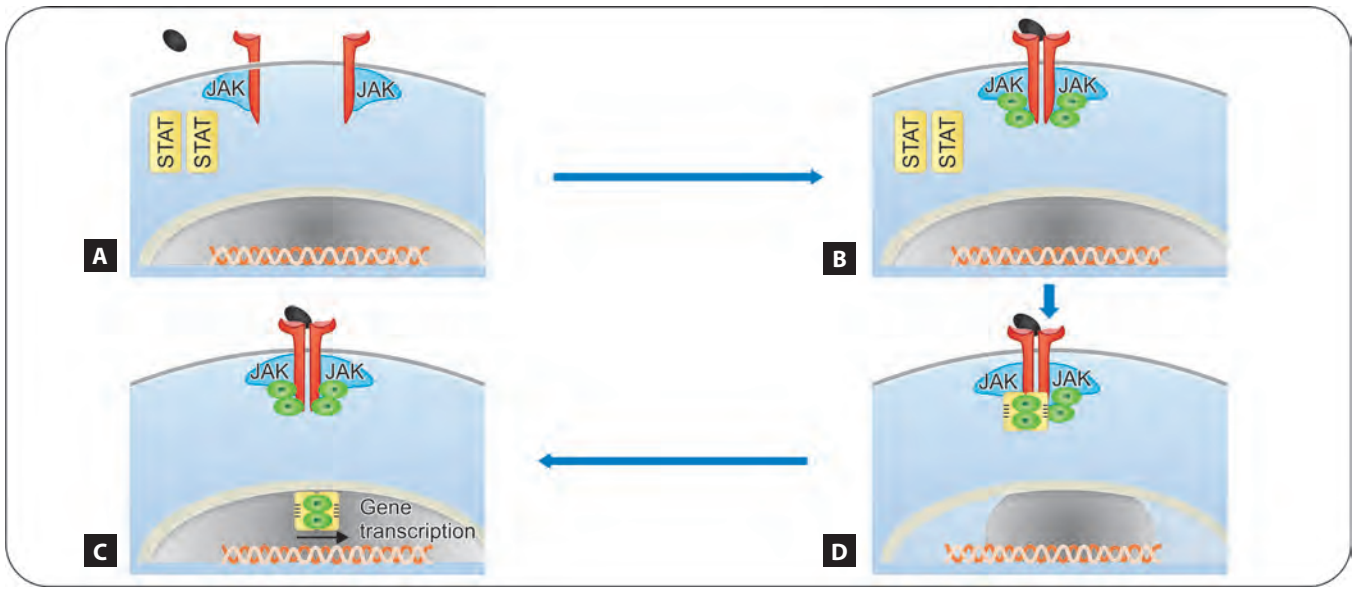
Flowchart 2: Small molecules—intracellular targets



Tofacitinib, one of the early Jakinibs, was approved in the USA in 2012 for the treatment of moderately severe RA not responding to conventional therapy and was approved in India by 2016. Baricitinib, another Jakinib, is also approved in India for the treatment of RA more than a year ago. Upadacitinib and Filgotinib are other Jakinibs yet to enter Indian market. All these molecules have undergone robust clinical trials for efficacy in RA[6] **(Tables 1 and 2)**. Randomized controlled trials (RCT) and long-term extension (LTE) studies have shown that Jakinibs are as efficacious as biologics. Safety profiles of these Jakinibs have also been carefully monitored long term.[7] Tofacitinib in Indian patients with RA had confirmed its efficacy and safety by a post hoc analysis in Phase 3 and LTE studies over 7 years.[8]

The Place of Jakinibs in Contemporary RA Management

Tofacitinib and baricitinib are currently available Jakinibs for the treatment of patients with moderately severe RA



Figs. 2A to D: JAK signaling pathways

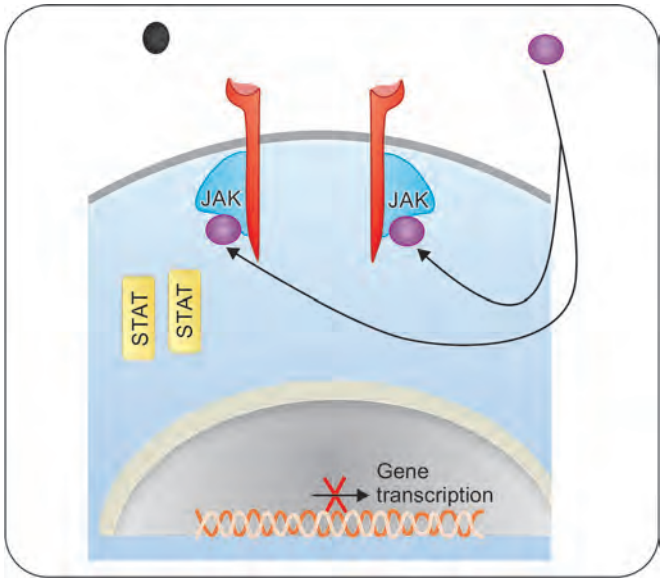


Fig. 3: Mode of action of JAK inhibitor (see text for the explanation)

not responding to conventional DMARDs. Tofacitinib targets mainly JAK1, JAK3 and Baricitinib JAK1, JAK2. Tofacitinib is also approved in other disorders such as psoriatic arthritis (PsA) and ulcerative colitis (UC). Many more Jakinibs are in the process of randomized clinical trials[9] **(Table 3)**.

Drug Target Indications

American College of Rheumatology (ACR) guidelines and European League against Rheumatism (EULAR) recommendations for the management of RA advise use of MTX to begin with.[10,11]

However, only a third of patients with early RA benefit from MTX monotherapy in controlling disease activity, improving patient reported outcome measures (PROMs) and slowing radiographic progression.[12] The ACR guidelines recommend combination of csDMARDs or

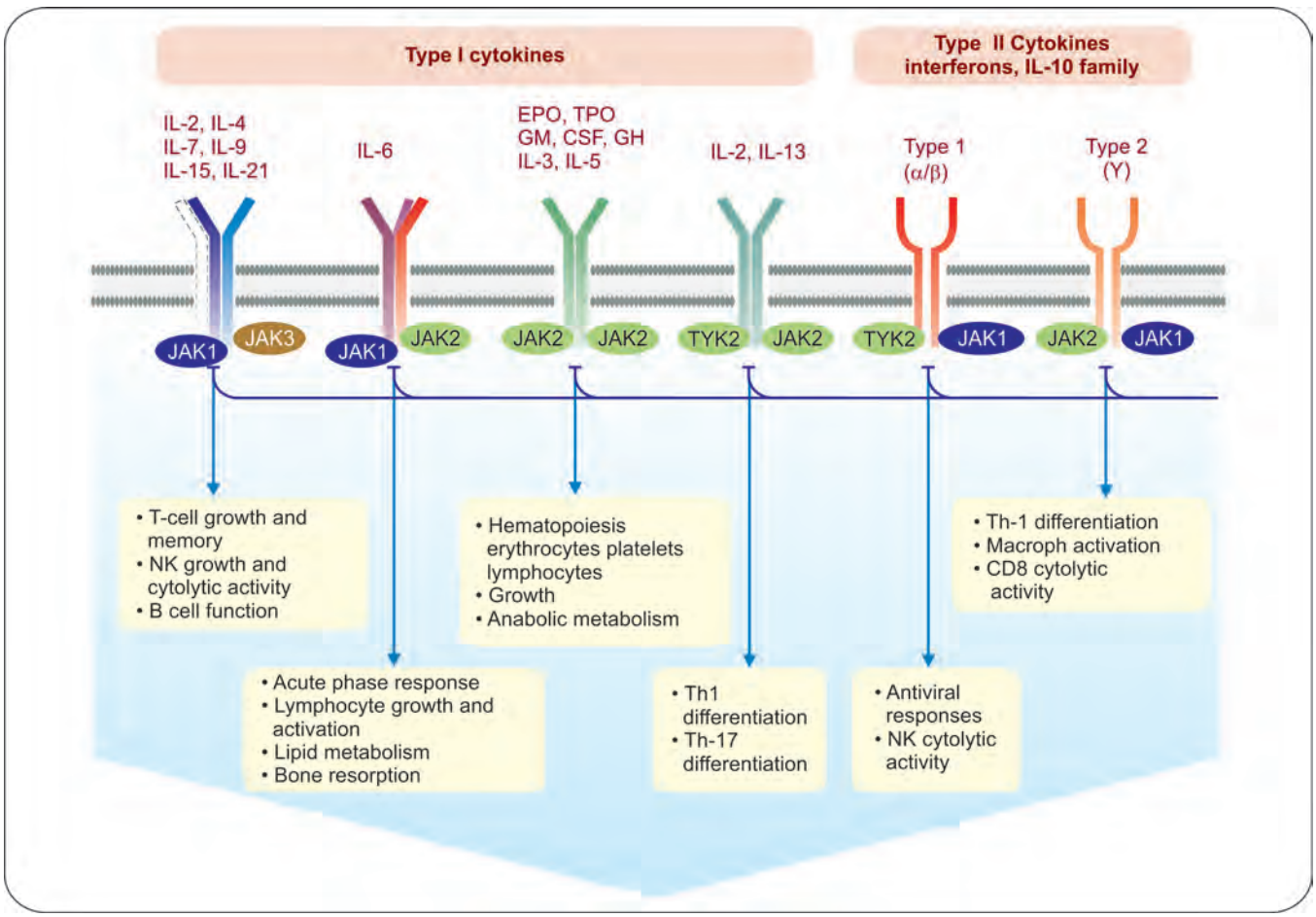


Fig. 4: Cytokines, JAK combinations and functions

TABLE 1 Tofacitinib in RA—phase 3 studies: overview

	DMARD-IR		***MTX-IR***		***TNFi-IR***	***MTX naïve***
Study(N)	**ORAL solo** (N=610)	**ORAL Sync** (N=792)	**ORAL Standard** (N=717)	**ORAL Scan** (N=797)	**Oral Step** (N=399)	**ORAL Start** (N=952)
Duration months	6	12	12	24	6	24
Background treatment	None	Nonbiologic DMARDs	MTX	MTX	MTX	None
Feature	Monotherapy	Background cDMARDs	Active control (ADA)	Radiographic outcomes	TNFi failure	Radiographic data (X-ray) monotherapy
Primary endpoints	ACR20 HAQ-DI DAS28-4 (ESR)	ACR20 HAQ-DI DAS28-4 (ESR)	ACR20 HAQ-DI DAS28-4 (ESR)	ACR20 HAQ-DI DAS28-4 (ESR)	ACR20 HAQ-DI DAS28-4 (ESR)	ACR70 mTSS

ACR, American College of Rheumatology; ADA, adalimumab; BARI, baricitinib; cDMARDs, conventional disease modifying antirheumatic drugs; DAS, disease activity score; HAQ-DI, health assessment questionnaire-disability index; IR, inadequate responders; mTSS, modified total sharp score; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

TABLE 2 Baricitinib in RA—phase 3 clinical trials overview

DMARD naïve	***cDMARD-IR***		***Biologic IR***
RA BEGIN MTX-naïve	RA BEAM MTX-IR	RA BUILD cDMARD-IR	RA BEACON TNFI-IR
MTX	PBO	PBO	PBO
BARI 4 mg mono	BARI 4 mg + MTX	BARI 2 mg	BARI 2 mg
BARI 4 mg + MTX	ADA 40 mg + MTX	BARI 4 mg	BARI 4 mg
52 weeks	52 weeks	24 weeks	24 weeks
RA BEYOND (long-term extension)			

ADA, adalimumab; BARI, baricitinib; cDMARDs, conventional disease modifying antirheumatic drugs; IR, inadequate responders; MTX, methotrexate; PBO, placebo; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

TABLE 3 Some JAKINIBS—their targets and indications

Drug	***Target***	***Indication***
Tofacitinib (Xeljanz)	JAK1, JAK3, JAK2	RA (approved in India also), PsA, UC
Baricitinib (Olumiant)	JAK1, JAK2	RA (approved in India also)
Peficitinib (Smyraf)	JAK1,2,3, TYK2	RA (approved in Japan)
Upadacitinib (Rinvoq)	JAK1	RA (approved in USA)
Filgotinib	JAK1	RA (completing clinical trials)
Decernotinib	JAK3	RA (continuing clinical trials)
BMS-986165	TYK2	PsA (started clinical trials)

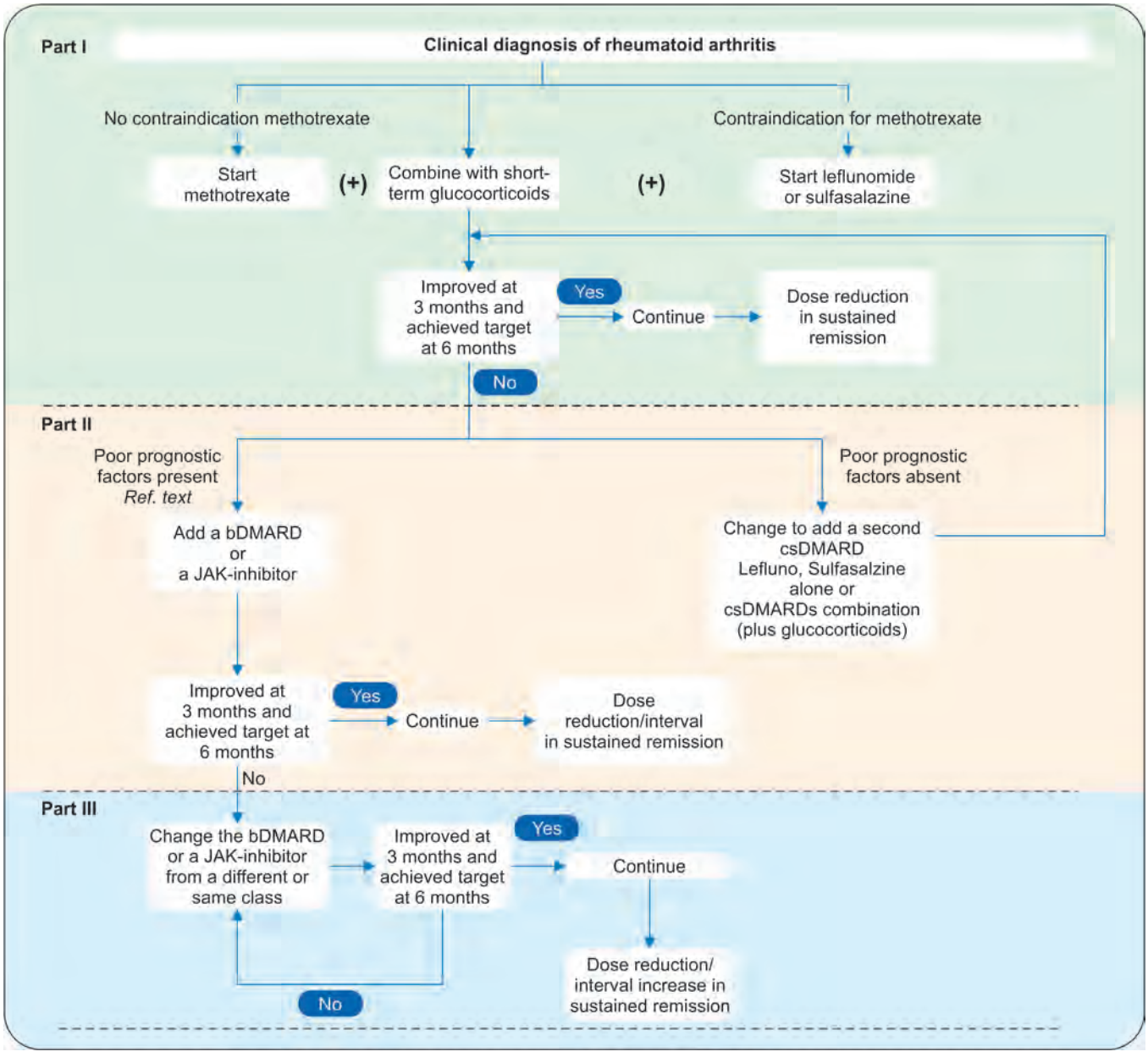


Fig. 5: RA treatment—EULAR recommendations 2019 update

addition of a bDMARD or a Jakinib, when the patients fail to achieve a satisfactory response to MTX monotherapy and a short period of glucocorticoids. Jakinibs with or without MTX are also considered in bDMARD inadequate responders. EULAR recommendations also advise similar management for RA, especially with poor prognostic factors such as high titers of RF/ACPA (anti cyclic citrullinated protein antibodies), high disease activity, early joint damage and/or failure of two or more csDMARDs **(Fig. 5)**.

Real world evidence for safety and efficacy of Jakinibs is also necessary to bridge the gap between RCTs and rheumatology clinics.[13] Usually there is little difference in the screening and monitoring of infections between Jakinibs and biologics. Increased risk of Herpes zoster may be common to all Jakinibs. In real world practice,

TABLE 4 Some of the ongoing clinical trials with JAKINIBS other than RA

• Juvenile arthritis	• Psoriasis
• Ankylosing spondylitis	• Alopecia areata
• Psoriatic Arthritis	• Atopic dermatitis
• Crohn's disease	• Vitiligo
• Ulcerative colitis	• Scleroderma
• Uveitis	• Lupus
• Sjogren's syndrome	• Vasculitis

accumulation of cases to evaluate risks of relatively rare serious adverse events (SAEs) is needed. Some of the SAEs are thromboembolic events, gastrointestinal (GI) perforation, and interstitial lung disease. Pharmacovigilance activity is required to establish the efficacy and safety of Jakinibs in patients with RA and other rheumatic diseases **(Table 4)**.

Advantages of Jakinibs

Jakinibs are orally administered small molecules unlike biologics, which are large proteins and given only by subcutaneous or intravenous.[14] Jakinibs act fast showing their benefits within 1–2 weeks. Small molecules can be synthesized easily, carried easily, and do not require cold chain. They do not have immunogenicity seen in some biologics; hence do not generate drug antibodies. Since their half-life is short for a few hours, they can be stopped in situation where infection is suspected with a rapid reversal of drug-related side effects. Blockade of a wide spectrum of cytokines may cover many inflammatory pathways. Tofacitinib and Baricitinib with background MTX proved to be non inferior and superior respectively over standard of care biologic Adalimumab in active RA.[15] PROMs, such as pain, function and fatigue are improved very well with Jakinibs.[16,17]

Jakinibs are proved to be beneficial and convenient even as monotherapy in RA. Tofacitinib in ORAL-Start study, Baricitinib in RA-Begin study, and Upadacitinib in SELECT-Early study have shown superiority over MTX on clinical, functional, and radiographic measures.[18]

Side Effects of Jakinibs

Infections

Usage of Jakinibs may increase serious and opportunistic infections. However, the rate of infections is not more than biologics except Herpes zoster.[19] The risk of reactivation of varicella zoster virus is increased by the use of Jakinibs with the combination of steroids and MTX. Before starting therapy with Jakinibs, vaccination against Herpes zoster is considered. Treatment with Jakinibs can cause anemia and decreased cell counts including lymphocytes, neutrophils, and platelets.[20] There is no particular association of these changes with serious infections or malignancy.

Tuberculosis

RA itself can increase the susceptibility to tuberculosis (TB). Biologics especially the TNF inhibitors increase the risk of TB, mostly in an endemic area. The incidence is less with Jakinibs. Among 5,671 subjects enrolled in Phase 2 and 3 and LTE studies of Tofacitinib, 26 cases of TB were reported. The median time between the start of Tofacitinib and diagnosis of TB was 64 weeks (15–161). Extrapulmonary infection occurred in fifteen (58%) cases. Most cases (20/26, 77%) were reported in those taking Tofacitinib 10 mg twice a day. However, globally Tofacitinib dosage is only 5 mg BID in RA. TB rate with Jakinibs was also associated with endemicity.[21]

Thromboembolic Events

Possibility of increased risk of thromboembolic events is noted with the use of Baricitinib. RA itself has a tendency to develop the risk of deep venous thrombosis and pulmonary embolism. Relating this complication to the action of a specific or a group of cytokines is difficult. JAK2 inhibition disturbs thrombopoietin signaling and platelet homeostasis, but its relation to thrombosis is ill-defined.[22]

Malignancy

Patients with RA have an increased incidence of malignancy including lymphoma. The rate of cancer in patients on Jakinibs is similar to those on biologics[23] **(Table 5)**.

Other Problems

Jakinibs are associated with an increase in total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) particles. Jakinibs may limit vascular damage by decreasing inflammation in spite of increased cholesterol.[24] Minimal increases in creatine phosphokinase levels are observed without overt muscle disease. The use of Jakinibs may be associated with increased liver enzymes and GI perforation. Jakinibs are

TABLE 5 Incidence rates of adverse events of special interest of JAKINIBS in RA

Adverse events	*Tofacitinib*	*Baricitinib*
Serious infection	2.7 (2.5, 3.0)	2.9 (2.5, 3.4)
Herpes zoster	3.9 (3.6, 4.2)	3.2 (2.8, 3.7)
Tuberculosis	0.2 (0.1, 0.3)	0.15 (0.07, 0.27)
Malignancy excluding NMSC	0.9 (0.8, 1.0)	0.8 (0.6, 1.0)
NMSC	0.6 (0.5, 0.7)	0.4 (0.2, 0.5)
Lymphoma	0.1 (0.1, 0.2)	0.09 (0.03, 0.19)
MACE	0.58 (0.39, 0.88)	0.5 (0.4, 0.7)
DVT/PE	DVT: 0 in PBO-controlled cohort and 0.1 (0, 0.3) in dose-comparison cohort PE: 0 in PBO-controlled cohort and 0.1 (0, 0.4) for 5 mg bid	DVT/PE: 0.5 (0.3, 0.7)
GI perforation	0.11 (0.07, 0.17)a	0.05 (0.01, 0.13)

Incidence rates (95% CIs) in RA patients treated with each JAK inhibitor were shown.
DVT, deep vein thrombosis; GI, gastrointestinal; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PE, pulmonary embolism.

contraindicated at the time of pregnancy. Women of childbearing age should use effective contraception while on treatment. During breastfeeding, Jakinibs should not be used.

Conclusion

- JAK inhibitors are the latest addition of the treatment of RA in the last decade.
- They act by blocking intracellular JAK/STAT signaling pathways inhibiting the production of inflammatory cytokines.
- They are rapidly acting, oral targeting anti-rheumatoid drugs with convenience.
- They showed sustained efficacy and established safety by robust clinical drug trials and real world experience.
- Recommended as a second line therapy for csDMARDs inadequate responders or Biologic inadequate responders by several guidelines.

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CHAPTER

210 Biosimilars: Bane or Boon for India

Durga Prasanna Misra, Pallavi Patro, Vikas Agarwal

Abstract

Biosimilars are structural analogues of innovator biological drugs which have undergone rigorous development and testing. In this chapter, we overview definitions of biosimilars, biomimics, and biocopies; review regulatory processes for biosimilar approval; and discuss the concepts of extrapolation, switch, substitution, re-switch, and nocebo effect as assess perspectives for biosimilar use (including cost) from an Indian perspective.

Introduction

Better understanding of pathophysiological process driving disease has given rise to targeted therapies for the treatment of these diseases. Biologic drugs are drugs administered parenterally, which target specific molecular pathways resulting in disease phenotypes. Biologic drugs are now used in many medical specialties such as Rheumatology, Hematology, Oncology, and Nephrology.[1-3]

The classical example of a biologic drug that has revolutionized patient management in drugs targeting the proinflammatory cytokine tumor necrosis factor alpha (TNF-α) in disease settings like rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Such anti-TNF therapies have become frontline agents for the management of these lifelong inflammatory diseases, and markedly improved disease control in those refractory to conventional disease-modifying antirheumatic drugs. However, despite their use being described in RA and AS since the late 1990s, anti-TNF agents remained out of reach for a majority of the Indian populace until recently, in no small part due to prohibitive costs.[2] A major reason for increased accessibility has been the advent of biosimilar drugs, which are copies of the innovator biologic drug, however, are amenable to manufacture locally as well as not covered by any existing patents. Therefore, biosimilars are cheaper and more accessible. The recent past has seen a flooding of the local market for such biosimilar drugs. In this chapter, we discuss the impact of biosimilar agents (benefits as well as costs) and their comparability in terms of effectiveness and adverse effects, as well as issues such as nocebo effect, which potentially limit their use in patients.[4] We also discuss certain peculiar adverse effects occasionally described with biosimilars.

Biosimilars and Biomimics/Biocopies

Biologic drug synthesis is complex, in that it relies on recombinant deoxyribonucleic acid (DNA) technology for synthesis of these molecules. Biosimilars are similarly synthesized using recombinant DNA technology,[5] so also are biomimics or biocopies with similar molecular structure (primary, secondary, and tertiary). However, biosimilars differ from biomimics or biocopies in that they also have been demonstrated to have equivalent effect on disease states in preclinical and clinical trials, as well as demonstrate similar pharmacokinetic and pharmacodynamic properties (including immunogenicity) to the innovator biologic drugs.[6]

Regulatory Processes for Approval of Biosimilar Drugs

The two major agencies regulating drug approval in the world, the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) have laid down guidelines for the approval of biosimilar drugs. Broadly, the similar protein structure of the innovator biologic drug and the biosimilar should be demonstrable, followed by studies that demonstrate equivalence in pharmacokinetic and pharmacodynamic properties with innovators. Thereafter, efficacy and safety of biosimilar drugs with innovator biologic drugs should be demonstrated before consideration for approval. Ideally, equivalence with innovator (i.e. neither a clinically significant detriment nor benefit when compared with innovator biologic) should be demonstrated rather than non-inferiority (i.e. simply the lack of a clinically significant detriment). Furthermore, since these are foreign proteins, the lack of significant difference in immunogenicity when compared with innovator biologic drugs should also be demonstrable. Mere identity in protein structure without demonstrating the other steps mentioned simply results in a biomimic. Such biomimics have been noted to have a greater propensity to develop adverse effects than innovators, and are often in vogue in regions of the world with poor regulatory policies.[7-9] The approval processes for biosimilars in India are broadly in line with the EMA and US FDA standards. This requires approvals from the Central Drugs Standards Control Organization (CDSCO).

Are Biosimilars the Same as Generic Drugs?

A common source of confusion is generic drugs and biosimilars. It is important to understand that generic drugs are mere chemicals with identical structure to the original molecules. The generation of biologic drugs has the added complexity that they require biologic systems for the generation of their recombinant protein structure; hence, they are thematically more complex to generate and attain equivalence to innovators when compared with chemical generic drugs.[7]

The Need for Post-marketing Surveillance for Long-term Safety of Biosimilars

An often-quoted tale of caution regarding biosimilar use has been the example of recombinant erythropoietin biosimilar, which was introduced in South America as a cheaper alternative to innovator erythropoietin analogue. This drug was primarily intended for use in patients with chronic kidney disease with anemia (which often results due to erythropoietin deficiency). Unusually, some patients treated with erythropoietin biosimilar developed pure red cell aplasia, resulting in refractory transfusion-dependent anemia.[10] This was a consequence of antibodies that neutralized the effect of erythropoietin due to differences in immunogenicity of the biosimilar molecule.[10] Such issues were later rectified in future erythropoietin biosimilars by modifying the protein structure to ameliorate such abnormal immunogenicity.[7] This is a case in point, which reiterates the need to seek long-term safety of biosimilars that are eventually approved and marketed by means of continual post-marketing surveillance.[11]

Extrapolation

Another term often used in the context of biosimilars is extrapolation. Many a times, the same biologic drug is used for a number of disease states. For example, anti-TNF agents are used in RA, AS, psoriatic arthritis (PsA), inflammatory bowel diseases (IBD), and sarcoidosis. Should a biosimilar be shown to be equivalently efficacious to the innovator in RA, this is often extrapolated to assume its effectiveness to a similar degree in the other disease states it is indicated for, such as AS, PsA, and IBD. This is a common practice with biosimilars; however, due caution and careful post-marketing surveillance should accompany any such extrapolation of indication for the use of biosimilars.[12]

Switch, Substitution, and Re-switch

Switch refers to the decision of the treating clinician to change a biologic drug from innovator to biosimilar, or vice versa. If such a decision is taken by somebody who is not the treating physician, say, a regulatory authority or the hospital administration (due to costs or other concerns), this is instead referred to as a substitution (also known as a non-medical switch). After an initial switch, it is possible to re-switch back and forth between the two products, depending on feasibility issues such as availability, ability to afford, etc.[1]

Switching offers an opportunity to provide head-to-head comparisons between innovators and biosimilars. Analysis of more than 300 patients with IBD from Sweden

switched from innovator infliximab to biosimilar infliximab CT-P13 revealed similar disease activity state at 12 months of observation.[13] In another study from the Netherlands, 625 patients switched to biosimilar etanercept were compared with a historical cohort of 600 patients treated with innovator etanercept at the same region. Indications for etanercept use in these patients were inflammatory arthritides (RA, AS, and PsA). At 6 months, retention rates of the biosimilar (in the switched cohort) or innovator (in the historical cohort) were nearly 90%, although patients switched to etanercept biosimilar had a slightly higher risk of discontinuation.[14] A Scandinavian biologic registry spanning five countries compared retention rates for infliximab (innovator 320, biosimilar 999 patients) and etanercept (innovator 493, biosimilar 522) in patients with spondyloarthritis. At 1-year follow-up, 66% treated with etanercept biosimilar continued the same compared with 73% treated with etanercept innovator; corresponding figures for infliximab at 2-years were 44% for biosimilar and 46% for innovator, suggesting similar rates of retention irrespective of biosimilar or innovator molecule.[15] A comparison of more than 1,600 etanercept biosimilar switchers with more than 400 non-switchers (continuing on innovator etanercept) from Denmark for RA, AS, and PsA revealed numerically higher retention rates at 1 year for switchers than non-switchers (although of little difference in magnitude and not significant statistically).[16] A long-term follow-up of patients for 52 weeks switched to biosimilar infliximab compared with innovator infliximab in a randomized trial (NOR-SWITCH trial) for a variety of multisystem inflammatory diseases revealed similar rates of efficacy and safety.[17] An expected benefit of switching is lesser health-care costs; however, a recent analysis of 1620 recipients of etanercept biosimilar from Denmark did not reveal a significant cost-saving in the year following the switch compared to the year preceding it.[18] Hence, the cost-effectiveness of switching biosimilars needs further evaluation.

Nocebo Effect

A perceived lesser degree of response to a drug owing to psychological or contextual factors might be described as a nocebo effect. This is thematically the antithesis of a placebo effect (i.e. perceived positive effect of a placebo, when no active drug is being administered). Biosimilar drug use in real life might be affected by the nocebo effect. In the setting of rheumatic diseases, biosimilar drugs have not shown significant differences compared to innovator drugs in blinded randomized controlled trials. However, open-label clinical trials and real-life registry data have often demonstrated lower retention rates (and higher rates of switch back to innovator drug) with biosimilars. This might be due to the perceived ineffectiveness of these drugs by the patients, which is supported by the fact that many such switches are based on subjective (rather than objective) measures of ineffectiveness. Such a nocebo effect has the potential to limit the cost-saving effect of biosimilars at an aggregated level by limiting their utilization.[4] However, the authors perceive that nocebo effect might be a particular problem in societies where health care is nationalized. In countries like India, where a majority of the time patients pay out-of-pocket to afford biologic drugs, the lower cost of biosimilar agents is likely to reduce the likelihood of nocebo effect (since affordability now becomes the major concern rather than perceived effectiveness).

Perspectives from India Regarding Biosimilars

Overall published literature regarding the effectiveness of biosimilars from India is scarce. A significant chunk of the available literature relates to a biosimilar of adalimumab (ZRC-3197). Regulatory approval was obtained after proving efficacy of this adalimumab biosimilar in patients with RA when compared with innovator adalimumab.[2] Thereafter, real life data regarding ZRC 3197 use in 51 patients with spondyloarthritis and 39 patients with RA was published. At an observation period of 1 year after treatment, more than 90% patients with spondyloarthritis had attained clinical remission. Nearly 60% of the cohort with RA also attained control of disease activity.[19] Post-marketing surveillance under the Adalimumab Biosimilar Patient Registry (ASPIRE) further recently reported data in relation to RA and spondyloarthritis. In 73 patients with RA, significant reductions in disease activity were noted by 24 weeks; nearly one-half patients attained good control of disease activity.[20] For 100 patients with AS treated with adalimumab biosimilar in this same ASPIRE registry, adequate control of disease activity with attainment of Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) below 4 at 24 weeks of observation was possible

BOX 1 Recommendations of the EULAR, GRS, and PANLAR regarding the use of biosimilars in rheumatology practice[22-24]

- Biosimilars should have lesser cost than the reference/innovator product
- Biosimilars should undergo strict regulatory processes to demonstrate equivalence in safety, efficacy, and immunogenicity with innovator molecules
- In the absence of having undergone strict regulatory processes, such drugs shall only remain as biomimics and should not be referred to as biosimilars
- Biosimilars should be preferably prescribed by their brand name to differentiate them from innovator biologics (also prescribed preferably by their brand name)
- Biosimilars should not be substituted for innovator products, or vice versa, without the knowledge of the prescribing physicians
- All patients receiving biologic drugs, whether innovator or biosimilar, should preferably be enrolled in registries
- Ongoing surveillance should be done to assess any unexpected adverse effects of biosimilars, which might be evident only after marketing

EULAR, European League against Rheumatism; GRS, Greek Rheumatology Society; PANLAR, Pan American League of Associations for Rheumatology

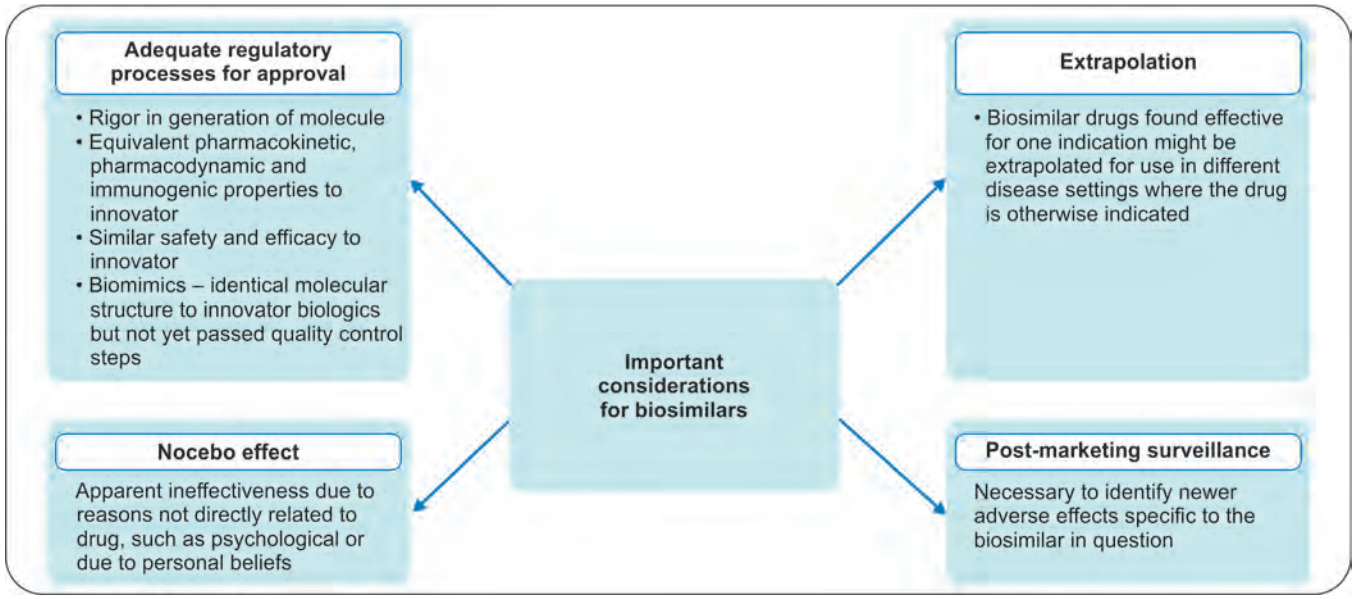

Fig. 1: Issues related to biosimilars and their approval processes

in more than 90% patients.[21] Neither of these two studies identified any adverse safety signals with adalimumab biosimilar during post-marketing surveillance.[20,21] There remains an unmet need to generate and publish such real-world data in a larger number of patients for biosimilar drugs used for different indications in India.[22]

Recommendations for Biosimilar Use in Rheumatic Diseases

Considering the proliferation of available biosimilar drugs worldwide for the management of rheumatic diseases, as of now various international societies have provided guidelines for the prescription of biosimilar drugs. **Box 1** summarizes the relevant information from the guidelines for biosimilar use provided by the European League against Rheumatism, the Greek Rheumatology Society, and the Pan American League of Associations for Rheumatology.[23-25] Briefly, these recommendations suggest that biosimilars should be cheaper than reference biologics, share similar safety and efficacy profile, undergo suitable regulatory approvals before marketing, and be subject to post-marketing surveillance.

Conclusion and Future Perspectives

Figure 1 summarizes the various issues associated with biosimilar approval and use. Despite potential advantages of biosimilar drugs in terms of cost savings and greater accessibility with similar efficacy/effectiveness and safety to innovator biologic drugs (provided they have passed through rigorous regulatory processes), the uptake of biosimilars has not been uniform. An analysis of a database from the United States of America reviewed prescriptions of innovator and biosimilar infliximab amongst patients visiting rheumatology practices. Only 3.5% patients took up infliximab biosimilar, despite this retention rates were similar to innovator infliximab.[26] As discussed earlier, one of the barriers toward uptake or retention of biosimilars could be a nocebo effect.[4] It is important to evaluate such factors and attempt to reduce factors, which limit their uptake despite adequate efficacy and safety. This could be facilitated by conducting qualitative research in this area. Furthermore, despite some studies showing no definitive cost-saving with biosimilars, it is reasonable to hypothesize that in a country, like India, where a majority of health-care settings where biosimilars are used is out-of-pocket expenditure,[27] use of biosimilars shall result in saving of significant costs. Literature suggests that a significant proportion of physicians might not be adequately aware about the nature and utility of biosimilars; hence, better education in this regard might help improve the appropriate utilization of biosimilars in the proper setting.[3]

To conclude, biosimilars are a boon for India, particularly since they are cheaper and equally efficacious and safe alternatives (after appropriate regulatory approvals) and can potentially improve the sustainability of biologic use when used appropriately. At the same time, it is necessary to caution about biomimics until they have undergone appropriate regulatory approvals to prove their equivalence in safety and efficacy.

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CHAPTER

211 An Approach to Vasculitis

Packiamary Jerome

Abstract

Vasculitis is an immunological disorder leading to inflammation of the vessel wall. The clinical symptoms range from a mild self limiting illness to severe life threatening complication. Vasculitis affects blood vessels of all types and all organs. It may happens as a de novo phenomenon or secondary to other causes like infection, drugs, malignancy, and so on. Vasculitis affects all organs in the body including skin, eye, ear, nose, throat, lungs, heart, joints, etc. The clinical manifestations mimics like that of a viral illness. There will be an elevation of acute phase reactants. Biopsy of the involved organ can give a clue to the diagnosis of vasculitis. Treatment includes supportive care, followed by steroids and immunosuppressants. A comprehensive approach is needed for an accurate diagnosis of vasculitis.

Introduction

Vasculitis is a group of disorder characterized by the inflammation of the vessel wall. The clinical manifestations of vasculitis range from a mild self limiting cutaneous involvement to severe life threatening multiorgan involvement. The diagnosis of vasculitis is difficult as the clinical presentations mimic many other illnesses and the diagnosis of vasculitis often gets delayed. A high degree of suspicion, detailed history and systematic physical examination may help in arriving at the diagnosis of vasculitis.

Epidemiology

The incidence of vasculitis in western population is 20 per million per year. The exact incidence and prevalence in India is not available. Among the various types of vasculitis, the most common is Takayasu's arteritis and the most uncommon is Temporal arteritis. Wegener's granulomatosis is more common in north India than south India.

Classification

Vasculitis affects blood vessels of all the types and all the organs. Vasculitis should be suspected in any patient with unexplained ischemia in the absence of atherosclerosis. Because of the increased vasculature skin is more prone for vasculitis. The vasculitis is primarily classified into two types:

- *Primary vasculitis:* It is presumed to be immune origin.
- *Secondary vasculitis:* It is mainly secondary to other causes like infection, drugs, malignancy, or idiopathic.

Chapel Hill Classification (1993)

This classification is currently considered as "Gold Standard." *See* **Table 1**.

LIE Classification (1994)

Primary Vasculitis

- Vasculitis of Large, Medium, and Small Vessels:
  - Giant cell arteritis

TABLE 1 Classification based on vessel size

Large vessel vasculitis	• Giant cell arteritis • Takayasu disease
Medium vessel vasculitis	• Polyarteritis nodosa • Kawasaki disease
Small vessel vasculitis	• Microscopic polyangiitis • Wegener's granulomatosis • Churg strauss syndrome • Henoch schonlein purpura • Essential mixed cryoglobulinemia • Cutaneous leukocytoclastic vasculitis

TABLE 2 Granulomatous and non granulomatous vasculitis

	Granulomatous	***Non-granulomatous***
Large	• Temporal arteritis • Takayasu arteritis	–
Medium	–	• Classic PAN • Kawasaki disease
Small	• Wegener's granulomatosis • Churgstrauss syndrome	• Microscopic polyangiitis • Henoch schonlein purpura • Essential mixed cryoglobulinemia

  - Takayasu disease
  - Isolated angiitis of CNS
- Vasculitis of Medium and Small Vessels:
  - Polyarteritis nodosa
  - Churg strauss syndrome
  - Wegener's granulomatosis
- Vasculitis of Small Vessels:
  - Microscopic polyangiitis
  - Henoch schonlein purpura
  - Cutaneous leukocytoclastic vasculitis
- Miscellaneous:
  - Burger's disease
  - Behcet's disease
  - Cogan's syndrome
  - Good pasteure's syndrome
  - Kawasaki's syndrome

Secondary Vasculitis

- Infection
- Connective tissue disease
- Drug hypersensitivity
- Essential mixed cryoglobulinemia
- Malignancy
- Hypocomplementemia
- Post organ transplant

Savage Classification (1997)

See **Table 2**.

Causes of Vasculitis

- Immune (idiopathic)
- Infection (Bacteria, Fungus, Viral, Rickettsia)
- Drugs
- Tumors
- Radiation
- Extremes of temperature

Approach to Vasculitis

Vasculitis has multiple presentations. There are no definite guidelines or approach to the diagnosis of vasculitis. To diagnose vasculitis systematic approach is essential with proper history taking, clinical examination, and laboratory parameters.

- Clinical Findings
- Laboratory Findings
- Radiology
- Histology

Clinical Manifestations

Vasculitis may present with isolated cutaneous involvement or with a diffuse systemic involvement. Systemic vasculitis presents usually around 2nd to 5th decade except that Henoch schonlein purpura and Kawasaki disease in pediatric age group. Takayasu arteritis is common in young females.

General Manifestations

The clinical manifestations of vasculitis mimic like that of a normal viral illness. It includes fever, weight loss, malaise, fatigue, night sweats, generalized ache and a feel of physical unwell. These manifestations are due to the systemic inflammatory response which is produced by the release of chemical mediators from the inflamed blood vessels. These findings may not occur in patients with localized form of vasculitis.

TABLE 3 Systemic manifestations of vasculitis

Organs involved	*Manifestations*
Skin	Pupura, Nodules, Plaques, Infarcts, Ulcers, Pyoderma gangrenosum, Widespread skin necrosis, Gangrene, Urticarial wheels
Muscles & joints	Arthralgia, Arthritis, Myalgia, Weakness
Eyes	Scleritis (prelimbic area), Ring ulceration, Scleromalacia, Globe perforation, Uveitis and Retinal vasculitis, Loss of vision
Ear	Recurrent otitis media unresponsive to grommet insertion, Hearing loss, Recurrent ear drum perforation
Nose	Recalcitrant sinusitis, Nasal septal perforation, Collapsed bridge of the nose
Throat	Recurrent oral ulcers
Airways	Tracheal and bronchial stenosis
Lungs	Infiltrates, Nodules, Cavities, Mass lesions, Abscess, Areas of hemorrhage
Heart	Coronary arteritis—Kawasaki Pericardial and myocardial involvement at necropsy
GI tract	Mild abdominal angina, Perforation, Peritonitis, Hemobilia, Hepatic/splenic infarction, Pancreatitis
Kidneys	Renovascular hypertension, Hematoma around the kidney, Glomerulonephritis, Renal failure, Proteinuria, Microscopic hematuria
Reproductive system	Testicular infarction, Penile ulcers on glans & shaft, Scrotal ulcers
Central nervous system	Mononeuritis multiplex, Polyneuritis cranialis, Diffuse brain dysfunction

Systemic Manifestations

See **Table 3**.

Symptoms of Individual Vasculitis

See **Flowchart 1**.

Red Flag Signs in Vasculitis

- Polymyalgiarheumatica—classical of Temporal arteritis
- Jaw claudication during mastication—Temporal arteritis
- Stridor—Wegener's granulomatosis
- Abdominal pain, vomiting, intestinal obstruction, bleeding
- Proteinuria, microscopic hematuria, active urinary sediment in the absence of infection
- Mononeuritis multiplex, Polyneuritis cranialis
- Acutely progressing skin lesion

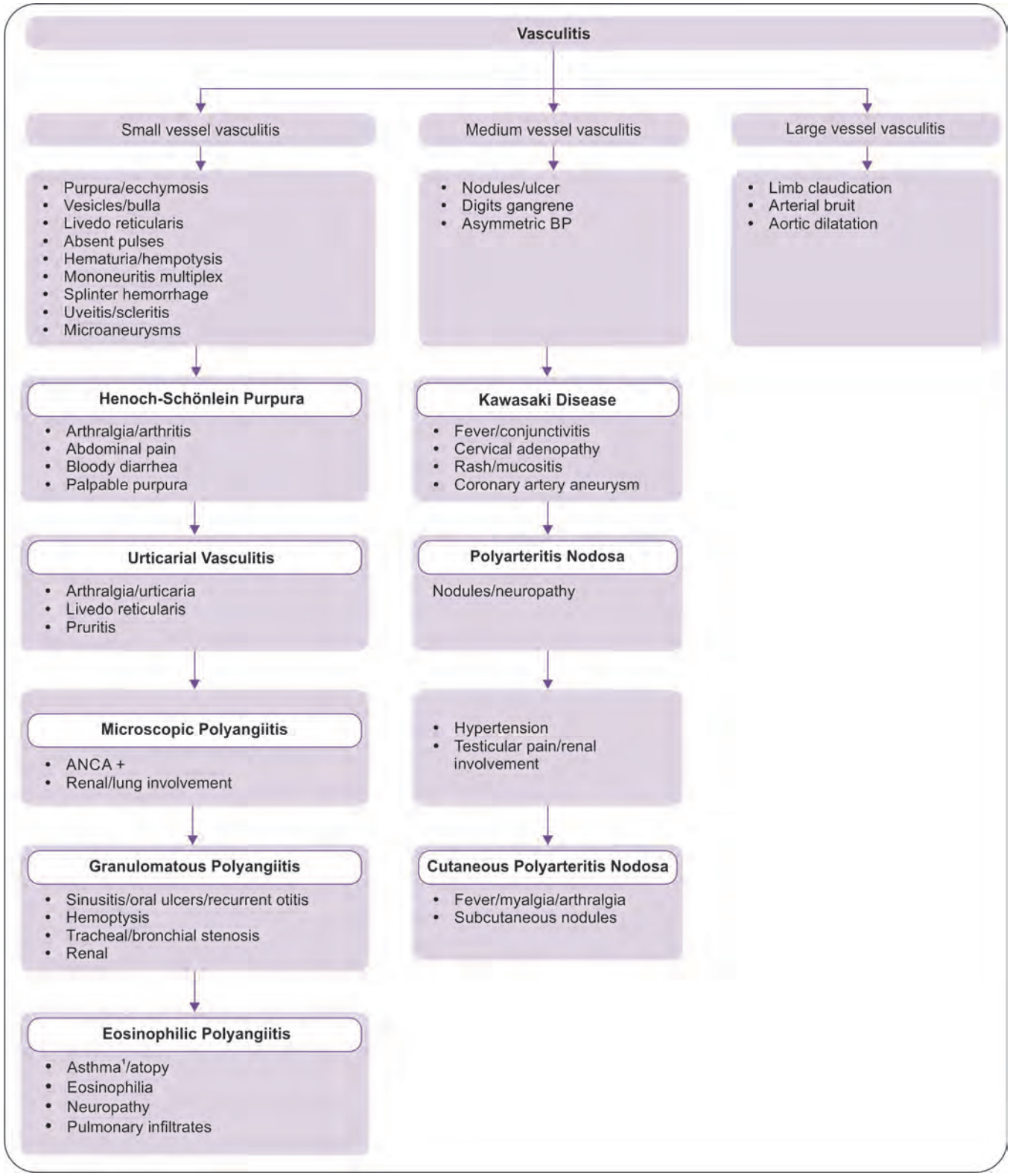
Drug-iduced Vasculitis

Drug-induced vasculitis should never be missed as the withdrawal of the offending drug is the main treatment. The same picture like that of isolated cutaneous involvement to diffuse organ involvement can happen with certain drugs. Some common drugs causing vasculitis are propylthiouracil, antiepileptics like phenytoin, carbamazepine, valproate, antibiotics including macrolides, quinolones, aminoglycosides, penicillins, antitubercular drugs like rifampicin and isoniazid. Several antihypertensives like hydralazine, methyldopa, nifedipine, atenolol, frusemide, diltiazem can cause vasculitis. Other drugs include heparin, warfarin, streptokinase, allopurinol, methotrexate, antidepressants. Drugs which cause ANCA positive vasculitis include hydralazine, propylthiouracil, ciprofloxacin, minocycline, phenytoin, clozapine, allopurinol, sulfasalazine, D-penicillamine.

Vasculitis Mimics

- Infections—infective endocarditis,[2] tuberculosis, syphilis, invasive fungal infections, viral/rickettsial infections.
- Drug induced vasculitis
- Cholesterol embolus disease, antiphospholipid syndrome, sarcoidosis, amyloidosis
- Malignancy, atrial myxoma

Flowchart 1: Vasculitis



Investigations

Hematology

The laboratory picture of vasculitis mimic like that of an infection. ESR will be elevated. Hematology shows normocytic normochromic anemia, leukocytosis, and thrombocytosis. Eosinophilia is most common in Churgh strauss syndrome.[3] CRP will be increased.

Biochemistry

Renal function and liver function tests are helpful in determining the extent of the disease, organ damage, and therapeutic intervention. Elevated serum creatinine and decreased creatinine clearance occurs in PAN, GPA, MPA.

There will be hypoalbuminemia with hyperglobulinemia. Gammaglobulinemia is predominantly of IgG type but in WG, HSP it is of IgA type. IgE levels are increased in CSS.

Urine Analysis

Urine investigations should be a must to rule out infection. Urine may show proteinuria, hematuria, and cylindruria. ANCA associated vasculitis may show active urinary sediment with red cell casts.

As the treatment of vasculitis involves the use of immunosuppressants, infections should be ruled out as it can lead to disastrous complications. Procalcitonin is a good diagnostic tool to rule out vasculitic mimic like infection. It will be elevated in infections rather than non-infective inflammatory etiology. But the cost and availability hinders its usage. Apart from the basic workup, specific autoimmune workup has to be done for further evaluation.

Serology

Rheumatoid factor is frequently positive in vasculitis. Very high titre of rheumatoid factor is a hallmark of systemic rheumatoid vasculitis. ANA will be positive in high titres in SLE, Systemic sclerosis, Sjogrens syndrome, and Overlap syndrome. hepatitis B, hepatitis C is a must to rule out classical PAN, cryoglobulinemia vasculitis. Anti GBM antibody will be positive in Good Pasteur's syndrome.

Antineutrophil Cytoplasmic Antibodies (ANCA)

ANCA is specific diagnostic tool for diagnosing vasculitis. ANCA is done by indirect immunofluorescence/ELISA.

TABLE 4 ANCA and its specificity

Pattern		***Antibodies directed against***	
C–ANCA	Central, coarse, dense, granular, cytoplasmic fluorescence	Anti-serine protease 3(PR3)	Wegner's (>90%) MPA (100%) CSS (50–60%)
P–ANCA	Perinuclear fluorescence	Anti-myeloperoxidase (MPO)	MPA (70–90%) WG(<10%)
Atypical ANCA	Mixed pattern	Lactoferrin, cathepsin G, elastase, lysozyme	

During the acute phase of vasculitis, ANCA will be positive in very high titres.[4] But, ANCA has a poor correlation between tires and clinical disease activity. There are three different patterns of ANCA shown in **Table 4**.

Imaging

X-ray Chest

Nodular, cavitating infiltrates is characteristic of Wegner's granulomatosis. Vasculitis must be included in the differential diagnosis, when there is unresolving, rapidly progressive consolidation during adequate antibiotic/ATT. Rapidly enlarging parenchymal lesion suggestive of pulmonary hemorrhage is characteristic of Wegner's granulomatosis, microscopic polyangiitis.

CT/MRI/PET Scan

The above imaging modalities are used in the diagnosis, delineation of disease extent, identification of biopsy site, and monitoring response to therapy.

FDG PET scan will help in detection of aortic wall inflammation.[5]

Angiography

Angiography defines the extent of disease involvement. It is also useful in classifying the type of vasculitis, identifying the areas for intervention like angioplasty and stent insertion. It is important in large and medium vessel vasculitis. It shows the pathognomonic visceral aneurysms in Polyarteritis nodosa.

2D Echo

Done to rule out left ventricular dysfunction, myxoma.

Histology

Skin Biopsy

Skin biopsy may show features suggestive of inflammation. The same histology may be seen in patients with benign cutaneous vasculitis and SNV. For ideal histopathological examination, sample should be taken less than 48 hours of onset of symptoms.[6] Nodular skin lesions and involved muscles are preferred sites for PAN.

Renal Biopsy

Granulomatous inflammation in tissue biopsy is suggestive of Wegner's granulomatosis.

Nerve Biopsy

Vasculitis of the vasa vasorum is characteristic of mononeuritis multiplex. Sural nerve biopsy is indicated if peroneal neuropathy is seen on electromyography. In giant cell arteritis, Temporal artery biopsy is done. Biopsy of subclavian artery is done in Temporal arteritis.

Mucosa of Sinus and Nose

As vasculitis is a patchy process, it may be easily missed in a small biopsy.

Open Lung Biopsy

It is a highly rewarding procedure. Pulmonary tissue biopsy is highly specific for Wegener's granulomatosis.

Treatment

General Measures

Avoid stress, bed rest, and keep extremities warm. Avoid smoking in case of severe pulmonary involvement. Antihistaminics to reduce itching and NSAIDs to decrease pain.

Specific Therapy

- *Antibiotics*: To control infections according to culture and clinical profile.
- *Drug*: Stop the offending drug in case of drug induced vasculitis.
- *Dapsone:*[7] It can be used as the initial agent for CSVV in the absence of systemic involvement (Dose: 50–200 mg/day in divided doses). The response can be observed within 2 weeks. In urticarial vasculitis dapsone can be combined with indomethacin or hydroxychloroquine.
- *Hydroxychloroquine* (200–400 mg/day): It can be used in HUV but not in other small vessel vasculitis.
- *Corticosteroids:* Low dose steroids (<10 mg on alternate days) are used to reduce the inflammation in patients not responding to steroids in small vessel vasculitis. High dose systemic steroids are indicated in severe necrotic/ulcerative cutaneous lesion, acute glomerulonephritis, peripheral neuropathy with impending palsy and gastrointestinal bleeding.

  Steroid has a good response in HSP in preventing nephritis as well as improves the outcome of existing nephritis. In classic PAN disease control can be achieved with steroids. In HCV associated cutaneous vasculitis, short-term systemic steroids are beneficial in controlling renal and CNS manifestations.[8] Steroids should be short term in virus associated vasculitis in order to prevent the risk of viral replication.

  Steroids show a good remission. It helps in decreasing the infection rate, cumulative dose of cyclophosphamide to achieve remission and decrease rate of secondary malignancy. Temporal arteritis shows a very good response to steroids. After remission it can be maintained with immunosuppressants like azathioprine or methotrexate. Systemic steroids are contraindicated in Kawasaki disease to avoid coronary aneurysm formation.

  Intravenous pulse steroid (methylprednisolone 1 gm/day for 3 days) therapy is indicated in life threatening organ involvement in diseases like WG, MPA, CSS.
- *Cyclophosphamide:* Between 2–3 mg/kg/day. It can be continued for a year after remission was attained. The side effects are hemorrhagic cystitis, bladder cancer, marrow toxicity. There is an increased occurrence of relapse after withdrawal of the drug.

  Alternative regimen is intermittent "pulse" Cyclophosphamide therapy (750 mg/m^2) every 2–3 weeks initially for 2–3 doses every 4 weeks till 6 pulses.
- *Azathioprine:* It prevents recurrence in CSSV either used alone or in combination with steroids.
- *Rituximab:* Used in frontline drug in patients with HSP. Two doses 1 gm each with an interval of 2 weeks. It gives prolonged remission.

- *Antivirals:* Interferon α is the preferred drug in hepatitis C virus associated CV. Significant improvement has been documented with decrease in cryoglobulin levels. Ribavirin may be used for treatment as well as in prevention of relapse in hepatitis C induced vasculitis.
- *Immunoglobulins:* It may be of use in Kawasaki disease. Dose: 2 g/kg single dose in combination with aspirin. Early administration prevents the risk of aneurysm formation. c-PAN was treated successfully with IVIg (2 g/kg over 2–5 days), but relapse rate is common.
- *Plasmapheresis:* It is helpful in cryoglobulinemia and hepatitis B related classical polyarteritis nodosa in severe cases refractory to other treatments.
- *Mycophenolate Mofetil:* Used in steroid dependent, steroid resistant cases of HSP, especially with renal complications.
- *Deoxyspergualin:* Monoclonal antibodies have a variable success rate.
- *Infliximab:* Used in steroid non-responsive necrotizing CSSV.

Conclusion

The mortality and morbidity related to vasculitis is mainly due to late diagnosis. As the symptoms are very subtle at the initial stage, there is a delay in the suspicion and diagnosis of vasculitis. Treatment is individualized. A comprehensive approach is needed for successful management of vasculitis.

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CHAPTER

212 How to Manage DMARDs Failure in RA?

N Subramanian

Abstract

Rheumatoid arthritis is the most common disease affecting the musculoskeletal system and the immune-inflammatory cascade causes avalanche of detrimental effects to the human systems. Incidence appears to be increasing worldwide and treat to target after early identification of the condition remains the current approach to tackle RA. DMARDs have been the conventional drugs of choice for years together and with the advent of cytokine inhibitors since 2000, prognosis and outlook of immune mediated diseases have improved remarkably. Biologics and Biosimilars have revolutionized the management of RA; however, DMARDs remain the gold standard care for these patients. This article focuses on the management of patients with RA who fail to respond to DMARDs.

Introduction

Rheumatoid arthritis (RA) is the most common of all arthrides and current incidence in India is increasing. The prevalence of RA was available from only four studies, ranging from 0.28% to 0.7%.[1] Literature review suggests the RA prevalence, based on the ACR criteria, ranged from 2.8 per 1,000 to 7 per 1,000, varying throughout India. Patients with RA taking disease-modifying antirheumatic drugs (DMARDs) ranged from 11% to 100%, with the majority of the studies reporting proportions more than 75%.[1]

Various studies report that the DMARDs available to the patients in India include the methotrexate (1990), leflunomide (2001), and sulfasalazine (1998).[2,3] Shankar et al. reported that on comparing the characteristics among erosive and non-erosive RA patients in northern India, the median DMARD-naive time period was recorded as 3 years among patients with erosive disease and 2 years among those without erosive disease.[4] Shankar and colleagues reported again in a study focused on only female RA patients, the median DMARD-naive time period was 3 years.[5]

RA occurs frequently in females and around 30 new patients per Lac population each year are diagnosed with RA. Stress and environmental triggers may trigger the disease onset. About 5% of first degree relatives are at risk of developing RA.[6] Cigarette smoking, coffee, and oral contraceptive pills appear to increase the risk of development of RA.[7] In developing countries due to various factors in accessing medical help, delayed diagnosis occurs thereby causes functional disability and reduced quality of life.[8]

Diagnosis and Current Management

Rheumatoid arthritis, most common form of inflammatory arthritis is usually diagnosed by the presence of joint swelling, raised inflammatory markers, positive anti CCP and imaging evidence of erosions, if required. Ultrasonogram and MRI have been beneficial in identifying the early changes in the synovium and marrow.[9]

Currently RA is managed using multimodality treatment. Diet, counseling, physiotherapy, and occupational therapy compliment drug treatment.

Drug management aims to relieve symptoms as soon as possible followed by disease modification that slows or stops radiological progression, which is closely correlated with progressive functional impairment.

Disease modifying conventional drugs included methotrexate (10–15 mg) given weekly once, sulfasalazine (1–2 gm), leflunomide (10–20 mg) and iguratimod (25–50 mg). Monitoring of bloods for patients while on DMARDs will have to be done every 4 weeks for 2 months and then once in 3 months.

Poor prognostic factors:[10]

- Persistently moderate or high disease activity despite DMARDs
- High ESR < CRP
- Presence of high titers of RF and/or ACPA
- Presence of early erosions

Evidence points to reduced compliance to oral DMARDs and also effective in two-thirds of patients with RA while achieving remission.[11] Hence, there is unmet need to improve the patients health, quality of life, and induce remission for the remainder of population with RA.

Causes for DMARDs Failure in RA

- Compliance issues
- Cost factors
- DMARD intolerance issues
- Comorbidities
- Fear of toxicities and long-term side effects

As RA is chronic and long-term drug treatment is necessary, it is important for the physicians to explore the patients understanding and family support in daily life. Compliance can be a problem due to fear of side effects driven by the society or cost issues or intolerance to DMARDs. Few patients may have comorbidities that might preclude to effective DMARD therapy. Hence, it is imperative to explore all these factors before we call as DMARD failure.

Clinical disease activity should be measured using DAS 28 ESR score—including swollen joint, tender joint, VAS scale, and ESR.

How to Manage the Resistant RA?

International guidelines including American College of Rheumatology (ACR),[12] British Society of Rheumatology and NICE guidance (BSR),[13] European League of Association of Rheumatologists (EULAR)[10] have supported the use of various biologics in patients with resistant rheumatoid arthritis and evidence has shown time and again that Biologics have achieved remission and improved the quality of life.

Before starting on biologics, we must ensure adequate optimization of oral DMARDs with regards to dose, compliance, and side effects. Many occasions, patients do not share the compliance issues, and hence it is important to explore the problems in taking DMARDs and address those issues.

Biologics are expensive to most patients in India as developing nation; therefore, biosimilars tend to be preferred in patients who can afford. Evidence shows approved biosimilars are equally efficacious in the management of various inflammatory rheumatic diseases.

Biologics and Biosimilars

We have seen tremendous developments in the use of biologics and biosimilars during the last decade and monoclonal antibodies are used in various rheumatic diseases with Treat to Target approach.

Biologic therapies have been used in various inflammatory rheumatic diseases like RA, spondyloarthritis (SpA), psoriatic arthritis, ANCA associated vasculitis, and osteoporosis.[14-17]

Biosimilars are similar to biologics intended to offer comparable safety and efficacy to the reference molecule. They are often manufactured in cell lines and subject to modification like glycosylation. Biosimilars must be shown to be identical to innovator biologics based on data from clinical and analytical studies.[18]

Methotrexate remains the anchor drug for RA, which has been proven to reduce anti-drug antibodies and also retains radiological remission.[19]

The list of currently licensed biologics for use in RA in shown in **Table 1**.

Pretreatment Screening[20]

Although biologics and biosimilars can be used in various indications in rheumatology, patients need to be screened for TB, Hepatitis, and HIV. They also need to be vaccinated against hepatitis, chickenpox, influenza, and pneumonia.

Screening tests include blood count, CRP, LFT, renal function tests, hepatitis B, C screening, mantoux, and immunoglobulins for rituximab. ECG and ECHO when appropriate.

TABLE 1 NICE UK approved Biologics for RA

Drugs	*Mechanism of action*	*Route of administration*	*Frequency*
Infliximab	Chimeric anti TNF	IV and Sc	After loading, every 8 weeks
Etanercept	Fusion protein receptor blocker	Sc	Once weekly
Adalimumab	TNF blocker	Sc	Once fortnightly
Tocilizumab	IL-6 blocker	IV and Sc	Once a month
Sarilumab	IL-6 blocker	Sc	Fortnightly
Rituximab	CD20 blocker	IV	Once in 6–12 months
Tofacitinib	JAk inhibitor	Oral	Daily
Golimumab	Human Mab to TNF alpha	Sc	Once in 4 weeks
Certolizumab	Pegylated anti TNF	SC	Once in 4 weeks

Contraindications for use of biologics:

- Uncontrolled heart failure, multiple sclerosis, active infections, Hep B, and Hep C positive and untreated cancers.
- Previous septic arthritis, pregnancy, and lactation.
- Risk of TB has been found to be more in Asian countries.[21]

Nearly a decade of experience in using biologics and biosimilars has given a wide range of choices for patients with RA and those drugs are used in India and gaining acceptance too.[22]

What do we do if not Affordable to Biologics or Biosimilars?

Recently RA affects women and men of both socioeconomic groups and being a chronic disease it's understandable for patients with low income to default on DMARDs. Hence, it would be prudent to consider low dose long-term steroids and NSAIDs along with monotherapy like methotrexate for disease remission,[23] after having explained the risk for diabetes and stomach upset.

Conclusion

DMARDs are effective in RA, but resistant rheumatoid needs careful approach to devise the management program tailor made to the patient and holistic intervention is required that includes biologics/biosimilars, physiotherapy, and yoga. Apart from disease remission and improved quality of life, we also need to achieve cardiovascular risk reduction and healthy family life.

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CHAPTER

213 IgG4-related Disease

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Abstract

IgG4-related disease is a chronic inflammatory condition characterized by tissue infiltration with igG4-secreting plasma cells. It manifests as organomegaly, fibrosis, and organ dysfunction. Elevated IgG4 level in blood gives an important clue to the diagnosis. CD4+ cytotoxic T cells and plasmablasts are central to the pathogenesis, and IgG4 antibody may be a bystander. Biopsy is essential for diagnosis whereas CT, MRI, and PET scan help in defining the extent of the disease. Response to steroid is excellent. Steroid resistant cases are treated with Rituximab.

Introduction

Immunoglobulin G4 (IgG4)-related disease (IgG4-RD) is a multiorgan immune mediated fibroinflammatory condition of unknown etiology. It was in 2013 in an international symposium that term IgG4RD was adopted.[1]

Epidemiology

Due to the low awareness of disease, there is difficulty in ascertaining the epidemiology of the disease. IgG4-RD has an elderly and male preponderance (Male:Female 3:2).[2] It tends to involve pediatric age group less commonly. Presently, there are not much epidemiological studies on IgG4-RD in India.

Pathogenesis

The pathogenesis of IgG4-RD suggests about disease to be autoimmune in nature though incompletely understood. In the past it was suggested that IgG4-RD to be T helper cell-2 (Th-2) mediated condition. But the concept of Th-2 memory cells circulating in IgG4-RD presently has been rejected since only a small subset of patient of IgG4-RD having atopy had this feature. Recently, researchers noticed that $CD4^+$ cytotoxic T lymphocytes, which are clonally expanded, are found in both peripheral and fibrotic lesion of IgG4-RD.[3] The cytotoxic T cells release interleukin-1 (IL-1), transforming growth factor-beta (TGF-beta) and Interferon gamma and these cytokines/chemokines are responsible for increased fibrosis, which is the dominant part of IgG4-RD.

Further, the disease has a sustained $CD4^+$ cytotoxic T cells effect due to continuous antigen presentation by B cells and plasmablast. In addition to $CD4^+$ cytotoxic T lymphocyte effect, there is also a follicular helper T(Tfh) response that is responsible for development of germinal centers (within the lymph node/involved organ) and production of cytokines (esp IL-4). The germinal center/cytokine drives the IgG4 class switch, producing IgG4 plasmablast and long lived plasma cells.[4] The IgG4 antibodies positivity in IgG4-RD is due to the downregulating response to another primary process.

So IgG4 antibodies are not pathogenic of IgG4-RD, rather $CD4^+$ cytotoxic T lymphocytes and plasmablasts play central role in the pathogenesis.

Clinical Features

The symptomatology in IgG4-RD is based on organ/s affected. It is subacute in onset. Clinical presentation in IgG4-RD is due to the resultant inflammatory infiltration/fibrosis, which cause the tissue or organ dysfunction. Additionally, tumor like effect may cause obstructive/compressive complications. Despite the multiorgan involvement, four clinical types can be more commonly identified. These are:

- Group 1: Pancreato-hepatobiliary disease
- Group 2: Retroperitoneal fibrosis and/or aortitis
- Group 3: Head and neck limited disease
- Group 4: Classic Mikulicz syndrome with systemic involvement

Symptoms of asthma or atopy may be present but fever is rare. Salivary and lacrimal glands, pancreas, biliary tract, and kidney are commonly involved.

Auto immune pancreatitis (AIP) is of two types. In the context of IgG4-RD, type 1 AIP is generally a pancreatic disease and biliary tract involvement (mimicking Primary Sclerosing Cholangitis) in combination.[5]

IgG4-RD commonly involves retroperitoneal tissue often resulting into fibrosis. This fibrosis may result in obliteration of adjoining structures (aorta and ureter).

Eye involvement (25–50%) in IgG4-RD usually presents as a mass (orbital pseudotumor) due to dacryoadenitis or MALT lymphoma.

Major salivary gland (parotid/submandibular) involvement mimics Sjögren syndrome, although in IgG4-RD the symptoms of dryness of eyes and mouth are milder along with seronegativity for anti Ro/La antibody.

Lung involvements are often asymptomatic or may present with respiratory-related symptoms. These symptoms may be due to the alveola/interstitial involvement or due to opacities (ground glass/nodular). The pulmonary manifestations of IgG4-RD may mimic sarcoidosis.

Kidney involvements related to IgG4 are tubulo-interstitial nephritis (TIN). Membranous nephropathy is much less common. IgG4-related TIN presents with profoundly hypocomplementemia (due to the complement activation by other IgG subclasses—IgG1 or IgG3).

Riedels thyroiditis is IgG4-RD of the thyroid gland disorder.

Cutaneous pseudolymphoma, hepatopathy, gastritis, sclerosing mastitis, central nervous system involvement (esp. patchy meningitis) with or without hypopituitarism, prostatitis, IgG4-related disease of the ovary, constrictive pericarditis, generalized lymphadenopathy are other organ presentation described.

Laboratory Tests

If there is a suspicion of IgG4-RD one should start work up with routine blood investigations, IgG4 level, imaging studies and finally tissue biopsy, if possible.

Blood Tests

Blood investigations usually reveal hypergammaglobulinemia. Peripheral blood shows eosinophilia with elevation of serum IgE (especially in presence of atopy) and IgG4 level. Serum IgG4 levels can also be elevated in other conditions, which may mimic IgG4-RD.[6] Plasmablast concentration is a better marker than IgG4 level, as it predicts response to treatment and also relapse.[7] Hypocomplementemia is particularly common in IgG4-related kidney disease as well as with mild proteinuria. Serum amylase and lipase may be planned if pancreatitis is suspected.

Imaging

On contrast enhanced CT, lesions look homogeneous with well-defined margins.

MRI (T2-weighted) shows hypointense to isointense images depending upon fibrosis/cellularity.

Increased metabolic activity on FDG-PET/CT helps in locating the extent of involvement.

Histology

Findings include lymphoplasmacytic infiltrate, storiform fibrosis (cartwheel appearance of the arranged fibroblasts and inflammatory cells) and obliterative phlebitis.[8] In addition, an increased number of IgG4-positive plasma cells greater than the cut-off point and elevated IgG4/IgG cell ratio more than 40% needs to be proven. There may be modest tissue eosinophilia.

Diagnosis

IgG4-RD is diagnosed by a combination of clinical (organomegaly), serologic (increased IgG4 level), radiologic (masses on CT, MRI), and pathologic findings (as described above). Biopsy of the involved organ is

crucial for diagnosis. Japanese comprehensive clinical diagnostic criteria (CCD) 2011,[9] are used for diagnosis. Organ-specific diagnostic criteria is used when CCD criteria does not properly fit in for the diagnosis of IgG4RD.

Differential Diagnosis

The major disorders that should be distinguished from IgG4-RD are cancers (pancreatic cancer, cholangiocarcinoma), primary sclerosing cholangitis, connective tissue disease like (Sjögren syndrome, granulomatosis with polyangiitis), Castleman disease, idiopathic RPF, and infectious aortitis.

Treatment

Treatment should be initiated early to impede the progress from the inflammatory to fibrotic stage (treatment nonresponsive). There is no international consensus on treatment guideline at present. The approach to treatment in IgG4-RD is discussed here.

Pretreatment Evaluation

Evaluation of the extent of disease after establishing the diagnosis is desired before initiating treatment, so baseline investigations are desired pretreatment. These are:

- Complete blood count, RFT, LFT, serum amylase and lipase, IgG subclass levels—esp IgG4, IgE concentration, serum C3 and C4 concentration, HbA1c.
- Fecal elastase in pancreatic involvement.
- Urinalysis to document asymptomatic proteinuria related to TIN.
- Imaging—CECT/PET scanning to determine the extent of disease.

Initial Therapy

All symptomatic or those with progressive disease should be started on therapy. The others—asymptomatic, non-progressive and limited disease need serial watchful waiting approach.

Steroid

Glucocorticoids are the drug of choice for initiation, unless contraindicated. The initial recommended oral dose of prednisolone for remission induction is 0.6 mg/kg/day for 2–4 weeks followed by tapering to 2.5–5.0 mg/day over a period of 2–3 months. Steroid pulse therapy is considered for acutely ill patients.

In the early stage of disease majority responds to glucocorticoids (decrease in size of mass, betterment of organ function, decrease in IgG4 value), though duration of response remains variable. But disease flare is seen during or after tapering of glucocorticoids. Also, patients with fibrotic changes respond poorly.

Rituximab

Patients with multiorgan disease (≥3 organs) or extremely high serum IgG4 concentration (>5 times UNL) are very likely to require an agent other than glucocorticoid alone for induction of remission. Rituximab (anti-CD20 antibody) is effective for both induction and maintenance in a dose: 1 g IV for a total of 2 doses 2 weeks apart.[10]

Rituximab do not directly kill plasma cells as they lack the CD-20 receptor. It acts by depleting the pool of CD20+ progenitors—either naïve B cells or memory B cells. Thus, it wipes out plasmablasts, which have a short lifespan. This loss of plasmablast results in decrease in IgG4 production.

Maintenance Therapy

High relapse rate is reported with multiorgan disease or extremely elevated IgG4 level. An IgG4-RD responder index (RI) has been developed to predict relapse. Low-dose prednisolone (2.5–5 mg/day) needs to be continued as maintenance therapy to avoid relapse for a period of at least 3 years, but keeping watch on steroid related complications. However, in case of relapse initial dose of steroid is recommended.

Mycophenolate (up to 2.5 g/day) and azathioprine (2 g/kg/day) are the other options for maintenance therapy.

Rituximab is very effective as maintenance therapy especially where steroid and other immunomodulator fails. It has a very low relapse rate. The reason being memory B-cell count appeared to be unaffected by steroid treatment, therefore partly explaining why the maintenance of remission in IgG4-RD often fails during glucocorticoid withdrawal.

Surgery

Selected patients may require surgery like—hydronephrosis due to ureteral obstruction in retroperitoneal fibrosis/obstructive jaundice due to sclerosing cholangitis requires biliary stenting and drainage/aortic aneurysm in aortitis/

compressive symptoms in Riedell's thyroiditis/vascular and organ compression from sclerosing mesenteritis requires debulking surgery.

Prognosis

IgG4-RD has a variable course. Some treatment naïve patients are reported to have spontaneous remission though short lasting. Whereas, most of them have relapse/chronic progression at variable rate. Baseline levels of serum IgG4, IgE, and eosinophil serve as markers for relapse prediction. Non-treatment results in a significant morbidity and mortality due to irreversible damage of organs and its sequalae because of the associated fibrosis. There is a divided opinion regarding increased risk of malignancy with IgG4-RD.

Conclusion

So to conclude, IgG4-RD results in a subacute multiorgan dysfunction/enlargement. The diagnosis is made in a background of clinical features which shares specific serological and pathlogical findings. Measurement of plasmablast concentration correlates better than IgG4 level with disease activity and is a promising tool to be used in future. A good initial response to steroid is a characteristic behavior of the disease, steroid needs to be tapered over a period of 2 months and any relapse or failure to the initial response, Rituximab holds a good promise.

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CHAPTER

214 Treatment of SLE beyond Steroids

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Abstract

Systemic lupus erythematosus (SLE) is a multi-system connective tissue disorder where immunosuppression is the mainstay of therapy. Steroids, although effective immunosuppressant, have a lot of side effects in the long run. Thus, there is a need of steroid sparing immunosuppressive agents for long-term therapy in SLE. In the first part of this chapter, the conventional steroid sparing drugs like Methotrexate, Cyclosporine, and Mycophenolate, which have been mentioned in the 2019 EULAR guidelines, have been discussed in details. In the second part of this chapter, newer therapies like Voclosporin, anifrolumab, Belimumab, and Baricitinib have been discussed along with the recent clinical trial results. Lastly, newer frontiers of therapy like Glucocorticoid induced leucine zipper (GLIZ) and other experimental drugs have been explained. Discussion of each drug is also associated with mention of the dose and side effects.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem connective tissue disorder with considerable mortality and morbidity. Since it mainly affects the young adult, economically productive, age group, the financial burden of this disease is also significant. Treatment of this disease continues for a long time, sometimes even lifelong. With developments in immunology and medical genetics, our understanding of the pathogenesis of this disease is also evolving. This is opening up newer avenues for therapeutic target.

SLE is a disorder of autoimmunity. Thus, immunosuppression or immunomodulation in various forms is the mainstay of therapy. In the early days, the main drug used for this purpose was steroids. While steroid is an effective immunosuppressant and quite effective in saving lives (especially in acute flares), it also has a lot of side effects in the long run[1] **(Table 1)**.

Thus, for long-term treatment, steroids are not an ideal choice. The current SLE guidelines also advice quick tapering of oral steroids to avoid these side effects.

The mainstays of SLE therapy, especially in acute flares, are cyclophosphamide and steroids with steroid sparing drugs like Azathioprine and MMF for maintenance. But in spite of quick diagnosis and early treatment, mortality from SLE is still very high. In 2017, Jorge et al. from the Harvard Medical School published an article, which showed that over 15 years, between 1999 and 2014, the mortality from SLE has not been decreased appreciably.[2] As early as in 2000, researchers from Baltimore, USA, had also shown that long-term steroid therapy in SLE is associated with significant organ damage.[3] Thus, it is evident that the current therapies including steroids are not adequate and there is a large *unmet need* in SLE management.

Conventional Agents

There are many drugs, besides steroids, which are used in SLE. They include hydroxychloroquine (HCQ), mycophenolate mofetil (MMF), azathioprine (AZT), cyclophosphamide, methotrexate (MTX), cyclosporine (CYC), and tacrolimus (TAC). But they are all not equally effective. HCQ is used as a background therapy but it is

TABLE 1 The different systemic effects of long-term steroid use

Musculoskeletal	*Endocrine*	*Cardiovascular*
• Osteoporosis • Myopathy • Osteonecrosis	• Dysglycemia • Cushingoid features • Adrenal suppression • Growth failure in children	• Edema • Hypertension • Premature atherosclerosis • Arrhythmia
Ophthalmologic	***Psychiatric***	***Dermatologic***
• Cataract • Glaucoma • Central serous chorioretinopathy	• Depression • Hypomania • Sleep disturbance • Akathisia	• Acne • Hirsutism • Skin thinning • Recurrent infections

TABLE 2 2019 EULAR recommendations for non-steroid drugs in SLE

Main target of treatment	• Complete remission • Low disease activity status (if remission is not obtained) • Prevention of flares
HCQ	To be used in all patients (5 mg/kg), long term; if HCQ intolerant, quinacrine
MTX	To be added when symptoms not controlled with HCQ+GC; once weekly dose; 10–25 mg/week
AZT	To be added when symptoms not controlled with HCQ+GC; safe in pregnancy; 2–3 mg/kg/day
MMF	Can be used for both induction and maintenance; *not effective* in neuropsychiatric lupus; costly; discontinue 6 weeks before planned pregnancy Induction: 3 g/day Maintenance: 1–2 g/day
CYC	Used in moderate to severe disease activity; avoid in severe renal disease; 1–3 mg/kg/day
Cyclophosphamide	Mainly used as rescue therapy; gonadotoxic Use either Euro-Lpus or the NIH regimen; avoid after induction dose; oral therapy not recommended
IV Ig	1 g/kg/day (1–2 days); mainly used for hemolytic anemia
Rituximab	RCTs negative; still used off-label; only after failure of above drugs 1000 mg on days 1 and 15; may be repeated after 6 months

AZT, azathioprine; CYC, cyclosporine; GC, glucocorticoids; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate.

not effective in acute flares or life threatening conditions. A French study (PLUS) in 2013 found that HCQ is unable to prevent life threatening flares.[4] But this does not mean that HCQ is a non-essential drug in SLE. Continuous HCQ is effective in preventing flares of skin rashes or arthritis and this drug should be given to all lupus patients **(Table 2)**.[5] AZT and MMF are both steroid sparing agents. In the MAINTAIN trial, both of them were found to be equivalent in preventing relapse of nephritis in SLE.[6] In the ALMS study, MMF was found to be equivalent to IV Cyclophosphamide in inducing remission in renal flares.[7] Thus, although cyclophosphamide (in NIH or Euro-Lupus protocol) remains the mainstay of rescue therapy in renal flares, MMF may be tried as an alternative. AZT is mainly used to help reduce the dose of oral steroids. It is safe in pregnancy (in contrast to MMF that must be stopped at least 6 weeks before conception) but neutropenia may be a rare, yet serious, adverse reaction.

There have been very few studies of MTX in SLE. A 2014 systematic review concluded that MTX is effective in treating arthritis and mucocutaneous manifestations of SLE and it also helps to reduce the dose of oral steroids.[8] Another study from Germany also depicted that SLE patients, who had not improved despite 6 months of oral steroids, did respond to oral MTX 15 mg/week.[9] There was not much side effect of MTX in this regimen. However, the efficacy of MTX in lupus nephritis is still debatable.[10]

Cyclosporine, a calcineurin inhibitor (CNI), is another drug, which has been tried in SLE. Although this is a good immunosuppressant, it has common side effects like hypertension and nephrotoxicity, which makes it unsuitable for high-dose therapy. But low-dose maintenance therapy can always be used in SLE. There are very few RCTs with CYC in SLE. These have shown that CYC is effective in decreasing proteinuria and improving renal function.[11] Also, the doses of other immunosuppressants and steroids could be reduced when CYC is used long term. Some studies have also shown that CYC may improve the renal histology in lupus patients.[11] However, the serological markers like anti-ds-DNA or complements do not change appreciably with CYC. One reason may be that CYC mainly acts on T-cell subset with very little effect on the humoral immunity. But despite persistence of serological abnormalities, clinical improvement occurs after CYC use.

Tacrolimus, another CNI, till now used in organ transplant recipients, is now being used in combination with steroid as well as MMF in refractory proteinuria. Several small studies have looked into the use of TAC in Class III, IV, and V lupus nephritis, both as induction and as maintenance therapy in patients refractory to other treatment. Majority were Asian patients.[12] Another study by Szeto et al. in 18 patients with biopsy proven Class V lupus nephritis treated with TAC 0.1 to 0.2 mg/kg/day with tapering doses of prednisolone showed 76.2% decrease in proteinuria compared to historical control group treated with cyclophosphamide or azathioprine.[13] Side effect profiles are same as CYC with glucose intolerance.

IV Ig use is still considered experimental in SLE. A 2014 meta-analysis found that IV Ig is effective in reducing disease activity.[14] In some studies, it has also been shown to be effective as a steroid sparing agent. But till now, only a few studies have assessed IV Ig for lupus nephritis. The results have been mixed. Thus, it is an uncommon choice in acute renal flares.

Table 2 gives a summary of the 2019 EULAR recommendations for the use of non-steroid drugs, as discussed earlier, in SLE.[15]

Newer Agents

The drugs discussed above are effective in controlling disease activity in many cases but still a large percentage of SLE patients continue to have flares and worsening of organ failure. However, there are newer therapies in the horizon for SLE. These will be discussed next.

A newer analog of CYC, which is in development, is *Voclosporin*. This drug was first developed in the 1990s, but its potential uses are being investigated only recently. In January 2019, Rovin et al. published the results of the AURA-LV study, where Voclosporin was used in addition to MMF and rapidly tapering oral steroids for induction therapy in lupus nephritis.[16] The dose of Voclosporin used was 23.7 mg (low dose) or 39.5 mg (high dose) BD.[16] It was found that there was significantly high complete renal remission (CRR) rate in the Voclosporin group (both low and high dose) and this advantage was sustained at 48 weeks. Very recently, in March 2020, Aurinia Pharmaceuticals, the company promoting Voclosporin, announced the results of the *AURORA* study.[17] This was a Phase 3 Global RCT, which assessed the efficacy of Voclosporin in addition to MMF and rapidly tapering oral steroids for induction phase. The results showed that Voclosporin was effective in inducing a superior and faster renal response. The side effect profile in the AURORA trial was similar to standard therapy. There was no excess mortality. In this trial, the dose of Voclosporin was 23.7 mg BD. Thus, if this new drug is approved, it may be a valuable addition in SLE treatment strategy.

Type I interferon (INF) is known to be an important mediator in the pathophysiology of SLE. Recently, an inhibitor of the type 1 IFN receptor, *Anifrolumab*, has been developed. In January 2020, Morand et al. published the results of a trial of Anifrolumab in active SLE (*TULIP-2* trial).[18] Anifrolumab (300 mg) was given i.v. every 4 week for 48 weeks. At 52 weeks, there was significantly more response (assessed by BILAG) in Anifrolumab group compared to placebo.[18] Anifrolumab mainly helped in reduction of the glucocorticoid dose and decreasing severity of skin disease. But there was not much difference in tender joint count. This was the first successful trial of a biological drug in SLE since Belimumab almost a decade ago. The first trial with Anifrolumab was the *TULIP-1* trial, published in the Lancet, in 2019.[19] In this trial, the primary end point was SLE responder index (SRI-4) at 52 weeks. But this first trial was, however, a failure as there was no difference in SRI-4 between the groups.[19] But secondary end-points like reduction in corticosteroid dose and BILAG response were achieved. The researchers then quickly published the results of the second trial (as

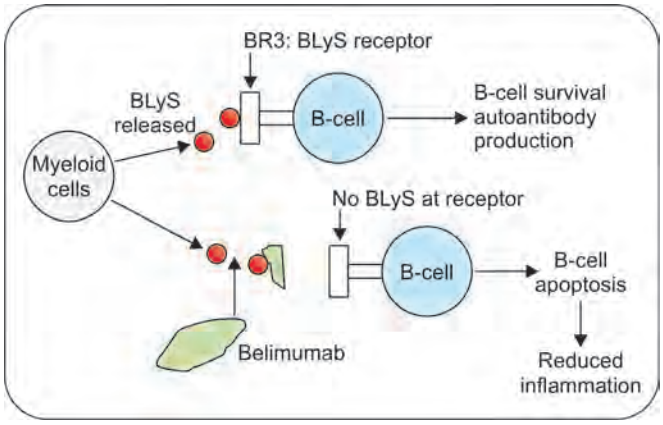

Fig. 1: The pathway of action of Belimumab ©RP

mentioned earlier) where favorable results were shown. Anifrolumab is generally safe for human use. But in 2017, a Phase IIb trial with the drug found some excess incidence of Herpes Zoster and influenza, compared to placebo.[20] The maker of the drug, AstraZeneca, plans to move ahead with application for approval although expert opinion is still divided about potential efficacy of the drug.

Belimumab, which was approved by the FDA in March 2011, is the first targeted biological therapy for active SLE.[21] B lymphocyte stimulator (BLyS) is a costimulator for B-cell survival and function **(Fig. 1)**. It is expressed by a variety of cells like macrophages and is also found in soluble form in tissues. BLyS receptor is present on B-cells, the most important receptor being BR3. Interaction of BLyS with BR3 prevents apoptosis of B-cells and promotes autoantibody production. Overexpression of BLyS increases activity of autoreactive B-cells and this is important in the pathogenesis of autoimmune conditions like SLE. Belimumab is a human monoclonal antibody against BLyS. Binding of belimumab with BLyS prevents its interaction with BR3 and thus, reduces B-cell survival and antibody production.[21] There have been two Phase III trials of Belimumab in SLE: *BLISS-52* and *BLISS-76*. The numbers (52 and 76) indicate the number of weeks for which the study subjects were followed up. While both the studies demonstrated efficacy of the drug, it was also seen that the effects were not sustained at 76 weeks.[22] *The dose of the drug is 10 mg/kg, given i.v. at weeks 0, 2, 4, and then monthly*. It is used with standard therapies like MMF. But one problem of the drug is that, in the trials, it was not studied in active lupus nephritis or active CNS lupus. *Thus, use of the drug in these conditions is not approved.* However, as more data becomes available, the recommendations will change. Adverse effect profile of belimumab is also favorable.[22] In December 2019, GSK, the maker of belimumab, announced results of the *BLISS-LN* trial where belimumab was shown to be effective in reducing nephritis. However, the approval of belimumab for treatment of lupus nephritis is still pending.

Rituximab is an anti-CD20 antibody, which is an important drug in the treatment of rheumatoid arthritis, some malignancies, and some dermatological conditions. There have been many trials of rituximab in SLE also.[23] The first few published studies were open, uncontrolled studies. For example, the data published by Leandro et al. in 2002 shows that there were improvements in both clinical and laboratory features of SLE after treatment with rituximab (500 mg: 2 doses, 2 weeks apart).[24] This therapy was used along with oral steroids and i.v. cyclophosphamide. In 2006, Ng et al. published results of a trial using rituximab for refractory SLE.[23] They showed that repeated cycles of rituximab may be helpful in difficult-to-treat lupus. However, most of these were clinical open studies. Later, two RCTs were undertaken to assess the efficacy of rituximab in lupus: *LUNAR* (renal lupus) and *EXPLORER* (non-renal). Both trials studied rituximab as an add-on therapy to the standard regimen of immunosuppressants like steroids. Overall, the EXPLORER trial did not reveal any extra benefit of rituximab when added to standard therapy.[25] But subgroup analysis revealed significant effect on the primary end point in African-American and Hispanic patients. Also, there were significant fall in anti-ds-DNA levels and rise in complement levels. The dose of rituximab used was 1000 mg, 2 doses, 14 days apart. Oral steroid was also used in tapering doses. In the LUNAR trial, patients with Class III or IV lupus nephritis were randomized to receive rituximab as two 1000 mg doses, 14 days apart, to be repeated after 6 months.[26] The primary end point of renal response at week 52 was not met. The only significant findings were, like EXPLORER trial, decrease in anti-ds-DNA and increases in complement levels. However, further analysis revealed that patients of African ancestry were more likely to respond to rituximab. Also, there was more reduction in proteinuria in the long term in the rituximab group. So, overall, both these trials were negative. So, although clinical results were encouraging, the randomized trial data did not support

the use of rituximab. This made the use of rituximab for SLE controversial. In 2019, a meta-analysis was published on this topic.[27] Twenty-four studies were analyzed. It was seen that, overall, in controlled trials with rituximab, there was more probability of total remission (OR=2.02, 95% CI: 1.23–3.32, P<0.01). Also rituximab is associated with more decrease of proteinuria compared to controls. So, based on this meta-analysis, rituximab may be considered as a viable option in lupus nephritis. The ideal dose is still debated because some of these trials used four 375 mg/m^2 weekly doses and some used two 1000 mg fortnightly doses.[28]

Another anti-CD20 therapy tried in clinical trials for SLE was *Ocrelizumab* (OZM) (humanized antibody).[28] There were two trials: BEGIN (non-renal) and BELONG (Renal). The BEGIN study was stopped early. In the *BELONG* trial, OZM was used at doses 400 mg or 1000 mg on days 1 and 15, and then 4 monthly.[28] This trial was also stopped early due to increased risk of infections in the group receiving OZM+MMF. The intention-to-treat analysis at 32 weeks showed that there was some improvement in renal response in the OZM group, although it did not reach statistical significance. But the data also showed that there was more probability of response when OZM was combined with the *Euro-Lupus* protocol. But as of now, OZM is not a priority candidate drug for lupus trials. The drug is only approved for some forms of multiple sclerosis.

Ustekinumab (UKB) is an IL-12/23 antagonist.[29] IL-12 is involved in activation of various T-cell subsets involved in autoimmune response. IL-23 is involved in expansion and survival of pathogenic Th-17 cells. These two pathways are closely related **(Fig. 2)**. In September 2018, Vollenhoven et al. published a study of UKB in active SLE in the Lancet.[29] In this study, UKB was given intravenously at the beginning, followed by 90 mg subcutaneously every 8 weeks. Like other biologics, this was also given along with standard therapy. At 24 weeks, there was significantly more response with UKB, compared to placebo. The same group of researchers published a follow-up study in 2019.[30] In this, it was shown that the benefits of UKB were maintained at 48 weeks. There were no excess malignancies or opportunistic infections. Presently, UKB is approved for Psoriasis, Ulcerative colitis, and Crohn's disease. But in the future, this may be a promising therapy for active SLE.

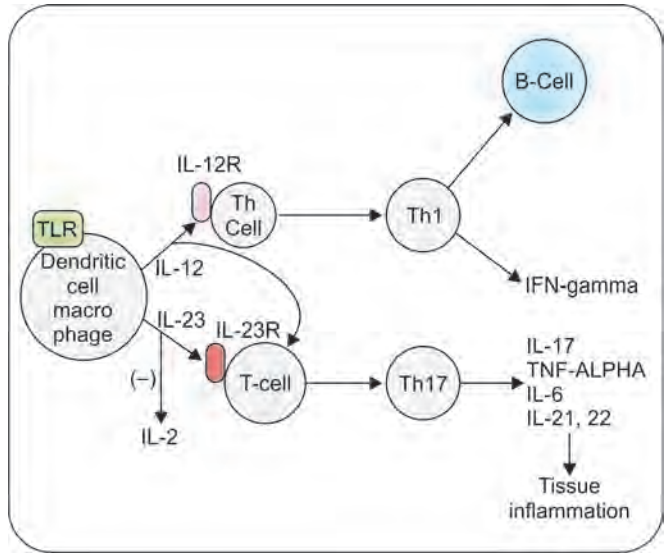

Fig. 2: Schematic representation of the IL-12/23 pathway in tissue inflammation ©RP

Baricitinib is an oral Jak1 and Jak2 inhibitor, which has been approved for use in rheumatoid arthritis. Recently, there have been trials of baricitinib in SLE. In 2018, Wallace et al. published the results of a Phase II trial of baricitinib in SLE patients with arthritis or dermatological manifestations.[31] Here, it was found that baricitinib significantly improved these manifestations at 24 weeks. Thus, this was a proof of concept that baricitinib can be a viable option for SLE patients in addition to standard therapy. However, the dose of baricitinib used (4 mg) has raised some concerns about the potential for serious side effects like neutropenia.[32] A Phase 3 trial (*SLE-BRAVE-X*) is underway to test the efficacy of baricitinib in SLE. This and similar other studies can clarify the role of this drug in the future.

New Frontiers

The most promising new target in controlling inflammation is the glucocorticoid pathway **(Fig. 3)**.

Glucocorticoid-induced leucine zipper (GILZ) is one of the GREs in the cell nucleus and it is one of the earliest areas in the DNA activated by the hormone.[33] GILZ is one of the principal mediators of anti-inflammatory activity of GCs. The most robust evidence of the anti-inflammatory activity of GILZ is its effect on the NF-κB/MAPK pathway.[33] It directly inhibits NF-κB and prevents induction of the

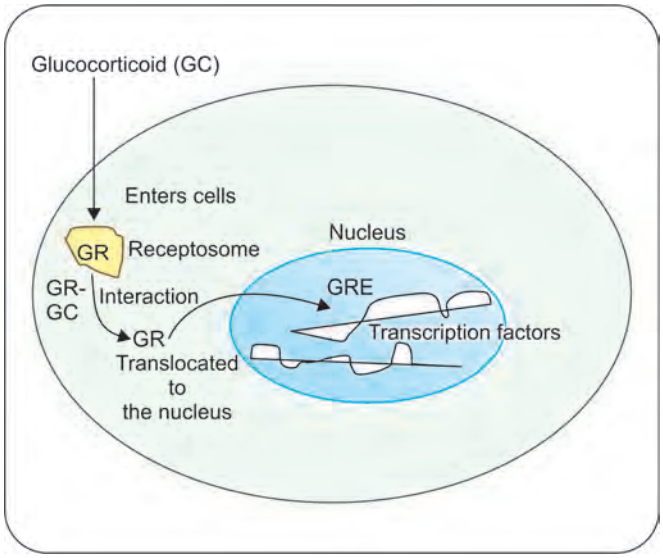

Fig. 3: Glucocorticoid cellular pathway
GR, GC receptor; GRE, GC recognition element

proinflammatory genes. Overall, it shifts the inflammatory milieu from Th1 to Th2 response. This molecule is encoded by the *Tsc22d3* gene located on the X chromosome.

In autoimmune diseases like SLE, it has been shown that active disease is associated with lower intracellular GILZ levels. This raises the possibility that GILZ deficiency is one of the factors in the pathogenesis of this disease and conversely, *GILZ augmentation may be a potential therapeutic target.* GILZ has effect on Th1, 17 cells and also B-cells.[34] Deletion of GILZ in mouse models is associated with an increase in B-cells in blood.[34] And increased B-cells means increased autoantibodies.

As discussed in the introduction section, glucocorticoids are associated with a lot of side effects and this raises a lot of problems in long-term treatment. So, it may seem like a paradox that the same glucocorticoid pathway is now the focus of research. But this new research is aimed at other intermediary compounds in that pathway which can *maintain the immunosuppressive effects without giving rise to the side effects*. So, there is a lot of research to find glucocorticoid receptor agonists and modulators, also called Selective Glucocorticoid Receptor Agonist & Modulator (SEGRAMs).[35] GILZ is one such target to bypass the glucocorticoid receptor.[35] It has good immunosuppressive activity and also, it lacks significant metabolic effects. It has neutral or even positive effect on bone density. However, all metabolic effects are still not known like its effect on glycemic status, skin thinning, or cataracts. So, although this is an exciting prospect, its potential for human use is still unknown. Research on GILZ till now is mostly animal model-based.[35] Some studies have used truncated regions of the protein while others have used virus vectors with transcription factors to induce GILZ expression in laboratory animals. Presently, two SEGRAM compounds under investigation, RU24858 and ORG 214007-0, are based on targeting GILZ.[36]

Other newer therapeutic options, which are in various stages of trial, are mentioned here:

- *Tabalumab:* Anti-BAFF monoclonal antibody; trials: *ILLUMINATE-1 and 2*
- Epratuzumab: Anti-CD22 antibody; trials: *EMBODY 1 and 2*
- *Atacicept:* Anti-TACI, tumor necrosis factor transmembrane activator and calcium modulator and cyclophilin ligand interactor; trials: *ADDRESS-II; APRIL-SLE*
- *Blisibimod:* Anti-BLyS antibody; trials: *PEARL-SC*
- *Rigerimod:* Peptide derived from a region of U1-70k snRNP protein; immunomodulator binding to MHC-II; can restore immune tolerance; Phase IIb trial encouraging; further trials in progress
- *Others:* IL-2 therapy, anti CD40 antibody etc.

Conclusion

As the earlier discussion makes clear, there are a lot of options in SLE management. Steroids are needed in the beginning and during life threatening flares. But once the patient is stabilized, we should try to shift to the steroid sparing therapies in order to avoid the long-term side effects. Choice of steroid-sparing agents or biologicals should be based on patient profile, affordability, and organ involvement.

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CHAPTER

215 Gout Is the Only Enemy That I Do Not Wish to Have at My Feet

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Abstract

Gout or monosodium urate (MSU) crystal arthropathy is a disorder caused by hyperuricemia (serum urate >6.8 mg/dL [>0.4 mmol/L]) that results in the precipitation of monosodium urate crystals in and around joints, resulting into recurrent acute or chronic arthritis. Acute gouty arthritis is characteristically monoarticular and often involves the 1st metatarsophalangeal joint or ankle. Symptoms of gout include acute, severe pain, tenderness, warmth, redness, and swelling. Definite diagnosis requires demonstration of monosodium urate crystals in synovial fluid. This chapter deals with practical approach to diagnosis and management of patients with gouty arthritis.

"Gout is the Only Enemy That I Do Not Wish to Have at My Feet"
–Reverend Sydney Smith (1841)

Introduction

Gout is one of the oldest joint diseases known to humanity. The term gout originated from the word 'gutta' meaning a drop (in Latin), as the ancient belief was that the devil is causing the disease by instilling the poisonous humor into the joint of the victim drop by drop.

Gout is a crystal-deposition disease that results from chronic elevation of uric acid levels above the saturation point for monosodium urate (MSU) crystal formation. Normal level of serum uric acid (sUA) is 7 mg/dL in males and 6 mg/dL in females. Initial presentation is mainly severely painful episodes of peripheral joint synovitis (acute self-limiting "attacks") but joint damage and deformity, chronic usage-related pain, and subcutaneous tophus deposition can eventually develop. Chronic recurrent gouty arthritis leads to development of tophi in the cartilage, tendon, or other soft tissues.

Epidemiology

The global burden of gout is substantial and seems to be increasing in many parts of the world over the past 50 years. Gout is most common inflammatory arthritis in men aged more than 50 years. Overall prevalence of gout in adult male is 1–2%. Prevalence in India is 0.1%, but incidence and prevalence have been doubled over past two decades probably because of adoption of western life styles.[1] Gout is rarely seen in premenopausal females and children. After menopause, due to lack of estrogens, females are at equal risk of developing gout.

Pathogenesis

The disease often runs in families, but the genetic basis of gout is not well understood. Uric acid is the end product of purine degradation in humans. Purines are derived either from the diet or by de novo synthesis. Normal metabolism includes conversion of purine first into hypoxanthine in presence of enzyme xanthine oxidase, then hypoxanthine into xanthine again in presence of enzyme xanthine

oxidase, and finally xanthine is converted into uric acid which is a trioxypurine. Most of the uric acid is eliminated through urine or intestine, the kidney excretes two-thirds, and rest one-third is excreted via intestine.

Classification

Primary Gout

- Unknown cause
- Genetic defects in renal handling of urate
- Under secretors (90%) and overproducers (10%)

Secondary Gout

- Increased urate production:
  - Inherited enzyme defects (HGPRTase deficiency, glucose-6-phosphatase deficiency)
  - Myeloproliferative disorder
  - Psoriasis
  - Hemolytic diseases
  - Malignancies
  - High purine diet, alcohol
- Decreased renal clearance:
  - *Renal:* Chronic kidney disease, polycystic kidney disease, lead nephropathy
  - *Endocrine:* Hyperparathyroidism, hypothyroidism, diabetes insipidus
  - *Metabolic syndrome:* Obesity, hypertension, dyslipidemia
  - *Drugs:* Diuretics, low dose aspirin, pyrazinamide, ethambutol, cyclosporine
  - *Others:* Down syndrome, sarcoidosis, toxaemia of pregnancy

Stages

These are the following four stages of gout:

- Asymptomatic hyperuricemia
- Acute gouty arthritis
- Intercritical periods (asymptomatic)
- Advanced/chronic gout (frequent or constant joint pain, tophi)

Asymptomatic Hyperuricemia

Asymptomatic hyperuricemia is accidental finding and does not warrant urate lowering therapy. Whenever patient comes at this stage, meticulous search for other comorbidities must be done and it's rewarding. Treatment of asymptomatic hyperuricemia should be done only in those patients who have history of kidney stones and asymptomatic patients with very high sUA, that is, more than 12 mg/dL in men and more than 10 mg/dL in women.

Acute Gouty Arthritis

In an acute presentation, patients will notice severe pain, redness, swelling, warmth, and severe tenderness in one or more joints. Symptoms worsen within first 24 hours. Joint involvement (in order of decreasing frequency) includes the metatarsophalangeal joint (podagra), forefoot, the ankle, the knee, the wrist, and the fingers.[2] In elderly women, an initial presentation may be acute arthritis of fingers, having inflamed Heberden's and Bouchard's nodes.[3] Untreated acute gout usually resolves within 1–3 weeks.

Intercritical Gout

This is the period between two attacks of gout. Approximately 60% of patients have a second attack within the first year, and 78% have a second attack within 2 years. Only 7% of patients do not have a recurrence within a 10-year period.[4]

Chronic Tophaceous Gout

Tophaceous disease is more likely to occur in patients with the following: a polyarticular presentation, a serum urate level higher than 9.0 mg/dL, and a younger age at disease onset (i.e., 40.5 years or younger).[5] The rate of tophi formation correlates with the duration and severity of hyperuricemia. The most common sites include the joints of the hands and feet. The helix of the ear, the olecranon bursa, and the Achilles tendon are classic, though less common, locations for tophi. Additionally, urate deposition in kidneys could lead to nephrolithiasis.

Diagnosis

- Clinical picture
- Crystal examination
- Serum uric acid
- Imaging

Clinical Pictures

Clinical features helpful in establishing provisional diagnosis of gout:

- Rapidity (12–24 hours) with which inflammation reaches maximal
- *Location:* 1st MTP (most common), intertarsal areas, ankle, knee, insertion of tendoachillis, olecranon
- Monoarticular, intermittent arthritis
- Spontaneous and complete resolution with or without treatment
- Presence of visible or palpable lesion, which by location, texture, or appearance is likely to be tophus
- History of similar episodes in past
- A recent history of trauma, surgery, intercurrent medical illness, or initiation of urate lowering medication or other culprit medicines
- Presence of hyperuricemia

Joint Aspiration and Synovial Fluid Analysis

Identifying urate crystals in fluid aspirated from an affected joint is the only definitive way to diagnose gout. MSU crystals are needle-shaped and negatively birefringent on simple polarized light microscopy.[6] In an acutely inflamed joint, these crystals are seen in polymorphonuclear cells.[7]

Hyperuricemia

Hyperuricemia should never constitute a sole criterion for the diagnosis of gout as hyperuricemia is not present in 40% episodes at the time of acute attack.

Imaging

Joint X-ray: X-ray in gout shows typical punched out lesions with scalloping margins/rat bite erosions (Martel's sign or G sign). These are asymmetrical, eccentric, and away from joint margins.

High resolution ultrasound: Detect subclinical Microtophi and MSU deposit within cartilage of 1st MTP Joint.

MRI: It shows bone "edema," soft tissue pannus, and swelling.[8]

Management

Aims in the Management of Gout

Maintain serum urate in non-tophus gouty arthritis patients less than 6.0 mg/dL and if chronic tophaceous gout then target serum urate level is less than 5 mg/dL to prevent future attacks and reverse prior damage (urate-lowering therapies).

Non-pharmacological Management[9,10]

Life style modifications that are important in reducing risk for gout and/or reducing urate levels **(Table 1)**.

Pharmacological Treatment of Acute Gout

Guidelines

- Affected joints should rest, fomentation should be done.
- Analgesic and anti-inflammatory drug therapy: commenced immediately and continued for 1–2 weeks.
- *Colchicine:* Effective alternative (preferably low-dose colchicine)

TABLE 1 Life style modifications important for reducing the risk of Gout

Risk factor	*Management modality*	*Result*
Diet	Reduction in meat, sea food	Decreased risk
	Increase in low fat dairy intake	Decreased risk
	Increase in protein/complex carbohydrate	Decreased risk
	Reduced fat	Decreased risk
	Reduced beverages beer > distilled spirits > fruit juices > and high fructose corn syrup containing soft drinks	Decreased risk
Obesity	Weight reduction	Decreased risk
Hypertension (HTN)	Reduce BP	Decreased risk
Culprit drugs	Substitute	Decreased risk

- Urate-lowering drugs (Allopurinol/Febuxostat) should not be started during an acute attack.
- In patients already on Allopurinol/Febuxostat, it should be continued with simultaneous treatment for acute attack.

Terminating the Acute Gout Flare

Options: Virtually all anti-inflammatory agents have been used effectively in terminating acute gouty flare.[11]

NSAIDs

- Most useful agent is indomethacin in a dose of 50 mg 6 hourly for 2 days followed by 50 mg 8 hourly. Once pain settles, it can be reduced further to 25 mg 8 hourly. Other nonsteroidal anti-inflammatory drugs (NSAIDs) that can be used are naproxen (750 mg/day), etoricoxib (120 mg/day), and diclofenac (50 mg 8 hourly).
- NSAIDs are relatively contraindicated in patients suffering from renal diseases, peptic ulcer disease, congestive heart failure, and hypertension.
- Aspirin used for cardiovascular prophylaxis can be continued during acute attack under cover of anti-inflammatory agents.

Colchicine

Colchicine is the ideal drug where diagnosis of gout is not confirmed, the latest recommendation is to start 2 tablets of 0.5 mg colchicine as loading dose then 0.5 mg, 1 hour later, if needed, one more tablet of 0.5 mg after 12 hours, then continue colchicine in a dose of 0.5 mg twice or thrice a day after meals until acute attack resolves.[12,13]

Corticosteroids

Preferred only when NSAIDs or colchicine are contraindicating or ineffective especially useful in polyarticular gout following surgery, renal or hepatic insufficiency, or congestive heart failure.

Intraarticular: 40 mg of triamcinolone acetonide or 80 mg of depot steroid (methylprednisolone).

Parenteral (intramuscular or intravenous): Methyl-prednisolone (100–150 mg), the dose can be repeated 12 hourly for 1–3 days in incomplete responders.

Oral: 20 mg of prednisone BD, taper to stop within 7–10 days.

ACTH (Adrenocorticotropic Hormone)

Dose: Between 25 and 50 IU IM/SC; the dose can be repeated 12 hourly for 1–3 days in incomplete responders.

IL-1β Inhibitors (Anakinra, Canakinumab, and Rilonacept)

Highly effective but cost is the constrain.

Gout Flare Prevention (Prophylaxis)

Aim: To decrease frequency and severity of acute gout flares, especially when starting urate lowering therapy.
Options:

- Oral colchicine (in dose of ≤0.6 mg twice daily after meals)
- NSAIDs-benefit not established but can be used in a patient who is intolerant or in whom colchicine is ineffective
- IL-1β inhibitors? (Rilonacept; canakinumab)

Prophylaxis is initiated when urate-lowering therapy is started and stopped when sUA is in goal range for more than or equal to 6 months.

Management of Recurrent, Intercritical, and Chronic Gout[11]

Goal of therapy: sUA < 6 mg/dL

Candidates for chronic therapy

- Patients with two or more attacks per year
- Patients with tophi
- Patients with renal insufficiency
- Patients with uric acid stones

Co-prescribe: Colchicine or NSAIDs for 6 months

Avoid use of medications that can increase sUA. Example: diuretics, ethambutol, pyrazinamide, etc.

Options: Agents that promote uric acid excretion (uricosuric agents):

- Probenecid
- Sulfinpyrazone
- Benzbromarone
- Losartan
- Fenofibrate
- Vitamin C

Agents that inhibit uric acid formation (xanthine oxidase inhibitors):

- Allopurinol
- Febuxostat

Agents that convert uric acid to allantoin (uricase preparations):

- *Rasburicase:* Recombinant fungal uricase (*Aspergillus flavus* and *Candida utilis*)
- *Pegloticase:* Pegylated, recombinant, porcine-baboon uricase

Biologic Agents

- Anakinra
- Canakinumab
- Rilonacept
- Start uric acid lowering therapy 1–2 weeks after inflammation has settled
- Initial long-term treatment of recurrent uncomplicated gout (Allopurinol or febuxostat)

Uricosuric Agents[14]

Promote uric acid excretion

- Hyperuricemia results from impaired renal uric acid clearance in 90% of gout patients (under-excretors of uric acid).
- Candidate patients for uricosurics are fewer than with xanthine oxidase inhibitors.

Limitations of uricosurics:

- Ineffective in renal insufficiency (CrCl < 50–60 mL/min)
- Results in modest decrease in sUA
- Risk of uric acid stone formation
- Cannot be used in presence of renal calculi

Probenecid: Achieve satisfactory control in 60–85% of patients and dose is 1–2 gm/day.

Sulfinpyrazone: It is uricosuric agent and related to phenylbutazone. It also acts as antiplatelet agent. Therefore, should be used cautiously in patients, who are anticoagulated, have bleeding problem and peptic ulcer disease.

The dosage is 100–200 mg twice a day and increase up to 800 mg/day.

Patients on uricosuric drugs are advised to maintain high urine flow (plenty of water intake) to avoid crystallization of uric acid in renal tubules.

Benzbromarone: Potent uricosuric drug used in patients with no improvement with allopurinol and in renal transplant patient. It is safe in mild to moderate renal impairment and rarely cause hepatotoxicity. Therefore SGOT/SGPT level should be monitored before starting and after continuation of therapy.

Dosage is 50–200 mg daily.

Angiotensin receptor blocker: Particularly losartan is also uricosuric drug and acts by inhibiting renal tubular reabsorption of urate.

Fenofibrate: It is a lipid lowering agent and has uricosuric effect.

Vitamin C: It can be given in a dose of 8 gm/day in divided dosage.

Urate-lowering Strategies

Inhibit uric acid formation by inhibiting xanthine oxidase inhibitors:

- Allopurinol
- Febuxostat

Allopurinol: Approved at daily doses of 100–800 mg/day but 95% of dosing is at less than or equal to 300 mg/day and at this dose it sub-optimally controls the sUA levels (only 21–55% patients achieve target sUA of 6 mg/dL).

Factors contributing to low dosing of allopurinol:[15,16]

- Intolerance (~10%) including rare but life-threatening rashes and hypersensitivity syndrome.
- Dosage reduction recommended with impaired renal function.
- Minimal RCT evidence for safety and efficacy of allopurinol at doses more than 300 mg/day.

Unmet needs with Allopurinol therapy:[14]

- *Under-dosing:* Only 53% patients achieve target sUA with the commonly used dose of 300 mg/dL
- *Intolerance and allergies:* Drug rash with Eosinophilia and Systemic symptoms (DRESS)
- *Dosing adjustment required in comorbid conditions:* Kidney impairment
- *Drug:* Drug interactions (Azathioprine, Mercaptopurine)

The above factors result into non-compliance (50%) and treatment failure.

Febuxostat: Non-purine, selective xanthine oxidase/xanthine dehydrogenase inhibitor, which completely inhibits activity of XO enzyme by obstructing substrate binding.[17-19]

Indications

- Chronic management of hyperuricemia in patients with gout
- Allopurinol hypersensitivity/intolerance/failure
- CKD, where the reduced allopurinol dose sub-optimally controls the sUA levels

Initiate dose is 40 mg OD. Monitor the sUA after 2 weeks. If target (<6 mg/dL) not achieved, shift to the higher dose (80 mg or 120 mg).

Adverse effects: Transaminitis, acute gouty flares, myocardial infarction, immune hypersensitivity reaction, renal failure, angioedema.

Uricase

- Apes and human beings lack uricase
- Uricase converts insoluble uric acid into soluble allantoin

Recombinant Uricase

Rasburicase: Short-term use in tumor lysis syndrome but unsuitable in gout due to short half-life and immunogenicity.

Pegloticase: It is useful in treatment failure cases and tophi. Dose 8 mg IV every 2 weeks. Limitation is infusion reactions, attenuation of clinical response due to development of inhibitory antibodies.

Conclusion

Hyperuricemia and gout are not synonymous. Do not treat asymptomatic hyperuricemia. At least half of patients who present with an initial attack of gout take a diuretic or other medication predisposing to hyperuricemia or gout. Do not start a urate-lowering agent during an acute attack of gout; however, do not stop one if the patient is already taking it and experiences a recurrence. Limiting allopurinol to 300 mg/day is insufficient to control gout in many cases; aim should be "dose to target." Febuxostat represents an effective treatment option to allopurinol may be considered as first-line treatment. Biologics are very effective option, but cost is the maim constraint.

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CHAPTER

216 Liver Dysfunction and NAFLD in RA: Is MTX Really a Culprit?

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Abstract

There is an increased risk of nonalcoholic fatty liver disease (NAFLD) in patients with rheumatoid arthritis (RA) as they share a lot of risk factors. Methotrexate (MTX), which used in the treatment of RA, further increases the risk as it is a potentially hepatotoxic drug. NAFLD related to MTX is believed to be related to folate antagonism and genetic (C677T) polymorphism. However, there is an absence of significant clinical and histological hepatic worsening seen. Possible options for monitoring include LFT, USG, Fibroscan, and scoring systems (like NAFLD-LFS). Transaminase elevations more than three times the normal values are rarely seen. If at all seen, then the first step should be to evaluate for other confounding causes. If MTX is the likely culprit, it should be withheld and restarted after normalization of values. As a last resort, other DMARDs can be tried; however, it should always be the priority to keep the patient on MTX for as long as possible as it is the sheet anchor drug in RA. Also, MTX is associated with a possible reduction in serious outcomes and has a possible protective effect from the development of metabolic syndrome.

Introduction

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis. It is an autoimmune disorder that can also affect other parts of the body including the liver. There is an increased risk of nonalcoholic fatty liver disease (NAFLD) in patients with RA as they share a lot of risk factors including obesity, and hence metabolic syndrome (MS) (which is worsened with decreased physical activity in these individuals). Additionally, a known hepatotoxic drug, methotrexate (MTX), which is commonly used and is the sheet anchor drug in the treatment of RA is associated with transaminitis as a common side-effect. NAFLD represents a spectrum of liver disorders ranging from steatosis, steatohepatitis (NASH), cirrhosis to primary liver cancer. In the United States, about 29% of patients with RA have mild to moderate NAFLD and about 1.4% have advanced disease.[1] The prevalence of NAFLD in general population of India ranges from 9% in rural to 32% in urban.[2] Asians have been found to have increased body fat as compared to the Europeans even at the same BMI, and hence Indians are at a greater risk for NAFLD even if having a normal BMI.[3] Reasons for this may be environmental factors and lifestyle related factors like high-fat diets and reduced physical activity. Having said that, still most of the Indian patients with NAFLD are overweight or obese instead of having a normal BMI as per the Asian-Pacific criteria even though they do not have the typical morbid obesity that is seen among the Western patients.[4] However, in the Indian patients with NAFLD, a lower prevalence of full-blown MS is found, which may be related to the lower frequency of hypertension and diabetes in patients presenting with raised transaminases.[5] In Indian patients with RA, the prevalence of MTX-associated NAFLD with transaminitis is found to be 4.7%. This is somewhat lower than expected and the methodological, ethnic, and genetic variations may

be a reason for this discrepancy in the actual prevalence. However, the simultaneous use of other disease-modifying antirheumatic drugs (DMARDs), viz. hydroxychloroquine and sulfasalazine, does not influence the development of NAFLD with transaminitis.[6] In another Indian study involving patients with RA on low-dose weekly MTX, only 7.5% were reported to have significant hepatic fibrosis as assessed by transient elastography.[7] There is a paucity of Indian studies regarding the exact prevalence of NAFLD (by USG) in patients with RA and on MTX.

Role of MTX in Pathogenesis

As per the studies conducted in the past, the duration of MTX therapy and especially its cumulative dose seems to be significantly related to the occurrence of transaminitis.[6,8] However, some also suggest that these factors are not significant in causing transaminitis in patients with RA.[9]

NAFLD associated with MTX therapy is believed to be related to folate antagonism in the hepatic tissues which have high cellular turnover. The probable mechanism involves inhibition of purine metabolism, polyamine synthesis, and homocysteine metabolism.[10] The liver biopsy specimens taken from the patients with RA have demonstrated hepatic folate deficiency and accumulation of MTX-polyglutamates in the liver.[11] The other culprit mechanism is related to the genetic polymorphism in metabolic pathways of MTX that resulted in the development of NAFLD. It is also been reported that C677T polymorphism increases the likelihood of MTX toxicity.[12,13] However, studies with new grading systems and electron microscopy now have confirmed an absence of significant changes in liver histology in patients with RA on long-term MTX. There is also an absence of clinical meaningful hepatic worsening. Hence, it is safe to use MTX for a long duration with proper monitoring in patients with RA.[14] In fact, many of the serious adverse effects of MTX are linked with the daily dosing or very higher doses (e.g., 100 mg/week) that was used in the past but with the introduction of lower and less frequent dosing regimens, these toxicities are hardly seen nowadays.

Does MTX have a Protective Role?

It is seen that the patients with RA on MTX, despite having minor or major transaminitis, do not have an increased risk of liver cell failure, cirrhosis, or death. There is a strong trend toward less of these serious outcomes in them although not reaching the statistical significance. However, the reason for this possible decrease in serious outcomes is not completely apparent.[15] Similarly, a negative association between MTX use and the presence of the MS is noted, which suggests that MTX may protect against its development. This protective effect of MTX is not a result of generic anti-inflammatory effect, but is likely to be drug-specific. This is not observed with any of the other DMARDs.[16] A similar association was also observed in another study where it was assumed to be purely due to the anti-inflammatory effect of MTX, although no data was presented to support it.[17] The lower incidence of MS in patients on MTX may be seen because of the increased physical activity in these individuals as the disease activity reduces with appropriate treatment; however, further studies are needed to confirm this postulate.

Clinical Features

Patients with RA and NAFLD are structurally obese with clinical evidence of insulin resistance in the form of acanthosis nigricans. They are usually asymptomatic but may have occasional pain in the right upper quadrant of abdomen due to underlying hepatomegaly. Clinical features due to enzyme derangements in the form of loss of appetite, nausea, or vomiting are minimal because the degree of transaminitis is generally minimal despite the usage of MTX. Peripheral stigmata of chronic liver disease and portal hypertension may be rarely seen in advanced cases (especially those with cirrhosis).

Diagnosis

Since the diagnosis of NAFLD does not require any invasive testing, it is always to be done by history, physical examination, liver imaging, and few blood tests (to exclude other liver diseases). History of ethanol consumption of more than 20 g/day in men and more than 10 g/day in women exceed the diagnostic cut-off for NAFLD. Intake of medications causing hepatic steatosis and other causes of liver injury like viral hepatitis, autoimmune diseases must be excluded.[18] Suspicious drugs including other co-prescribed hepatotoxic drugs in the treatment of RA like leflunomide and NSAIDs[19,20] and other risk factors for NAFLD like obesity, diabetes, dyslipidemia, insulin resistance, and MS may also increase the likelihood of NAFLD and they always need careful evaluation.[21] Hence,

it is not easy to simply mark the liver dysfunction to MTX in patients with RA.

Liver biopsy is the gold standard to confirm NAFLD, but it is an invasive procedure and is very rarely advocated for the confirmation of MTX related liver disease. It is rather indicated for the evaluation of other potential causes of transaminase elevations when the diagnosis is unclear.[15] A pretreatment liver ultrasound for patients at a high risk of NAFLD is recommended. Some centers even advocate a pretreatment liver biopsy for high-risk patients but is not recommended as a blanket practice in current guidelines.[22] Amongst the imaging modalities, ultrasonography of the liver is the imaging modality of choice for screening of fatty liver.[23] This has almost replaced the liver biopsy for the diagnosis of NAFLD.[21] Another imaging technique is the Transient Elastography or Fibroscan, which measures liver fibrosis by measuring liver stiffness. The other newer imaging modalities like Shear-Wave Elastography (SWE), Proton Magnetic Resonance Spectroscopy (^{1}H-MRS), MRI using Proton Density Fat Fraction (MRI-PDFF), and MRE (MR Elastography) are also useful in diagnosis.

Biochemical tests include estimation of alanine transaminase (ALT) and aspartate transaminase (AST) levels in serum. Elevation of ALT and AST is very modest and usually less than twice normal. As the hepatic fibrosis increases, the ALT levels fall further downward. The characteristic AST to ALT ratio of less than 1 seen in NASH patients reverses as the disease progresses toward cirrhosis.[24] Another biochemical test is the detection of Cytokeratin/Keratin (CK/K) 8 and 18 fragments in blood, which can help to differentiate NASH from simple steatosis or normal liver more reliably than serum aminotransferase levels.[18]

Many other noninvasive scoring systems can also be very useful. The FIB-4 score, for instance, is a valuable tool to diagnose liver disease in patients with RA treated with long-term MTX therapy.[25] Hepatic indices like NAFLD-Liver Fat Score (NAFLD-LFS), Hepatic Steatosis Index (HSI), Fatty Liver Index (FLI), and Aspartate aminotransferase-to-Platelet Ratio Index (APRI) are handy and easy tools and can also reliably predict NAFLD.[26,27] The Lipid Accumulation Product (LAP) is also useful to identify people with hepatic steatosis.[28] Out of the four NAFLD prediction scores—FLI, HSI, LAP, and NAFLD-LFS; it is found that the NAFLD-LFS score has the best noninvasive prediction value for NAFLD.[29]

Treatment

The treatment of patients on MTX having abnormal liver functions is always debatable. The first step in the treatment of such patients is to confirm the diagnosis. Evaluation for other potential causes, viz. NSAIDs, alcohol intake, obesity, and viral infections (hepatitis B and C), should be done. If no other cause is identifiable, then look at the degree of transaminitis. Though transaminase elevations do not necessarily correlate with the stage of NAFLD, most of the guidelines have used this to monitor hepatotoxicity with MTX. The estimation of baseline transaminase levels before MTX initiation is important. A person who previously had elevated transaminase levels which has not changed after starting MTX should not be subjected to further evaluation. Transaminase elevation more than three times the upper limit of normal is often an indication to withdraw the drug. In case of persistent low-grade elevations particularly if the trend is for a progressive increase in the levels, the dose of MTX is reduced and further investigations are carried out simultaneously.[15] Some also advise stopping MTX when transaminases rise to more than two times the upper normal limit.[22] However, irrespective of the cut-off used, it may be restarted at a lower dose after normalization of these levels. Some other modalities like USG of the liver, Fibroscan, and Scoring Systems (FIB-4 Score) can also be used to identify NAFLD and adjust the MTX dose accordingly.[25] Now, the question that still remains unanswered is—"What if significant transaminitis reappears even with lower doses of MTX and other causes being ruled out?". Here, we would like to suggest switching to other DMARDs or biologicals after considering the patient's disease severity, accessibility, and affordability. However, we need to remember that MTX is still the sheet anchor drug in RA with probably being the most efficacious, cheapest, easy for compliance, and with minimal side effects (especially at a dose less than 25 mg/week, which is far lower than the doses used in oncology) and its substitution should only be done if we are left with no options to continue with it.

Conclusion

MTX is a proven culprit causing liver dysfunction in patients with RA, although with the current data and studies available, it is seen in very few patients. It is mostly transient and not always

Contd...

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clinically significant enough to warrant its discontinuation. To exclude the other causes of NAFLD should be the first rule. Pharmacogenetic approaches may help to optimize the treatment with MTX but this may not be feasible in all parts of the world before starting this drug. Fibroscan is not available at all the diagnostic centers and the poor people of developing countries like India cannot go for repeat evaluations. At the most, what we can use for serial monitoring are LFTs, noninvasive scores (NAFLD-LFS), and occasional USGs of the liver for serial evaluation of such patients. MTX is and will always remain the gold standard backbone therapy in RA, and hence we recommend continuing therapy and keeping such patients on a regular follow-up to pick up liver dysfunction early. Careful small dose adjustments should be done as per the laboratory parameters and prompt reintroduction of the drug should be done as soon as the picture normalizes. To summarize the protective effect of MTX, it is associated with a possible reduction in serious outcomes and also has a possible protective effect from the development of MS.

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CHAPTER

217 Sexual Dysfunction in Rheumatic Diseases

Vinod Ravindran

Abstract

Normal sexual function is an important component of both physical and mental well being. Sexual dysfunction, therefore can negatively impact an individual's quality of life. Sexual dysfunction, though not uncommon, remains an under-explored area in Rheumatology. There are several unique factors contributing to the burden of sexual dysfunction in patients with rheumatic diseases. This review discusses pertinent areas which need specific exploration and offers some thoughts on how to effect the therapeutic aspects of management of this challenging comorbidity in day-to-day rheumatology practice.

Introduction

Sexual health has been defined by the World Health Organization (WHO) as a state of physical, mental, and social well-being in relation to sexuality and it has been recognized as an important factor having positive or negative effects on an individual's quality of life.[1] The WHO has recognized sexual health as extremely important necessitating well thought out plans to pick them up, start preventive measures and appropriate management.[1] Sexual functioning is a neglected area of quality of life in patients with rheumatic diseases and is not routinely addressed.[2] In a study assessing the impact of an outpatient based intervention to improve rheumatologists' identification of sexual health aspects in younger individuals with chronic rheumatological diseases found that only few rheumatologists ever screen their patients for sexual activity.[3] Existing health assessment questionnaire and other quality of life tools for rheumatological conditions do not assess sexual function.[4] **Box 1** lists some of the barriers in effective exploration of the sexual dysfunction.

Female preponderance of several rheumatic diseases is an additional factor which may negatively impact effective communication between not only female patient-male clinician but also between female patient-female clinician.[5] In addition, generally, cultural, religious and social barriers in India make the due assessment of sexual dysfunction difficult, irrespective of the gender. Shame and frustration prevent patients to volunteer the information on issues with sexual function. In addition, lack of specific exploration of this area by clinicians leads to under diagnosis of sexual dysfunction in such patients.

BOX 1 Barriers in exploring/assessing sexual dysfunction in rheumatic diseases

- I am too busy! (time constraints)
- Discomforting subject (uneasiness)
- Why should I screen? (ambivalence in role)
- How should I do it? (competence)
- Not a part of standard assessment, so not important! (perceived lack of applicability)
- Gender of the patient (barrier in communication)

The Sexual Response Cycle

Sexual function and the amount of satisfaction derived from it have the potential to positively or negatively impact on the individual's quality of life. Sexuality encompasses the sexual act itself, self-image and the valorization of self and the relationship with the partner. The sexual response cycle is comprised[6-8] of four distinct stages namely, desire, excitation, orgasm, and resolution. In either gender it leads to simultaneous and often reciprocal physiological changes allowing and facilitating the sexual act and its desirable outcomes. Any disturbances in sexual desire and physiological aspects of the sexual response cycle may cause distress and inter-personal difficulties and are labeled as sexual dysfunction.[8]

Mechanisms of Sexual Dysfunction in Rheumatic Diseases

Sexual dysfunction in rheumatic diseases is fairly common ranging from 36% to 70%.[9-11] The factors responsible for aberration in the sexual function in rheumatic diseases can be categorized into physical and physiological domains **(Table 1)**. In chronic rheumatic diseases both these domains are likely to play a part. Conditions such as osteoarthritis, ankylosing spondylitis and rheumatoid arthritis may prevent attaining relevant sexual positions. Both primary and secondary Sjogren's syndrome can lead to vaginal dryness, which may cause dyspareunia. Pain and fatigue which are a part and parcel of many rheumatic diseases also contribute. Altered body image and apprehension about partner's interest (for example, due to skin involvement in systemic sclerosis, psoriatic arthritis, and lupus or deformities of rheumatoid arthritis) may compound the problems. In some conditions such as ankylosing spondylitis erectile dysfunction has not only been reported to be common but appears linked to high disease activity.[12]

TABLE 1 Contributors to sexual dysfunction in rheumatic diseases

Physical domains	*Psychological domains*
• Heightened tactile sensitivity	• Diminished sense of sexual attractiveness
• Reduced endurance	• Reduced sexual desire
• Impaired motion	• Reduced satisfaction
• Vaginal dryness	• Issues with sexual arousal
• Inability to have an orgasm	• Impaired sensation of penile turgidity
• Inability to have erection	• Inability to achieve orgasm

Drugs and Sexual Dysfunction

Pharmacological treatment of the rheumatic diseases fortunately does not cause major issues as far as the sexual function is concerned. There are reports though of reversible erectile impotence caused by methotrexate, sulfasalazine, and hydroxychloroquine. Commonly used non-steroidal anti-inflammatory agents such as diclofenac, misoprostol, and naproxen may cause interference with libido. Antidepressant medications used in the management of fibromyalgia can lead to loss of desire and difficulty with orgasm. Steroids can contribute to sexual dysfunction in multiple ways including weight gain, abnormal hair growth, altered body image, psychosis, and striae.[13]

Determinants of Sexual Dysfunction

Factors such as severity of the disease, levels of fatigue, amount of pain, physical limitations, act of weight bearing leading to discomfort, perception of self, self-esteem and emotional status, adverse effects of pharmacologic agents, effects of surgery, and fatigue either alone or in combination can determine the sexual function in an individual with rheumatic disease.[14] Generally speaking, irrespective of the gender of the patient, sexuality is adversely impacted by level of pain, depression, and physical limitations. A recent study looking into sexual functioning and its correlates in premenopausal married Indian women with SLE found that dose of glucocorticoids, active lupus, presence of depression and anxiety, and marital satisfaction were all important determinants.[15]

Strategies to Manage Sexual Dysfunction

General Measures

Irrespective of the type of rheumatic diseases, some practical tips to patients and partners are useful and easily adoptable **(Box 2)**. They are generally aimed at relaxation, relieving pain and improving function. A useful resource in this regard is a booklet entitled "Sex and Arthritis" by the

UK based charity Arthritis Research UK.[16] This booklet has information on sexual positions which most couples can try and improve with a little experimentation and open discussion, and adopt positions that are comfortable and enjoyable for both partners.[16]

Specific Approaches

Panush and colleagues have proposed a specific multidisciplinary approach to manage sexual dysfunction entitled "PLISSIT" (for *P*ermission, *L*imited *I*nformation, *S*pecific *S*trategies and *I*ntensive *T*herapy).[17] Details of this approach have been provided in **Table 2**.[17] It is envisaged that an ideal team would have psychologist, physiotherapist, occupational therapists, sex therapist, rheumatologist, and gynecologist.[8]

It is also important to consider hip or knee arthoplasty as per the clinical needs. Both knee and hip arthroplasty have been shown benefit in improving sexual function mainly by allowing the liberty to choose a greater variety of sexual positions.[18,19]

BOX 2 Measures for patients and their partners

- Resting before sexual activity
- To ease stiffness of joints and muscles use of warm shower or hot bath, use of electric blanket
- Taking analgesics and anti-inflammatory drugs as required well before sexual act
- Massage during the act of foreplay to help relax muscles and joints
- Supporting joints appropriately by rolled up blankets or pillows
- Use pacing as a strategy to avoid fatigue
- Use specific positions to reduce discomfit

TABLE 2 PLISSIT approach to managing sexual dysfunction in rheumatic diseases*

Step	*Actions*
Permission	• Demonstrating readiness for the dialogue and exploration of patients' issues related to sexual function • Conveying that patient's issues related to sexual function are manageable • Exploring the issues related to sexual function by involving the patient and his/her partner
Limited information	• Seeking and furnishing information about sexual dysfunction • Trying to establish the cause of sexual dysfunction
Specific strategies	• Considering specific interventions to address the cause/reason of sexual dysfunction, e.g. considering hormonal replacement, review of exiting pharmacological treatment, stress management, measures to reduce vaginal dryness, and approaches listed in **Box 2**
Intensive therapy	• Involving a sex therapist as required

*Table created based on information available from Panush et al.[17]

Conclusion

Sexual dysfunction in rheumatic diseases is though common, remains either under or undiagnosed and affect men as well as women.[20] It is important for the clinicians to be aware of this important aspect of their patients' well-being and be prepared to explore it further and offer appropriate management with the help of a multidisciplinary team.

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CHAPTER

218 Interpretation of Common Investigations in Rheumatology

Renu Saigal, Amit Kansal, Vikram Raj Jain

Abstract

Autoimmune rheumatic diseases (ARDs) are multiple; diagnosis of these diseases depends on meticulous history, physical examination, and investigations. These diseases are characterized by inflammation, autoimmunity, and the presence of autoantibodies. Inflammation is assessed by acute phase reactants, viz. high leukocyte count, erythrocyte sedimentation rate, C-reactive protein, ferritin, alkaline phosphatase, and by low albumin levels. Various antibody tests are done to support the clinical diagnosis of ARDs, e.g., rheumatoid factor (RF), antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), etc. Positivity does not always confirm the diagnosis as false positivity may be seen in normal persons, in non-rheumatic diseases and other ARDs, e.g., ANA may be positive in rheumatoid arthritis (RA) patients and RF may be present in systemic lupus erythematosus (SLE); therefore, clinical setting and pre-test probability have to be considered before ordering or interpreting positive tests. Few patients may be suffering from ARD, but the tests may be negative. Therefore, a good correlation between clinical features and laboratory tests has to be done before the final diagnosis.

Introduction

Rheumatic diseases are multiple and are characterized by inflammation, autoantibodies and damage to the organs. To evaluate autoimmune rheumatic diseases (ARDs) it is very important to elicit a good detailed history and perform meticulous examination of patient before getting tests done. Ordering an "Arthritis Panel" should be avoided as tests of inflammation are non-specific and may be elevated in other conditions also. Similarly autoantibodies may be falsely positive in normal persons and in patients with non-rheumatic diseases. One antibody may be present in other ARDs too, for example, rheumatoid factor (RF) and antinuclear antibody (ANA).

Tests to Assess Inflammation

In response to inflammation there is increase in serum concentrations of acute phase reactants (APRs) **(Table 1)**, for example, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and alkaline phosphatase. Negative APRs are also there, which decrease with inflammation, for example, albumin.

ESR—ESR increases with age, upper limit for males is half the age while in females half of sum of age plus 10 (so for 70 year male it is 35 while in female will be 40).[1] ESR is also high in anemia, infections, cancer, pregnancy, trauma, kidney disease, obesity, and with high fibrinogen levels. Its rise and fall may be delayed with the onset and remission of inflammatory disease, respectively.

CRP—It is more consistent than ESR as it rises and falls quickly. It gets elevated within 4 hours of inflammation or infections and peaks at 24–72 hours. In systemic lupus erythematosus (SLE) CRP is usually normal except in presence of infection, severe serositis, or synovitis.

Autoantibodies

Rheumatoid Factor (RF)

It is an autoantibody directed against the Fc (constant) region of the IgG molecule. Antibody may be of various

TABLE 1 Acute phase reactants

Laboratory test	*Abnormality*	*Autoimmune rheumatic disease (ARD)*
CBC	• Anemia • Leukocytosis • Leucopenia • Thrombocytosis	• NCNC, IDA • Active inflammation • SLE, MAS • Active inflammation
ESR	• Increased • Low	• In most ARD • MAS
CRP	• Increased (>6 mg/L)	• In most ARDs except in SLE • Infections
S. Alkaline phosphatase	• Increased	Indicates active inflammation
S. Ferritin	• Increased • Very high	• Active inflammation • SoJIA, ASD, MAS
S. Albumin	Decreased	In inflammation

ASD, Adult onset still disease; CBC, Complete blood count; CRP, C-reactive protein; ESR, Erythrocyte sedimentation rate; IDA, Iron deficiency Anemia; MAS, Macrophage activation syndrome; NCNC, Normocytic normochromic; SoJIA, Systemic onset juvenile idiopathic arthritis.

isotypes, IgM, IgG, and IgA. IgM RF is routinely measured using latex agglutination while all the three isotypes are measured using nephelometry and enzyme linked immunosorbent assay (ELISA). RF is present in 70–80% patients of RA. Titer usually correlates with the severity of rheumatoid arthritis. RF may be present in normal persons and in various other rheumatic diseases (Sjögren syndrome 75–95%, Mixed cryoglobulinemia type II 100%, SLE 15–35%, mixed connective tissue disease 50–60%, Systemic sclerosis 20–30% ANCA associated vasculitis, Dermato-/polymyositis 20%, Systemic vasculitides 5–20%, etc. and in non-rheumatic conditions as well **(Table 2)**.[2]

Anti-citrullinated Peptide Antibody (ACPA)

It is an antibody against citrullinated peptide (post-translationally modified citrulline). It is better test for RA as compared to RF as it is 98% specific for RA but its sensitivity is equal to RF, that is, 70–80% and it is costly.

Seroprevalence of ACPA was found in 10% of other rheumatic diseases[3] and in non-rheumatic diseases. Presence of ACPA may antedate RA by several years and is indicative of severe erosive disease.

TABLE 2 RF positivity in non-rheumatic diseases

Condition	*Frequency of RF (%)*
Aging (>50 years)	5–25
Infection	
Bacterial endocarditis*	40
Hepatitis C*	40–76
Tuberculosis	15
Syphilis*	8–37
Parasitic diseases	10–25
Leprosy*	70–80
Other viral infections*	15–20
Pulmonary disease	
Sarcoidosis*	5–30
Interstitial pulmonary fibrosis	10–50
Silicosis	30–50
Asbestosis	30
Miscellaneous diseases	
Primary biliary cirrhosis*	45–70
Malignancy*	5–25
After multiple immunizations	10–15

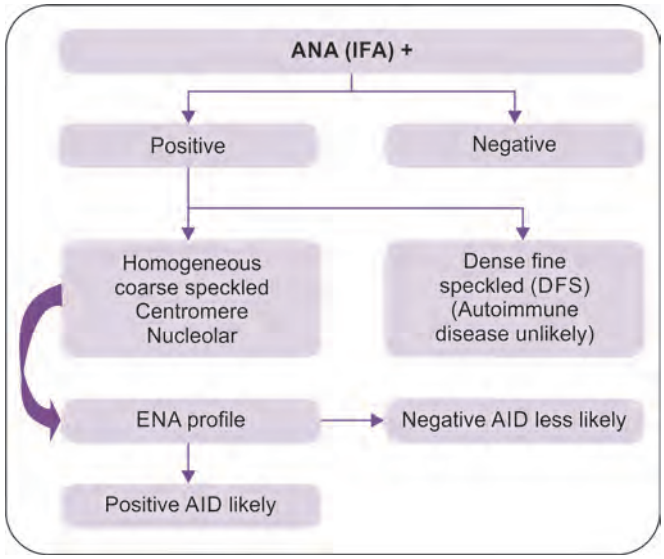
*May cause polyarthritis resembling RA. The best-documented examples of viral infection (in addition to hepatitis B and C) are rubella, mumps, influenza, HIV, dengue, coxsackie virus, EBV and CMV infections, Herpes virus, and parvovirus. Major parasitic diseases are Chagas' disease, Leishmaniasis, onchocerciasis, and schistosomiasis. B cell neoplasms are the most common malignancies.

Antinuclear Antibody (ANA)

The term antinuclear antibody describes a variety of autoantibodies that react with multiple intracellular antigens such as nuclear antigens (DNA, histone, nucleosomes, centromere, topoisomerase, etc.) and in some patients against cytoplasmic antigens (e.g., Jo1 or histidyl tRNA synthetase, mitochondria, smooth muscle cell, etc.).

ANA should be done by indirect immunofluorescent assay (IIFA) using human epithelial cells (HEP2) derived from human laryngeal carcinoma cell line as substrate. It is reported positive in 1: 80 or more dilution, depending on the kit manufacturer's recommendations. ANA may be positive in 20% of normal sera, majority of which are against dense fine speckled 70 antigen (DFS-70). Anti-DFS antibody may be diagnosed by immunoadsorption

Flowchart 1: ANA (IFA) algorithm



ANA, antinuclear antibody; ENA, extractable nuclear antigen; AID, autoimmune disease

method, which is seen in normal persons with false-positive ANA **(Flowchart 1)**.[4]

ANA should always be ordered when there are clinical features of connective tissue disease like fever, photosensitivity, alopecia, mucosal lesions, serositis, nephritis, Raynaud's phenomenon, inflammatory polyarthritis, skin ulcers, skin rashes, sicca symptoms, and proximal muscle weakness. It should never be repeated once it is positive in significant titers.

ANA detection by ELISA: It is of low sensitivity so is not a preferred method for detection of ANA.

The titer of ANA is more important than the pattern **(Figs. 1A to C)**.

It may be positive in many autoimmune diseases and in diseases other than systemic rheumatic disease **(Table 3)**.

Extractable Nuclear Antigen (ENA) Profile (Table 4)

If features of connective tissue disease (CTD) are present and ANA by IIFA is positive then the ENA profile should be ordered by Immunoblot or Line immunoassay (LIA) or by ELISA. ENA profile may be done in suspected Sjogren syndrome and inflammatory myositis even if ANA is negative.

- *Anti-dsDNA:* There are three methods of assessment:
  - IIF using crithidia Luciliae—It uses unicellular hemoflagellate, staining of its kinetoplast is seen with serial dilutions of plasma by IIF technique.
  - ELISA—Since titers are available by this method, so it is good for monitoring disease activity. Specificity for SLE by this method is 70%.[5] It also correlates moderately well with active nephritis.
  - Radioimmunoassay assay (Farr Assay)—Seldom used because of difficulty in disposing of radioactive material.
- *Anti-Sm and Anti-U1 RNP:* Both antibodies produce coarse speckled pattern **(Fig. 1B)** in IIF assay and corresponding antigens (Sm and U1 Ribonucleoprotein) colocalize in small nuclear ribonucleoprotein particles (sn RNP). Anti-Sm Ab is found in 20–30% patients of SLE and is specific for SLE unlike anti-dsDNA, it may remain positive in remission also. Anti-U1 RNP is present in all patients of mixed connective tissue disease (MCTD) and few patients of SLE **(Table 4)**.
- *Anti-Ro (SSA) & Anti-La (SSB):* Autoantigen Ro60 is localized to nucleus and nucleolus, while Ro52 is localized to cytoplasm. So, if Anti-Ro52 (in cytoplasm) is present ANA may be reported negative by HEP2 IIF method. Anti-Ro52, if present in juvenile idiopathic inflammatory myositis (IIM) it denotes severe disease. In adults IIM Anti-Ro52 may be associated with ILD.

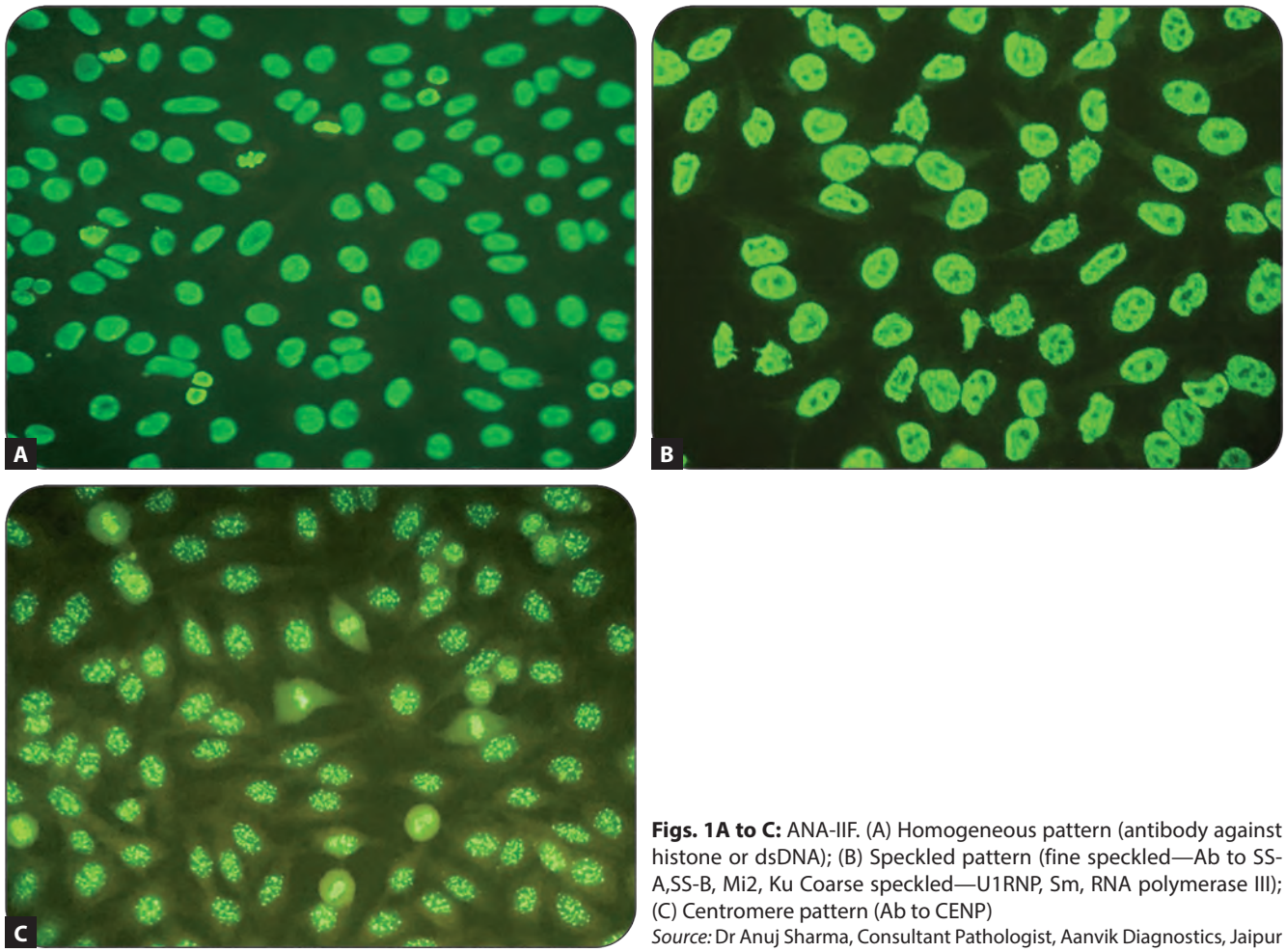
The presence of Anti-Ro antibody in pregnant lupus patient may lead to congenital heart block, neonatal lupus syndrome in fetus and may be present in ANA negative lupus patients and may antedate SLE by 4 years.[6] It may also be positive in subacute cutaneous lupus erythematosus.

Anti-La/SSB autoantigen is present in both nucleus and cytoplasm but it is predominantly found in the nucleus. Anti-Ro and Anti-la Ab should be ordered when sicca symptoms or salivary gland enlargement is present and in SLE patients who wish to become pregnant.

Anti-Neutrophil Cytoplasmic Antibody (ANCA)

This is done by high-quality ELISA (more specific) or IIF (more sensitive but subjective).

ELISA: Current consensus is that in suspected ANCA associated vasculitis (AAV) first high-quality antigen



Figs. 1A to C: ANA-IIF. (A) Homogeneous pattern (antibody against histone or dsDNA); (B) Speckled pattern (fine speckled—Ab to SS-A,SS-B, Mi2, Ku Coarse speckled—U1RNP, Sm, RNA polymerase III); (C) Centromere pattern (Ab to CENP)
Source: Dr Anuj Sharma, Consultant Pathologist, Aanvik Diagnostics, Jaipur

specific ELISA test should be done if it is negative and clinical suspicion is strong, then repeat testing may be done by ELISA or IIF.[7]

Specific ELISA tests for antibodies using purified specific antigens proteinase 3 (PR3) and myeloperoxidase (MPO) are associated with higher specificities and positive predictive value than IIF assays. Anti-PR3 ANCA is present in granulomatosis with polyangiitis (GPA) and Anti-MPO ANCA is present in microscopic polyangiitis (MPA). ANCA against both PR3 and MPO is seen in levamisole adulterated cocaine users.

ANCA by IIFA (Figs. 2A and B)

Using alcohol-fixed buffy coat leukocytes, there are two patterns.

- *Cytoplasmic ANCA (c-ANCA)* **(Figs. 2)***:* There is coarse granular staining of the cytoplasm. The main antigen is PR3, c-ANCA is seen in 90% cases of GPA (10% cases of GPA have ANCA against MPO antigen) and has greater specificity than p-ANCA. In limited GPA c-ANCA may be absent.
- *Perinuclear ANCA (p-ANCA)* **(Figs. 2A and B)***:* ANCA is directed against MPO antigen (occasionally against PR3). There is staining of the perinuclear area leaving cytoplasm clear. ANA positive patients may be falsely labeled as p-ANCA positive, this can be avoided if IIFA tests are done with both formalin and ethanol fixed substrates. p-ANCA is associated with MPA (90%), renal limited vasculitis (75–80%), eosinophilic granulomatosis with polyangiitis with renal involvement, drug induced AAV and ulcerative colitis.
- *Atypical ANCA:* The atypical patterns are usually confused with p-ANCA patterns and may be seen in

TABLE 3 Diseases associated with a positive ANA[12]

Systemic autoimmune diseases	
SLE	
Active	98–100%
Remission	90%
Scleroderma	95%
Rheumatoid arthritis	45%
Sjögren's syndrome	60%
Mixed connective tissue disease	100%
Drug-induced LE	80–95%
Raynaud's phenomenon	40%
Polymyositis/dermatomyositis	35%
Juvenile idiopathic arthritis	15–40%
Organ-specific autoimmune diseases	
Hashimoto's thyroiditis	50%
Graves' disease	50%
Autoimmune hepatitis	70%
Primary biliary cirrhosis	50–70%
Infectious diseases*	
Viral: EBV, HIV, HCV, Parvovirus B19	
Bacterial: Subacute Bacterial Endocarditis, Syphilis	
Malignancies:* Lymphoproliferative diseases, Paraneoplastic syndromes	
Miscellaneous diseases:* Inflammatory bowel disease, Idiopathic pulmonary fibrosis	

SLE, systemic lupus erythematosus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; *Although positive tests of ANA are reported in these diseases more often than in healthy controls, precise estimates vary.
Source: Reproduced with permission from Reference 12.

immune-mediated diseases such as CTD, inflammatory bowel disease, and autoimmune hepatitis. ELISA test for PR3 or MPO is negative.

Indications for getting ANCA done:[7]

- Glomerulonephritis, especially rapidly progressive glomerulonephritis
- Pulmonary hemorrhage, especially pulmonary-renal syndrome
- Cutaneous vasculitis with systemic features
- Multiple lung nodules
- Chronic destructive disease of the upper airways
- Long-standing sinusitis or otitis
- Subglottic tracheal stenoses
- Mononeuritis multiplex or other peripheral neuropathy
- Retro-orbital mass
- Scleritis

Facts about ANCA:

- Negative test does not exclude the diagnosis of AAV, sometimes biopsy is required to confirm the diagnosis.
- Positive test does not establish the diagnosis of AAV as false positive may be seen in other diseases.
- Titers do not correlate with severity so disease should be assessed clinically.

Anti-phospholipid Ab (APLA)

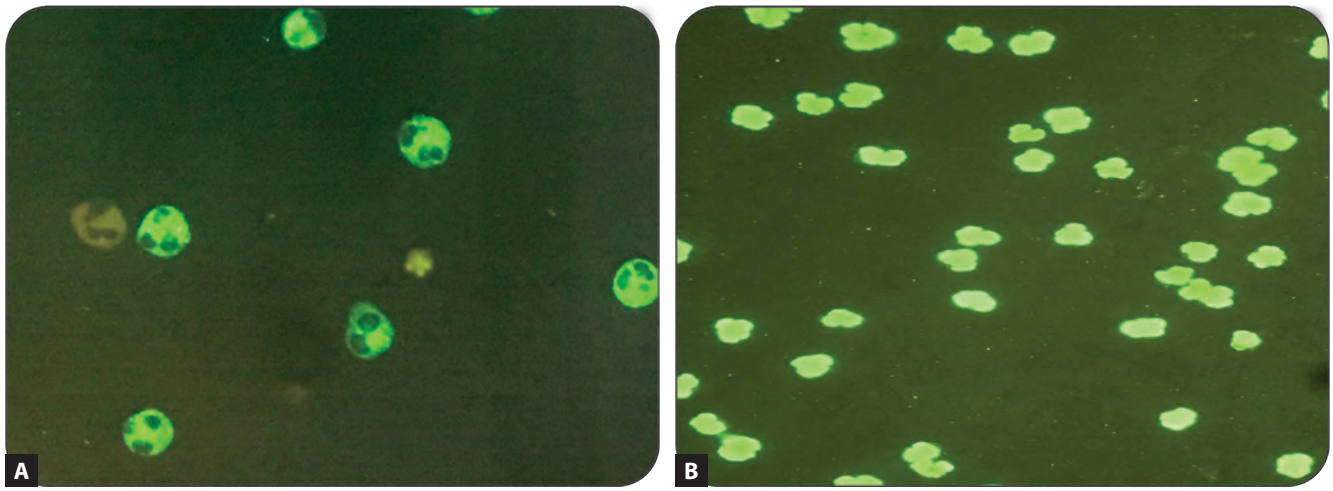
Commonly three APLA are being done.

1. Lupus anticoagulant (LAC):
   Screening tests:
   - dilute Russell viper venom time (dRVVT)
   - activated Partial Thromboplastin Time (aPTT) is prolonged and fails to get corrected when the patient's plasma is mixed with normal plasma excluding coagulation factor deficiency.

TABLE 4 ENA profile

ENA antigen	*Antibody*	*Clinical significance*
• Double stranded DNA • Smith Ag • Histones (proteins of nucleosomes) • Ribosomal P protein	• Anti-dsDNA • Anti-Sm Ab • Anti-Histone Ab • Anti-Ribosomal Ab	• 95% Specific for SLE + in active disease & with nephritis • Present in 10–20% SLE • + in drug induced lupus • Specific for SLE esp. neuropsychiatric lupus
• Ro/SSA-Ro60 (protein of cytoplasmic RNA) & Ro52 (ubiquitin ligase in cytoplasm) • La/SSB (present in nucleus & cytoplasm)	• Anti-Ro/SSA (Anti-Ro60 & anti-Ro52) • Anti-La/SSB	• + in Sjögren syndrome 40–95% and in ANA negative SLE • + in 25–40% Sjögren syndrome *(Both anti-Ro & anti-La associated with extraglandular manifestations*& glandular lymphocytic infiltration)*
Ribonucleoprotein (RNP)—RNA + Proteins	Anti-U1 RNP	• MCTD • 40–60% SLE (not specific)
Topoisomerase-I (Scl70)	• Anti-Topoisomerase-I/ • Anti-Scl70	+ in 30% cases of diffuse Cutaneous SSc, may be associated with ILD
Centromere	Anti-centromere Ab	• Limited cutaneous SSc • Pulmonary hypertension
Cytoplasmic • Histidyl tRNA synthetases • Ku Ag (also present in nucleus) • Mitochondria • Smooth muscle	 • Anti Histidyl tRNA synthetase (Anti-Jo1) • Anti Ku Ab • Anti-mitochondrial Ab • Anti-smooth muscle cell Ab	 • Polymyositis/Dermatomyositis, Strongly associated with ILD • With overlap syndromes, e.g., myositis + SSc or SLE, UCTD • Primary biliary cirrhosis • Autoimmune hepatitis
RNA Polymerase III	Anti RNA Polymerase III	DcSSc with renal involvement
PM-Scl	Anti PM-Scl	Systemic sclerosis

*Extraglandular manifestations – Purpura, vasculitis, lymphadenopathy, leukopenia & thrombocytopenia. DcSSc, diffuse cutaneous systemic sclerosis; ILD, interstitial lung disease; UCTD, undifferentiated connective tissue disease



Figs. 2A and B: Antineutrophilic cytoplasmic antibody (ANCA), c-ANCA, and pANCA. IIF Staining—c-ANCA, p-ANCA
Source: Dr Anuj Sharma, Consultant Pathologist, Aanvik Diagnostics, Jaipur

TABLE 5 APLA positivity in diseases other than primary APS

ARD[13]	*Infections (usually IgM aCL positive)*	*Drugs (usually transient IgM aCL)*
• SLE—25–50% • Sjögren syndrome—42% • Rheumatoid arthritis—33% • Autoimmune thrombocytopenic purpura—30% • Autoimmune hemolytic anemia – (Unknown) • Psoriatic arthritis28% • Systemic sclerosis—25% • Mixed connective-tissue disease—22% • Polymyalgia rheumatica or giant cell arteritis—20% • Behçet syndrome—20%	• Syphilis • Hepatitis C infection • HIV infection • Human T-cell lymphotropic virus type 1 infection • Malaria • Bacterial septicemia • Leptospirosis	• **Cardiac—**Procainamide, quinidine, propranolol, hydralazine • **Neuroleptic or psychiatric—**Phenytoin, chlorpromazine • **Other—**Interferon alfa, quinine, amoxicillin

– Kaolin clotting time

aPTT and dRVVT may sometimes be normal if there is acute large thrombus and it may be falsely prolonged if the patient is on anticoagulants.

2. Anticardiolipin Ab—IgG, IgM, & IgA*
   Most sensitive test for APS
3. Anti-beta-2 Glycoprotein Ab—IgG, IgM, & IgA*

Done by ELISA, not affected by thrombosis or oral anticoagulants

(*IgA isotype is included in the SLICC criteria of SLE but these are not routinely available in laboratories)

Significant APLA titers:

1. aCL IgG antibody more than 40 IgG phospholipid (GPL) units or aCL IgM more than 40 IgM phospholipid (MPL) units, or more than 99th percentile (measured by ELISA) are significant.[8] Titers are low (<40 GPL or MPL), moderate (40–80 GPL or MPL) or high (>80 GPL or MPL).[9]
2. Anti-beta-2 glycoprotein 1 antibody of IgG and/or IgM isotype in serum or plasma in titer more than 99th percentile (measured by ELISA).[8]

These tests are usually done at the time of acute thrombotic event and must be repeated after 12 weeks to exclude false positive tests secondary to infections or drugs **(Table 5)**.

Complement C3 and C4

These are measured by nephelometric immunoassay. Normal C3 levels range from approximately 80–160 mg/dL. Normal C4 levels range from 16–48 mg/dL.

Decreased C3 or low C3, C4 may be seen in immune complex-mediated diseases, viz. SLE, APS, Sjögren's syndrome, MCTD, hypocomplementemic urticarial vasculitis, mixed cryoglobulinemia, serum sickness, some glomerulonephritides including post-streptococcal nephritis. With the treatment of these diseases, C3 or C4 may normalize. Low C4 with normal C3 may be seen in hereditary angioedema and acquired C1 inhibitor deficiency.

HLA B27

This test is done by flow cytometry and polymerase chain reaction (PCR). PCR is preferred as it gives accurate results. This test should be ordered when there are clinical features of spondyloarthritis (SpA), viz. inflammatory backache, as in general population 8% population is positive for HLA B27, so if ordered injudiciously a person with mechanical backache may be wrongly diagnosed as a patient of SpA. Ankylosing spondylitis, a subtype of SpA, 85–95% are positive for this gene remaining 5–15% may be negative, while in SpA secondary to psoriasis or inflammatory bowel disease and in reactive arthritis, up to 50% may be positive for HLA B27.[10] False positive and false negative do occur so judicious ordering for this test is the need.

Serum Uric Acid (SUA)

It is lower in females (≤6 mg%) than males (≤7 mg%). SUA is usually assessed in the diagnosis of gout but during acute gout flare, the levels may be normal or low in up to 40% because of release of cytokines and ACTH during flare, which can lower the uric acid levels. High uric levels lend support to the clinically suspected case of gout but its estimation is neither diagnostic nor mandatory for confirmation of the diagnosis of gout.

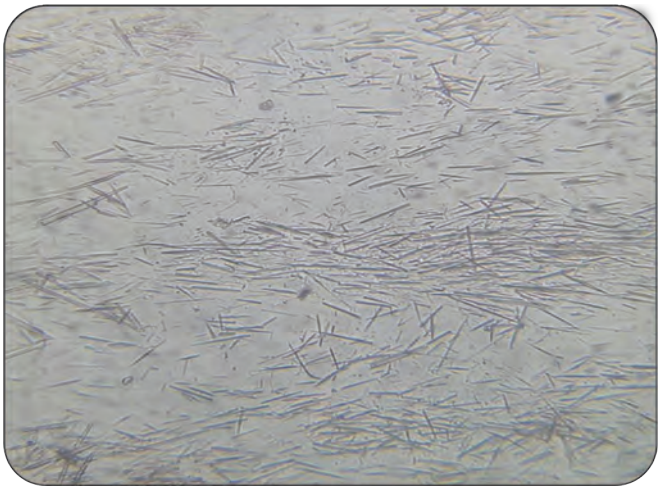


Fig. 3: Needle-shaped urate crystals as seen under low power microscope[11]

Synovial Fluid (SF)

In monoarticular involvement, SF may be examined for bacteria (tubercle bacilli or non-tubercle bacilli), fungus, and crystals. In the suspected case of gout, SF should be aspirated may be seen under light microscope **(Fig. 3)**[11] as polarizing microscope, which is ideal for the demonstration of urate crystals, is not routinely available.

Conclusion

In treating ARD, it is of utmost importance that a very good history and physical examination have been done before ordering investigations. False positives and false negatives do occur so one should be cautious in interpreting these investigations. "Arthritis panel" is to be avoided and should never be ordered.

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Section 17

Section Editor: **YS Raju**

Geriatric Medicine

CHAPTER

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Balance Gait and Fall in Elderly

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Abstract

Gait and balance disorders in the elderly act as harbingers of underlying serious medical disorders and are the major cause of one of the classic geriatric syndromes, fall. The decline in cognitive function, sensory processes, and muscle strength that occur with aging aggravated by a number of neurological, musculoskeletal, sensory, cardiovascular disorders along with environmental factors increase the susceptibility to fall in elderly. Elderly patients presenting with falls should be thoroughly evaluated in order to identify the underlying risk factors along with complete neurological, musculoskeletal, and cardiovascular examination. Various clinical trials have concluded that a comprehensive multifactorial evaluation for identifying risk factors followed by targeted interventions can reduce the risk of fall by about one-third.

Introduction

Impaired mobility is one of the major concerns for physicians attending to the elderly patients. Gait and balance abnormalities are often considered to be a common phenomenon of aging. However, this is an erroneous assumption as studies have shown that up to 20% of adults have normal gait patterns even in advanced age. Gait and balance abnormalities act as harbingers of underlying serious medical disorders and are the major cause of one of the classic geriatric syndromes, fall.[1] The annual prevalence of falls among adults aged 65 and above is 28% and it progressively increases with age with a higher incidence among women in contrast to men.[2] Falls in the elderly have devastating consequences with significant morbidity and mortality. Falls leading to serious injuries are the fifth most common cause of death among the elderly. Other serious consequences include increased hospitalization, reduced functional ability, social isolation, depression, and fear of falling.[3] Multiple factors are involved in the causation of falls and a multidisciplinary approach is required to identify and tackle them. With the expanding elderly population, globally and in our country, it becomes important to acknowledge the impact of this problem and develop an effective approach to manage it.

Physiology of Balance and Gait Disturbance in the Elderly

Balance is regulated through the complex integration of sensory input, central processing, and motor output. With aging, there occurs a gradual functional decline in all of these systems. Sensory information is relayed through vision, vestibular system, and proprioception. Diseases of the aging eye lead to dysfunction of acuity, depth perception, and dark adaptation. Vestibular impairment is a usual process of aging or can be seen in ischemia and head trauma. Peripheral proprioception may be weakened in older adults due to diabetes, peripheral vascular disease or any neuropathy. Studies have reported that visual decline contributes more to instability in elderly as compared to decreased proprioception.[4]

The central nervous system structures like the motor cortex, basal ganglia, cerebellum, and spinal cord are involved in planning motor sequences and regulating balance. Damage to these structures from hypoperfusion, neurodegenerative diseases, trauma, or sedative drugs contributes to balance disorders and falls. The righting reflex which produces correcting movements when there is imbalance is impaired in extrapyramidal lesions increasing the risk of falls. Cognitive decline seen in various forms of dementia is also an important risk factor for falls.

Muscle and joints are effector organs of the motor system. Disorders of the peripheral nerves and neuromuscular junction contribute to muscle weakness. This combined with the progressive decline in muscle mass called sarcopenia leads to decreased muscle strength. Arthritis causes pain, restriction of motion, and joint deformities leading to altered gait, balance and increased risk of falls. Musculoskeletal disorders have a strong association with reduced physical activity further aggravating functional decline, frailty, and increased risk of falls.[2]

Risk Factors Associated with Gait and Balance Disorders

Gait and balance disorders were found to be multifactorial in 75% of elderly patients. The most common associated underlying conditions were reported to be arthritis (37%) and orthostatic hypotension (9%).[1] Acute medical conditions such as infections, electrolyte imbalances may precipitate falls in elderly with underlying subclinical balance disorders. Chronic conditions which increase fatigue such as congestive heart failure or anemia also increase the risk of falls.

Musculoskeletal Diseases

Osteoarthritis reduces joint movement and alters gait due to joint deformities and pain. Osteoporosis is also associated with increased risk of fall and fractures in elderly. Lumbar canal stenosis, radiculopathies cause leg and back pain with reduced activity. Hypothyroidism is often associated with proximal muscle weakness, increasing the risk of falls.[1,3]

Cardiovascular Diseases

Any condition which reduces cerebral perfusion due to hypoxia, hypotension can present as unsteadiness and falls. These conditions include arrythmias, congestive heart failure, orthostatic hypotension, or thromboembolic disease.[1,3]

Neurologic Disorders

Parkinson's disease, cerebellar degeneration, multiple sclerosis, myelopathy, and stroke affect the vulnerable brain areas involved in maintaining gait and balance, increasing the risk of falls. Cognitive impairment seen in dementia is also associated with reduced attention, psychomotor slowing and increased susceptibility to falls. This is particularly apparent when cognitive stress is given along with performing a motor activity in an assessment called "dual tasking."[1,3]

Sensory System

Involvement can occur in the form of peripheral neuropathy due to diabetes and vitamin B12 deficiency. Vision can be impaired in age-related eye diseases like macular degeneration, glaucoma, cataracts, and presbyopia. Vestibular apparatus damage can occur in Meniere's disease and benign positional vertigo.[1,3]

Affective Disorders

Depression and sleep disorders increase the risk of falling. Fear of falling can further aggravate the risk of falls. Patients who fall limit their physical activity starting a vicious cycle which leads to functional decline, increased muscle weakness, and disability further amplifying the risk of falls.[1,3]

Medications

Among pharmaceutical agents, psychoactive and sedative drugs such as benzodiazepines, barbiturates, opioids, haloperidol, and risperidone are often the culprit drugs associated with falls. Cardiovascular drugs leading to arrhythmias, electrolyte imbalances, and postural hypotension are also linked to increased risk of falls. This category includes antiarrhythmics, diuretics, and alpha antagonists. Polypharmacy by itself proportionally

increases the risk of falls. Antiplatelet and anticoagulation drugs further increase complexity as they can lead to grave consequences in case of fall.[1,2]

Environmental Factors

An often underestimated risk factor for fall is the interaction of the person with the external environment. Elderly people tend to fall at lower levels of challenge provided by the environment as compared to young, healthy adults. Commonly associated environmental factors include poor lighting, slippery floors, uneven surfaces, and absence of stairway railings.[1,3]

Clinical Assessment

It is important for clinicians to meticulously obtain history of fall from elderly patients as well as family members because patients may fail to remember due to dementia or intentionally hide history of fall for fear of relocation or restriction of activity. It is also important to identify patients at high risk for future falls. Patients at high risk of falls often have other geriatric syndromes such as incontinence, depression, delirium, or frailty.[3]

- While eliciting history of previous falls, it is crucial to inquire about the circumstances that led to the fall such as time of day, location, frequency, injuries, and associated symptoms such as dizziness, vertigo, palpitations, musculoskeletal pain, instability. An abrupt onset is usually associated with cerebral hypoperfusion, toxic, or metabolic abnormalities.
- The physicians should also question about the extrinsic factors such as lighting, uneven surfaces, absence of railing, etc. in the residential environment, which increase the risk of falls.
- Patients should be asked about their previous medical history of underlying neurologic, cardiovascular, musculoskeletal, and visual/sensory impairment.
- A careful drug history to identify offending drugs such as sedatives, antiarrhythmics, diuretics, and alpha antagonists is essential. Associating the falls with the dosing schedule of the medications is also helpful.
- Symptoms of depression and sleep disturbance should be identified.
- The functional status of the patient should be evaluated not only to indicate disability but also to monitor the response to treatment. This can be determined by documenting the instrumental activities of daily living (activities for independent living such as housekeeping, cooking, shopping, use of transportation, management of finances) and activities of daily living (ability to care for oneself such as dressing, toileting, continence, bathing, and mobility).[5]

A thorough physical examination is fundamental for identifying the risk factors and distinguishing the patients at increased risk of falls.

- Gait should be carefully observed from the time the patient enters the examination room. Points to be noted include posture, stance, difficulty in initiation, step length, cadence (steps per unit time), instability, and need for assistance.
- Vitals signs with blood pressure measurement in the supine and standing position should be assessed. Pallor, signs of any diseases of the heart should be examined for recognizing underlying chronic illnesses that may cause fatigue.
- Cognitive impairment can be assessed using the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA).
- A complete neurological examination should be carried out with focus on sensory and motor examination. Testing for visual acuity, visual field, dark adaptation, and depth perception should be performed. Testing for vibration sense, light touch should be done to detect peripheral neuropathy. Romberg's test can be performed to identify impairments in vestibular function and proprioception clinicians should look for focal neurological deficits, spasticity, hyperreflexia for identifying cerebrovascular diseases. Pattern of gait can give an insight into the underlying neurological condition such as frontal lobe involvement, cerebellar involvement, sensory impairment, or Parkinsonism. Signs of extrapyramidal dysfunction such as rigidity, tremors, hypokinesia should be identified. Cerebellar signs such as psychomotor slowing (finger to nose test, dysdiadochokinesia), scanning speech, ataxic gait should be looked for.
- Testing of muscle strength and joint mobility, deformity, and swelling should be carried out to characterize underlying musculoskeletal conditions like myopathy or arthritis.[1,5]

Special Clinical Tests in Evaluation of Fall

No studies are available to indicate a specific clinical test for gait and balance assessment, till date. The "Get Up and Go" test is easy to perform and can identify older adults prone to fall. Patients are scored on their time taken to get up from a chair, walk 3 meters, turn around, and get back to their original position. A score of 14 seconds or more is considered abnormal and associated with an increased risk of falls.

Other tests of mobility include the Berg balance test for predicting risk of falls and the performance oriented mobility assessment (POMA) test for dynamic and static balance. Nowadays balance testing is combined with a cognitive task in order to unmask underlying cognitive defects. Patients who fail to perform such dual tasks are at increased risk for falls.[6]

Laboratory Evaluation

Laboratory evaluation can be carried out based on the findings of history and physical examination. A 12-lead electrocardiography should be obtained, if arrythmias or cardiac causes are suspected. A complete metabolic panel can be considered for electrolytes and renal function. A complete blood and differential count to rule out anemia or any underlying infection. Serum vitamin B12, thyroid function test, and vitamin D levels should be measured as they are associated with peripheral neuropathy, proximal myopathy, and increased propensity to fall respectively.

Interventions

Lack of effective outcome measures make the assessment of interventions for gait and balance disorders inadequate. However, medical therapies for underlying chronic conditions may produce modest improvement in gait and balance. It is evident by various clinical trials that a comprehensive multifactorial evaluation for identifying risk factors followed by targeted interventions leads to 30–40% reduction in the evidence of fall.[7]

The focus of therapy to reduce falls should be on the reduction of risk factors. Use of visual and hearing aids for increasing sensory input, antiarrhythmic medications and pacemaker insertion for cardiac rhythm disorders, correcting acute metabolic defects that may precipitate falls, appropriate management of arthritis, osteoporosis, correction of vitamin deficiencies such as Vitamin B12 and Vitamin D have resulted in a reduction in the risk of falls. Surgical intervention may be needed for cervical myelopathy, arthritis of knee or hip and lumbar canal stenosis. It is more important to recognize the sedative/psychotropic medications in elderly that precipitate falls and gradually taper their dose appropriately in patients at high risk. All of the prescribed medications should be reviewed and the goal should be to minimize as much as possible the doses and the absolute number of drugs.

Physical activity should be encouraged among the elderly to maintain strength, balance, and flexibility. Tai chi has proven to be an effective intervention in elderly patients for improving balance and reducing risk of falls. The combination of exercise along with visual evaluation and treatment has shown to considerably reduce the risk of falls.[8] Exercise plans should progressively increase physical activity over time with special focus on muscle strengthening and weight bearing. Physical therapists have an important role to play in management of patients with gait and balance disorders. Patients suffering from cerebrovascular diseases or Parkinson's disease should preferably be enrolled in rehabilitation programs.

All efforts should be made to ensure safety of the elderly in their homes by eliminating the extrinsic risk factors. Adequate lighting, strong stairwell railings, switching to safer footwear, avoiding loose rugs, and slippery floors should be ensured to provide a secure and protected environment to the elderly.

In selected patients, assisted devices like canes, walkers, or wheelchairs improve mobility and stability by increasing the base of support and unloading of the painful joints. It is also important to ensure the appropriate size of such devices as incorrectly measured devices may actually increase the risk for falls.[2,3]

Conclusion

The major aim for clinicians treating the elderly is to ensure an independent lifestyle for as long as possible. Gait and balance disorders leading to falls deprive them of such a lifestyle by adversely impacting the day-to-day activities of the elderly. It is vital for clinicians to identify patients at risk of falls, start prevention strategies by individualized multicomponent interventions in order to reduce the morbidity and mortality that result from fall. Recent researches have strongly suggested that interventions to reduce falls are effective. With the growing elderly population the world over, there is an urgent need for implementing fall prevention strategies on a larger scale.

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CHAPTER

220 Anemia in Elderly

Alpana Raizada, Ashish Goel

Abstract

Anemia in elderly is a common problem seen in out-patient as well as in-patient general and specialty medical care. The term, anemia of elderly has largely been replaced by anemia in elderly in current times to promote better understanding of the pathophysiology. Anemia in older persons has been found to be associated with increased hospitalization, longer hospital stay, and a higher mortality.

The present article presents an overview of the definition and epidemiology of anemia in older persons and discusses a broad etiological approach to the problem. Success of preventive medicine and infection control have resulted in an increase in the share of older persons in the Indian population. A wide variation has been noticed in the prevalence of anemia across different study groups in the Indian population owing to the variations not only in the definition employed but also in the cultural practices, nutrition and socioeconomic structure. Further, the chapter presents established therapeutic options such as iron and erythropoiesis stimulating agents. It revisits the role of blood transfusions and associated complications in older persons and provides a brief overview of newer therapies under development.

Introduction

The world population has witnessed a remarkable increase in the share of the older people owing to the success of public health measures over the last few decades resulting in an increase in life expectancy. Declining rates of fertility have also contributed to the changing demographic structure of the world population. As per World Health Organization (WHO), the 900 million population of elderly (>60 years of age) in 2015 is projected to increase to 2 billion by the year 2050, accounting for 22% of the world's population and outnumbering those under 15 years of age.[1] Parallel to these global projections, the population of elderly in India by 2050 is expected to be around 300 million accounting for 20% of the total population against 8% in 2015.[2] This demographic transition is likely to bring unprecedented challenges of disease and disability associated with longevity. Falls, frailty, incontinence, dementia, and nutritional deficiency are few recognized *geriatric giants* that have been recognized in recent times.

In addition to the traditionally described *geriatric giants*, anemia has been increasingly recognized in older persons, and it often goes undiagnosed. The previously used term *'anemia of elderly' signified the acceptance of fall of hemoglobin to be a natural accompaniment of aging against the currently used term 'anemia in elderly'* which considers declining hemoglobin with age as a disease entity. This change in terminology and thought has been evidence based as anemia has been found to be independently associated with multiple adverse outcomes like loss of muscle power, increased risk of falls, cognitive decline and dementia. Culleton et al. in a longitudinal study conducted on patients more than 66 years of age observed that anemia was associated with increased risk of hospitalization, longer hospital stay as well as increased risk of death.[3]

The present chapter presents a review of literature to provide an etiological approach to diagnose anemia in elderly and offers a broad management plan for physicians involved in the care of older people.

Definition

The definition of anemia has been a subject of debate among geriatricians, and hemoglobin cut-offs to use have often been discussed. To address this issue WHO has launched a novel ambitious program to revise hemoglobin thresholds for different populations including the elderly.[4] Until then, in most epidemiologic studies on anemia in elderly, the original WHO cut-offs of hemoglobin less than 12 g/dL for women and 13 g/dL for men are being used.[5] However, in place of absolute hemoglobin cut-offs, it might be more relevant if the definition of anemia in elderly is based upon clinical outcomes. This is exemplified by the Cardiovascular Health Study (CHS) study wherein hemoglobin concentrations above 13.7 g/dL for men and 12.6 g/dL for women gave survival advantage against those with lower hemoglobin levels.[6]

Epidemiology

Anemia in elderly (AE) is common, relevant, and rapidly increasing owing to an aging population round the globe. The overall prevalence of anemia in elderly ranges from 10% to 24% around the globe and is likely to depend on the level of hemoglobin used to define it.[7] The prevalence of anemia is higher among older people who are hospitalized (40%) or those residing in nursing homes (47%). The prevalence of anemia rises rapidly with age, approaching nearly 50% in men older than 80 years.[8]

The prevalence of anemia in elderly in India varies from 17.7% to 89%.[9] The prevalence of anemia in elderly men and women residing in old age homes in India was 65.1% and 70.9%, respectively, with an overall prevalence of 68.7%.[10] In a community-based cross sectional study 92.1% of the elderly subjects were anemic in high-altitude regions[11] whereas anemia was documented in 38.2% elderly population of rural India.[12]

Characterization

NHANES III study performed a laboratory evaluation of over 5,000 community dwelling elderly subjects. They reported that about 10% of men and women above 65 years of age had anemia according to the WHO criteria and that with increasing age beyond 65 years there was substantial increase in prevalence of anemia.[13] According to NHANES III, anemia can be characterized on the basis of underlying etiology into the following subtypes:

- Nutritional deficiency anemia
- Anemia of chronic inflammation (ACI)
- Unexplained anemia of elderly (UAE)

It has been established that anemia in elderly should be evaluated promptly because even mild anemia is associated with adverse clinical outcomes and may often be the first visible pointer towards an occult or subclinical disease.

Etiology

The myriad of causes of anemia in elderly are mentioned in **Table 1**. More often than not, anemia in older individuals is the result of interplay of multiple factors.[24,25] However, the underlying causes may be classified into the following three groups on the basis of pathophysiology.

TABLE 1 Etiology of anemia in elderly

Nutritional	*Chronic inflammation*	*Unexplained/Undifferentiated*
• Poor intake • Malabsorption • Iron deficiency anemia • Deficiency of vitamins such as B12 or folate • Deficiency of trace elements such as copper	• Rheumatic disorders • Chronic infections such as tuberculosis, osteomyelitis • Geriatric syndromes such as frailty • Inflammaging • Neoplasms	An important category of anemia in older persons that remains unexplained after evaluation. Most of the unexplained anemia can be classified into one or the other defined causes after appropriate follow-up. Neoplasms and hematological malignancies are important among them

This table presents the common etiologies of anemia in elderly. However, it is not a comprehensive list of causes and does not discuss some of the important causes that should be considered in detailed evaluation including blood loss (often in stools), drugs, and endocrine causes.

Nutritional Deficiency Anemia

The leading cause of nutritional deficiency anemia is iron deficiency anemia (IDA). In the older individuals, iron deficiency is common due to occult blood loss from the gastrointestinal tract, which in turn may be chronic or acute as per the underlying etiology. It may be the result of nonsteroidal anti-inflammatory drugs (NSAIDs) use, a gastric ulcer, colon cancer, diverticulosis, or angiodysplasia. Killip et al. noted that gastrointestinal malignancy was present in 6% of patients with iron-deficiency anemia.[14] Malnutrition is also responsible for IDA in elderly. Thus, iron replacement therapy should always be accompanied by a thorough gastrointestinal diagnostic workup in the elderly.

Folate deficiency may be present due to malnutrition as frequently seen in chronic alcoholics or can be secondary to medications like methotrexate or phenytoin. Pernicious anemia is another albeit a rare one. Malabsorption syndrome caused by *Helicobacter pylori* infections, anti-acidity drugs, or atrophic gastritis can also lead to cobalamin deficiency. Laboratory screening for Vitamin B12 and folate followed by prompt supplementation can correct both anemia and neurological manifestations associated with deficiency.

Anemia of Chronic Inflammation (ACI)

ACI, also known as anemia of chronic diseases, is the most prevalent anemia in older patients. It is a normocytic normochromic anemia found secondary to infections, which lead to activation of immune system, autoimmune disorders, various malignancies, chronic kidney disease, or to isolated age-associated inflammation. Underlying pathophysiological mechanisms in ACI are manifold and are overlapping **(Fig. 1)**.

Franceschi et al. in year 2000 introduced the term "*inflammaging*," a low-grade, chronic inflammatory state associated with ageing and having potential for tissue damage and degeneration. Inflammaging has been reported as a putative mechanism for some of the age-associated disorders like unintentional weight loss, frailty, anemia, and asthenia.[15]

Unknown/Undifferentiated Anemia of Elderly (UAE)

Anemia, which cannot be classified into a specific etiology and is considered a diagnosis of exclusion, which is

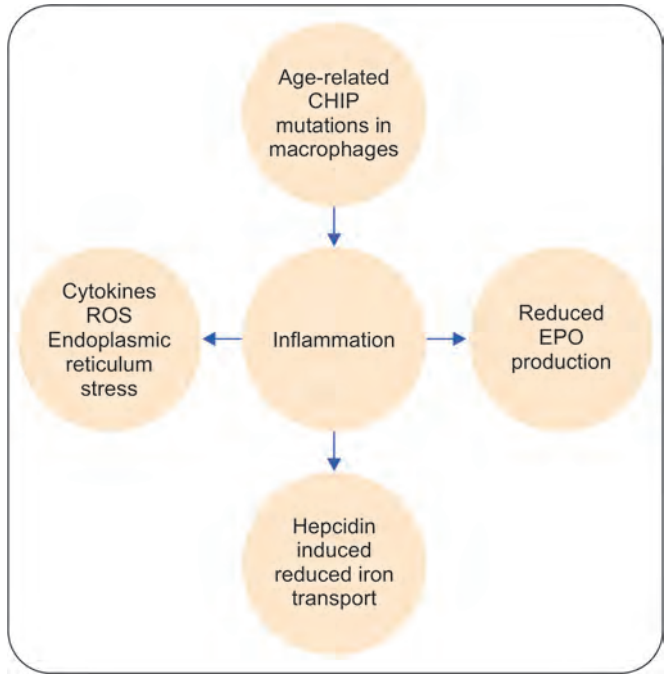


Fig. 1: Potential mechanisms for anemia of chronic inflammation
CHIP, clonal hematopoiesis of indeterminate potential; EPO, erythropoietin; ROS, reactive oxygen species

termed *unknown anemia*, *undifferentiated anemia,* or *anemia of unknown etiology*. This entity accounts for almost one third of all cases of anemia and is compounded by the fact that anemia in geriatric age group is often a result of multiple comorbidities. The various causes which underlie UAE are age-related renal insufficiency, decreased levels of testosterone, vitamin D insufficiency or deficiency, occult deficiency of iron, stem cell aging, and myelodysplasia (MDS).[16] The diagnosis of UAE is largely a diagnosis of exclusion and is complicated as the classical cut-offs of laboratory parameters like mean corpuscular volume (MCV) and ferritin used in younger individuals do not perform well in elderly. However, hypoproliferative anemia, that is, one with a low-reticulocyte index coupled with inadequate erythropoietin level for the degree of anemia should raise the probability of UAE after excluding other common causes.

MDS is more common in older adults, and more than 75% of patients with MDS are older than 60 years of age at diagnosis. Patients are either asymptomatic or have fatigue, pallor, frequent infections, easy bruisability, and petechiae. More often the disease is detected during routine blood tests due to presence of one or more

peripheral blood cytopenias. An estimated 30% of MDS progress to acute leukemia.

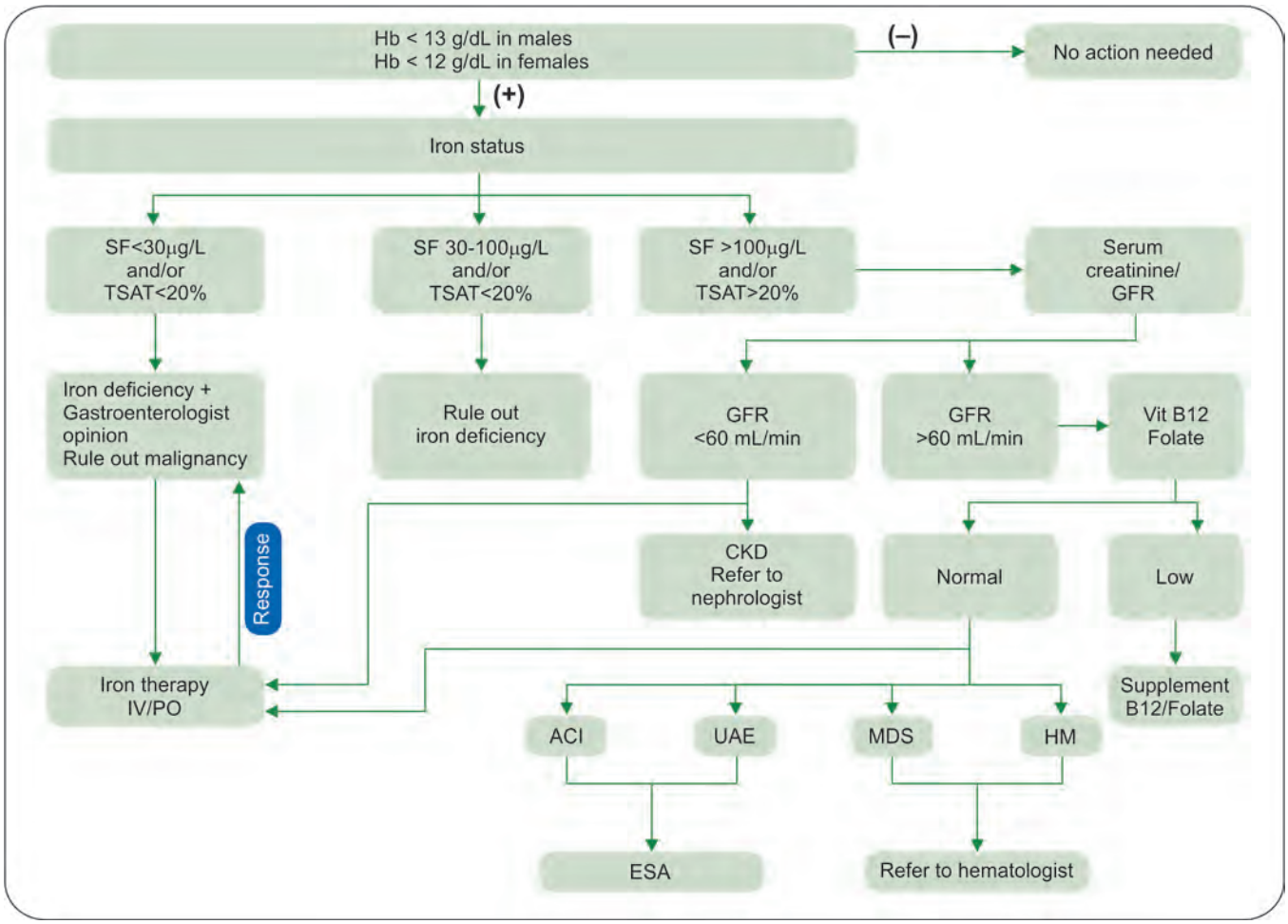
The management of UAE is a continuous process often requiring regular interactions between the patient and the physician, since in the absence of an etiology there is no definite treatment.

Diagnostic Evaluation

The initial evaluation of AE should include laboratory parameters like hemoglobin, total and differential blood count, red blood cell indices, reticulocyte count, reticulocyte hemoglobin, serum iron studies, C-reactive protein, fibrinogen, vitamin B12, serum folate, lactate dehydrogenase, haptoglobin, liver enzymes, kidney function tests, erythropoietin level, and serum electrophoresis. This basic workup is helpful in identifying nutritional deficiency anemia, ACI, and CKD **(Flowchart 1)**.

Due to higher possibility of underlying malignancies additional radiological investigations like ultrasound of the abdomen and kidney and gastrointestinal endoscopic procedures may be warranted as guided by clinical evaluation. The presence of anomalous blood counts or signs of clonal hematologic disease coupled with increased frequency of MDS in elderly may require performance of invasive procedures like bone marrow aspiration and biopsy. The invasiveness of such procedures makes it obligatory to weigh the benefits of establishing a diagnosis

Flowchart 1: Initial evaluation and treatment of AE



SF: serum ferritin; TSAT: transferrin saturation; GFR: glomerular filtration rate; CKD: chronic kidney disease; ACI: anemia of chronic inflammation; UAE: unexplained anemia of elderly; MDS: myelodysplastic syndromes; HM: hematological malignancy; ESA: erythropoiesis stimulating agent

followed by therapeutic intervention against its impact on life expectancy and functional improvement in the elderly. More specialized investigations like flow cytometry and cytogenetics may be required depending upon the findings of bone marrow aspiration and/or biopsy.

Treatment Options

Treatment plans need to be tailored according to the primary diagnosis and accompanying diseases. Anemia in the elderly is often complex and multifactorial necessitating more than one strategy for diagnosis and treatment. As no therapy is without the potential for adverse effects; therefore, it is important to introduce optimal age adjusted therapy, which can positively impact the quality of life of geriatric age group of patients.

Iron Therapy

Deficiency of iron either absolute as in IDA; or functional as in ACI is very commonly present as a factor in anemia in elderly and is complex due to multiple factors contributing to anemia in older individuals. Therefore, iron substitution is still the most recommended symptomatic treatment in IDA and ACI[17] as well as in iron-deficient UAE.[18]

Oral iron substitution is the cornerstone of treatment of anemia across all age groups. However, their use in geriatric patients may be relatively limited due to poor absorption of oral iron.[19] The quest for an oral iron substitute with good efficacy and reliable absorption was over with the FDA approval of ferric maltol for treatment of IDA in adults in 2019. The safety and efficacy of ferric maltol was established by three placebo-controlled trials [AEGIS 1 and 2 (IBD), AEGIS 3 (nondialysis CKD)], and led to its approval by FDA. Oral ferric maltol was found to be effective in raising hemoglobin without significant gastrointestinal side effects in patients with IBD.[20] Thus, ferric maltol is an efficacious and safe alternative to intravenous iron for patients, especially geriatric patients who cannot tolerate salt-based oral iron therapies and wish to avoid parenteral treatment.

As much as oral iron substitution is the gold standard for patients with absolute iron deficiency, it is ineffective for functional iron deficiency as seen in anemia associated with chronic inflammation and inflammation-associated increase of hepcidin. Also in situations with ongoing blood loss, oral iron is insufficient. In such cases intravenous iron substitution is recommended.[17] Complete or near-complete replacement of iron in a single setting using intravenous iron preparations is now the norm. Bygone are the fears of anaphylactic reactions with high molecular weight dextran preparations. The new and safer formulations like ferric carboxymaltose and iron isomaltoside are well tolerated though they too may rarely lead to severe hypophosphatemia with subsequent osteomalacia and bone fractures.[21] These bone mineral metabolic disorders are associated with recurrent and high doses needed in patients with severe IDA. This can be occasionally of concern in geriatric patients.

Erythropoiesis Stimulating Agents (ESAs)

ESAs are so far registered for the treatment of anemia in CKD and in patients with low risk MDS as per recommendations of the American Society of Hematology/American Society of Clinical Oncology Clinical Practice guideline update.[22] Data on efficacy of ESAs in other types of anemia are limited. The effect of epoietin alfa on hemoglobin and quality of life was studied in community dwelling older individuals aged 65 years or more. Erythropoietin was found to be safe and beneficial in chronic anemia.[23] However, there is lack of clear evidence to support the use of ESA in undifferentiated anemia of elderly.

It is important to recognize the potential of ESAs to cause increased risks of death and thromboembolic events and these should be considered while prescribing these drugs.

Blood Transfusion

Blood transfusion is the mainstay of treatment of severe and symptomatic anemia across all age groups including that in elderly patients. No specific cut-off level of hemoglobin is available to guide blood transfusions in geriatric patients. However, these patients should be transfused after due consideration to comorbidities, especially cardiovascular disease. The number and frequency of transfusions should be tailored according to clinical condition. The level of hemoglobin to be achieved in the elderly with chronic anemia following transfusion is also not well defined. Overall, liberal transfusion practices are not advocated and patient outcomes with restrictive transfusions maintaining hemoglobin levels closer to 10 g/dL were similar to those targeting higher hemoglobin levels. In general, transfusions in elderly should be slower and on a unit to unit basis after close monitoring of clinical condition.

Therapeutics on the Horizon

New drugs are currently being developed mainly for anemia in chronic kidney disease and anemia in cancer patients, but may serve as future therapeutic agents for a well-defined group of elderly patients with anemia. The major groups of these investigational drugs are:

- Hepcidin inhibitors
- Hypoxia inducible factor (HIF)—prolyl hydroxylase inhibitors
- Activin type II receptor agonists

These drugs are awaiting approval for dearth of sufficient clinical data.

Conclusion

Anemia in elderly is a significant health issue. The etiology of anemia despite extensive workup may still be elusive in a substantial number of older persons. Several pathophysiological mechanisms, which decrease erythropoiesis are under study and a better understanding of these should provide critical entry points for intervention, which can improve survival and quality of life older people. Patient-specific management strategies for anemia in elderly must be employed after thorough evaluation for the underlying cause.

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CHAPTER

221 Comprehensive Approach in Providing Geriatric Care in India

OP Sharma, AP Ambali

Abstract

The population of elderly (>60 years) is steadily rising in India, and health-care system is not yet ready to provide comprehensive geriatric health care. The more important issue is the elderly shall be living 17 added years after retirement age. The health and social issues in elderly people are challenging issues for the treating clinician. The presence of communicable disease, non-communicable diseases and their complications, degenerative diseases, and disabilities in elderly make them special group and requires multidisciplinary team to provide the comprehensive assessment and care. The role of preventive geriatrics like immunization, falls prevention should be emphasized before there is outbreak of health catastrophe in this segment of population.

The year 2021 will witness rise in number of medical colleges opting to start MD in Geriatric Medicine. As evident in any specialty, there is bound to be shortage in trained manpower. Hence, there is need to sensitize existing undergraduate and postgraduate students regarding geriatric medicine. The National Medical Council has already included geriatric medicine in undergraduate curriculum.

The majority of elderly are living in rural areas and seek health services from primary health centers. There is also need to sensitize medical officers of primary health centers regarding geriatric care. The National Program for Health Care of Elderly (NPHCE) is conducting training program for medical officers in few districts which needs to be across our country.

The clinician must restrain Ageism in all possible ways. We need to develop care system that meets the needs of elderly of India and not to copy western style. This chapter has reviewed the issues and possible solutions in providing comprehensive geriatric care.

Introduction

Ageing is progressive, generalized impairment of function resulting in loss of adaptive response to stress and in increasing risk of age-related diseases.[1]

The elderly constitutes the fastest growing age segment all over the world. Providing healthcare for the older people (>60 years) is a biggest challenge, the medical fraternity is facing today all over the world. The older people are blended with multiple diseases and are also associated with psychological, financial, and social issues. The approach toward healthcare in this set of population is holistic and multidisciplinary with a strong team coordination.

The majority of the older people reside in rural India. Hence, the healthcare services should concentrate more for older people residing in rural area. Now the scenario of family physician is slowly vanishing and there are specialist and super specialist to treat diseases of each organ in the body. This comes with riders for older people as this leads to multiple consultations and polypharmacy, which again need to be corrected by a geriatric physician or family physician.

The 542 medical colleges in India can become a role model for providing low cost, and quality healthcare for older people by initiating geriatric clinic in each college hospital.

The National Program of Health Care Elderly (NPHCE) has been launched in 100 district hospitals by Government of India from the year 2010-2011 with huge budgetary allocation.

Though the medical council of India had made it mandatory for all medical colleges to have geriatric clinic in their teaching hospital, unfortunately it has not been followed, citing shortage of doctors qualified in geriatric medicine.

The availability of palliative care, physiotherapy, and rehabilitation units should be ensured in all medical college hospitals, which will help provide comprehensive healthcare for older people of all walks of life.

Aging Situation and Projections around the World and in India

The elderly (>60 years) population in the world has been rising rapidly and the longevity is due to many factors, which include increasing health awareness and developments in medical field. In the year 1980, elderly population was 382 million, which by the year 2017 became 962 million and it is expected to be 2.1 billion by the year 2050. The 320 million people aged 60 years or over in upper-middle-income countries in 2015 represented a 64% increase over 2000 when older persons in those countries numbered 195 million. Between 2015 and 2030, upper middle-income countries are anticipated to continue to experience rapid growth in the number of older persons: the projected 545 million people aged 60 years or over in 2030 marks a 70% increase over the number in 2015[2] **(Fig. 1)**.

The age division of Indian population (0–14) is 30.8%, (15–59) is 60.3%, (60+) is 8.6%. According to Population Census 2011, there are nearly 104 million elderly persons in India. It has increased from 5.5% in 1951 to 8.6% in 2011 and projected a rise up to 19% in 2050.[3]

As regards rural and urban areas, 71% of elderly population resides in rural areas while 29% of elderly population resides in urban area. Among the challenges which India faces, UNFPA report says the feminization of ageing remained a key one.[4]

At age 60, average remaining length of life was found to be about 18 years (16.7 for males and 18.9 for females) and that at age 70 was less than 12 years (10.9 for males and 12.4 for females). About 65% of the aged had to depend on others for their day-to-day maintenance. Less than 20% of elderly women and majority of elderly men were economically independent.[4]

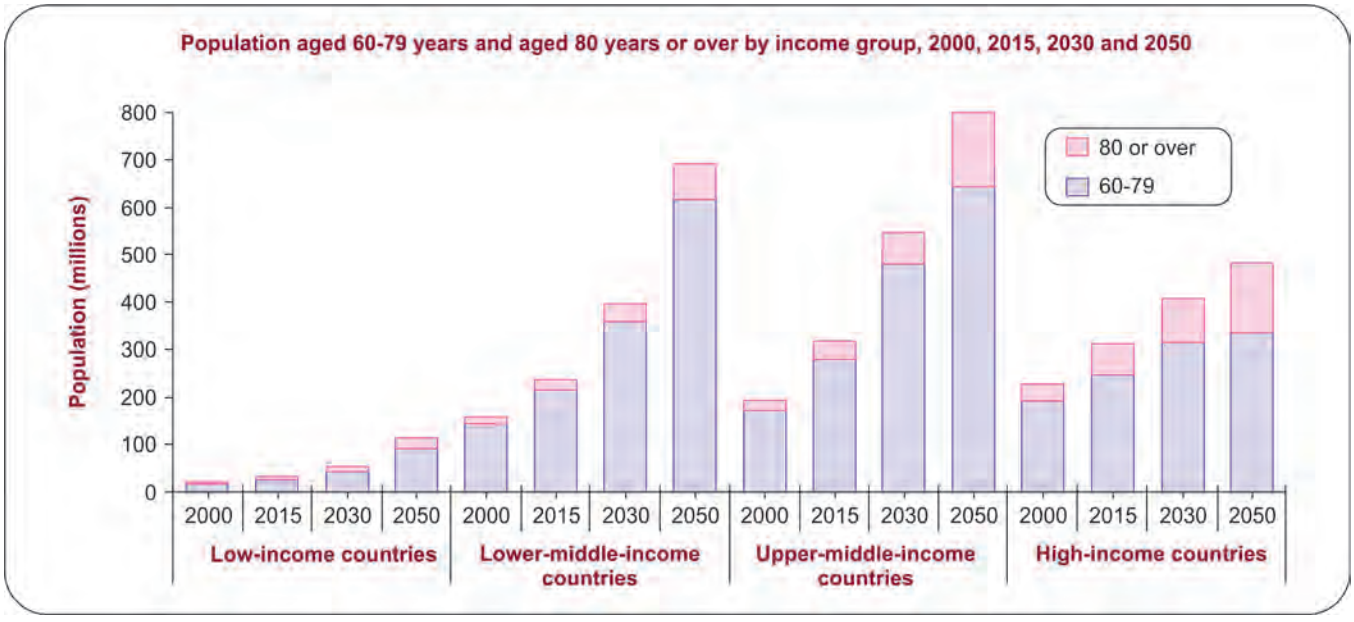

Fig. 1: United Nations (2015). World Population Prospects. The 2015 Revision

In rural areas 55% of the aged with sickness and 77% of those without sickness felt that they were in a good or fair condition of health. In urban areas the respective proportions were 63% and 78%.

The population of 80-plus people is on rise "with a predominance of widowed and highly dependent very old women" and so the special needs of such old women would need significant focus of policy and programs.[5]

Comprehensive Approach

The older people in India are diverse spread over 28 states. Their cultural background, economic status, lifestyle, behavior, nutrition, beliefs, family status, and disease pattern differ, hence 'there is no one solution to all the problems' for the older people in India.

The broad measures that can contribute toward comprehensive care to the older people are discussed here. Let us look at the health, financial, and social issues of the older people in India.

Health

The factors related to health of older people are:

- Multiple disabilities like blindness, locomotor disabilities, and deafness are most prevalent
- Multiple comorbidities, polypharmacy, and iatrogenic diseases
- Mental illness arising from senility and neurosis
- Complications of the chronic non-communicable disease
- Communicable diseases
- Absence of geriatric care facilities at hospitals in rural area.

Financial[4]

- Retirement and dependence of elderly on their children for basic necessity
- Sudden increase in out of pocket expenses on treatment.

Social[4]

The common social issues that are detrimental for the health status of the older people are:

- Elder Abuse and Neglect by the family members toward their old parents
- Disillusionment due to retirement
- Feeling of powerlessness, loneliness, uselessness and isolation, and widowhood

The geriatric care involves taking care of all the four aspects of the health, that is, physical, mental, social, and spiritual wellbeing. The challenge is during post discharge, as our social network and home services are still in nascent stage.

Apart from these four aspects, the care should continue to ensure quality of life, end of life care, and dignified death.

The most important issue in providing geriatric care is to prevent a disability. Because the older people fear disability more than death, it hampers the quality of life and makes them more dependent on family members. All these factors contribute of mental illness and social isolation. So, the main goal in providing the comprehensive care is to prevent a disability!

Services Available in Geriatric Care in India

The various medical colleges and district hospitals in India listed here are having geriatric care wards in their respective hospital. This has added special wards for senior citizens. The colleges are:

- Government Medical College, Chennai
- AIIMS, Delhi
- AIMS, Cochin
- CMC, Vellore
- St John's Health Sciences, Bengaluru
- KMC, Mangalore
- MGM, Navi Mumbai
- Yenepoya University, Mangalore
- JSS Medical College Mysuru
- Shri B M Patil Medical College Hospital, Vijayapura

Apart from inpatient services, the outpatient care for senior citizen is provided through Geriatric Clinics at:

- M S Ramaiah Medical College, Bengaluru
- Apollo Hospital, New Delhi
- Bangalore Medical College, Bengaluru
- BLDE DU, Shri B M Patil Medical College Hospital and RC, Vijayapura
- AIIMS, Bhubaneshwar
- JSS Medical College, Mysuru
- Deccan Medical College, Hyderabad
- KLEU Prabhakar Kore Hospital, Belagavi
- Bharati Vidyapeeth Medical College, Pune

- GMCH, Miraj
- BJGMC, Pune
- Osmania Medical College, Hyderabad
- SVS Medical College, Mahabubnagar, Telangana
- St John's Health Sciences, Bengaluru
- Baptist Hospital, Bengaluru
- Manipal Hospital, Bengaluru
- Yenapoya Medical College, Mangalore.
- S N Medical College, Bagalkot, Karnataka
- J J Hospital, Mumbai
- MGM, Aurangabad
- SMS Medical College, Jaipur
- AFMC, Pune
- Geriatric Psychiatry, NIMHANS, Bengaluru
- Jubilee Mission Medical College and Research Institute, Thrissur
- JLNM Hospital, Srinagar
- District Hospital, Lakhimpur Kheri, UP
- Kasturba Medical College, Mangalore

Doctors who are trained in geriatric care and are not attached to medical college are also contributing in health care for senior citizens through private clinics. The important aspect of these services is that these clinics are in rural areas. To mention a few clinics:

- Dr. P. R. Patgiri Elderly Care Clinic, Guwahati
- Dr Pathak Geriatric Clinic, Gokak, Karnataka
- Anand Hospital, Vijayapura
- Masters Medical and Geriatric Centre, Thirssur, Kerala
- Gericare, Chennai
- Neo Geriatric Care Hospital, Haridwar

The academic contribution is also picking up slowly. There is creation of consultants in geriatric medicine through Diploma/MD Geriatrics courses and DM in Geriatric Psychiatry in following colleges. A total of 45 consultants and 400 diploma degree holders pass out through these colleges or University every year and are available for geriatric care.[6]

- Madras Medical College, Chennai
- AIIMS, Delhi
- Christian Medical College, Vellore
- Mahatma Gandhi Missions Medical College, Kamothe, Navi Mumbai
- Amrita School of Medicine, Ponekkara, Kochi
- Government Medical College, Aurangabad, Maharashtra
- Netaji Subash Chandra Bose Medical College, Jabalpur
- DM - Geriatric Psychiatry – NIMHANS, Bengaluru
- Institute of Medical Sciences, BHU, Varanasi
- All India Institute of Medical Sciences, Rishikesh, Uttarakhand
- Indira Gandhi National Open University

The *Indira Gandhi National Open University (IGNOU)* is providing postgraduate diploma courses in geriatric medicine all over India for MBBS and above degree holders. The duration of the course is 1 year. The exam conducted is at par of MD degree standards. It is recognized by Government of India. The IGNOU has been creating 400 qualified geriatricians every year in India for last 15 years.[7] The need of the hour is to give due recognition for this huge cadre of geriatricians and utilize their services in primary health care centers across India with handsome salary.

Diseases Pattern among Elderly in India

The main presenting symptoms in one hundred older people presenting to geriatric clinic when analyzed by Ambali et al,[8] it was found that the 30% of elderly presented with breathlessness as the main symptom, followed by pain abdomen (17%), fever, and loose stools (10%) each, chest pain and giddiness (4%) each. The other symptoms were seizures, hemiparesis, cough, joint pain, headache, and lack of sleep.

The common comorbid conditions either in single or multiple were noted in all the patients. The commonest comorbid was hypertension in 21%, followed by chronic obstructive pulmonary disease (17%), anemia (12%), coronary artery disease (10%), diabetes mellitus (9%), epilepsy (11%), frailty (1%), obesity (1%), benign prostatic hypertrophy, fractured spine, hypothyroidism (5%), and human immunodeficiency virus infection (1%).[8]

In a study by Eram,[9] the most common complaints in elderly were generalized bodyache (53%), diminished vision due to refractive error (60%), joint pain (30%), chronic cough (25%), Asthma and impaired hearing (21%), Gastrointestinal upset symptoms (11%), and urinary symptoms (10%).

The common comorbidities were hypertension in 22%, diabetes in 8%, dental problems in 27%, and cardiac illness in 5%.[9]

The mental health issues like depression, loneliness, and attempted suicide are also on rise in Indian elderly and need to be addressed. The prevalence of depression in older people with chronic disease was highest among the

stroke patients (56.5%), coronary artery disease (47.8%), chronic obstructive airway disease (39.1%), diabetes mellitus (34.7%), and hypertension (26.1%).[10]

The older people attempting suicide too is matter of concern. In a study by Ambali et al.,[11] organophosphorus compounds were commonly used by 70% of participants to end their life and factors like depression and abuse were common precipitating factors to attempt suicide. These need to be addressed are primary care level as well as tertiary care.

The Government of India has passed stringent law to curtail elder abuse. The act "Maintenance and Welfare of Parents and Senior Citizens Act, 2007" has been passed and is been implemented in few districts of India.[12]

Approach

From healthcare point of view this group can be divided in three subgroups. Young old (60–74 years), who are independent and gainfully employed. Their Medical and Health needs are like young people and they may be looked after by physicians/geriatricians. Old old (75–84 years) need more of assistance and nursing care rather than medical help. Very old (>85 years) and above are mostly dependent requiring domiciliary Care or Hospital Care.

All the above three categories may be managed by a good general practitioner with an extra briefing on ageing, the clinical differences between adults and elderly, Geriatric syndromes, geriopharmacy and drug interaction, physiotherapy, diet, preventive aspects, and social issues like elder abuse needs to be carried out. **Figure 2** describes that the briefing can be by short courses, telemedicine, bulletins and Mass Mailing Service in regional languages. Help centers established in five areas of the country managed by Central Government/State Government/ NGOs/Pharma industry.

For the Population who is Approaching 60 Years

Regarding second category, that is, the people who are approaching old age; one can attempt to herald the process of ageing and prevent the diseases by:

- Lifestyle changes, which include a healthy lifestyle comprising of nutritious food, restrictions of calories to maintain proper body weight, regular exercises, adequate sleep, avoidance of alcohol, tobacco and other narcotics, and positive thinking.

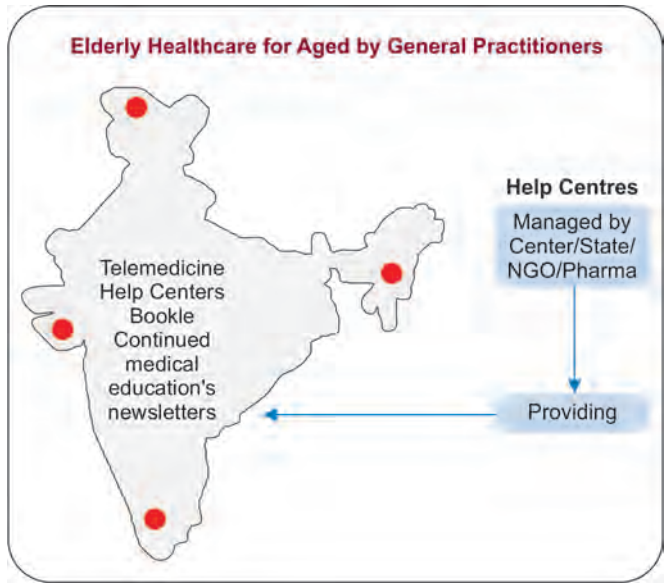

Fig. 2: Planning for the aged

- Appropriate management of comorbidities like diabetes, hypertension, etc.
- Prevention of diseases and risk factors by medicines (lipid lowering, antiplatelet drugs, etc.) and vaccinations.

For those who are getting aged, the planning may be done by adding geriatrics in the medical curriculum as shown in **Figure 3**. We may sensitize budding doctors about special aspects of geriatrics in their teaching and training.

General Measures

- Ageing will continue and number of elderly populations will rise. Number of comorbidities will also rise, due to changes in lifestyle. Accidents and falls will also increase. Due to change in social setups and migrations, the family support will dip and the cost of living as well as treatment will continue to rise.
- We have to have improvements in nutrition by making diet a balanced one, improving cooking, minimizing the effects of insecticides and pesticides, check the adulteration and improve the process of storage. Use of local foods should be encouraged.
- Housing for elderly need provisions for sunlight, adequate ventilation, water, sewage, and non-skid flooring.
- The transport system should be elderly friendly.

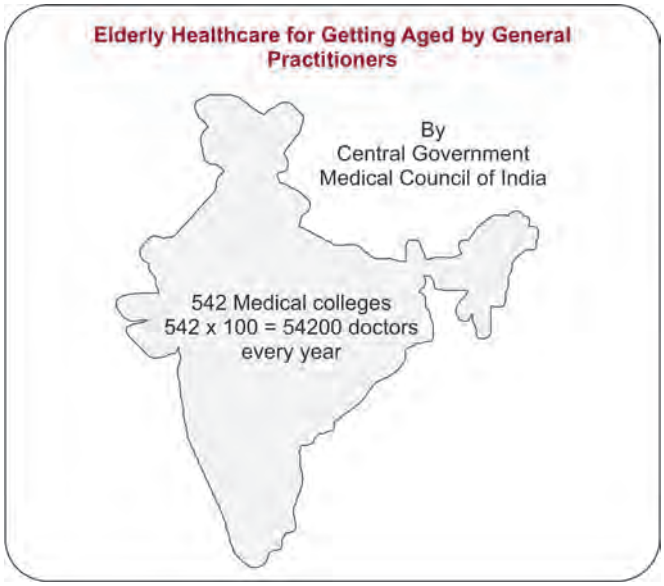

Fig. 3: Planning for the health care of getting aged

- People should be educated about the Misuse of over the counter drugs like analgesics, painkillers, and antibiotics. The polypharmacy should be minimized/avoided in elderly as it causes increased incidents of drug interactions.
- The use of vaccines like Hepatitis B, Influenza, Pneumococcal, T-dap, and Zoster, which are advised in elderly, should be encouraged.[13]
- Reach the unreached—healthcare services should reach the older people in villages with special attention to those who are bed-ridden, and differently abled.
- Yearly they should undergo consultation with ENT, ophthalmology, and dental surgeon.

National Program for Healthcare of Elderly

The NPHCE provides free, specialized healthcare facilities exclusively for the elderly people through the state health delivery system. It also provides training services in geriatric care to the medical officer of primary health centers.

The main objectives of NPHCE[14] are to provide comprehensive healthcare to the elderly by preventive, curative, and rehabilitative services and build capacity of the medical and paramedical professionals as well as the care-takers within the family for providing healthcare to the elderly.

Role of Caregiver and Training

The caregivers in our country are either a family member or relative or member of society without formal training. It is now recognized as very important service.

There is need to train the nurses in geriatric care. In fact, the trained nurses in geriatric care are in huge demand in urban areas.

The family members can be trained to a specific disease pattern like care of person with dementia, stroke, or person who is bed ridden. The larger aspects are rendered by nurse. The main goal is to assist in activities of daily living.

The caregiver should uphold the dignity of the elderly receiving the care.

Conclusion

The western countries became rich first and then their population grayed, while in India, its population is graying fast while we are yet to be a rich country.

We are still not prepared to face the so-called tsunami of older population and related problems. We need to provide services to the elderly who are above 80 years, bed ridden, and living with disabilities, dementia, and Parkinson's disease.

The Government of India has priority for health issues related to infants, pregnant mothers, immunization in children, communicable diseases like tuberculosis to mention a few. The projects for older people are in process of implementation through regional research center across India.

The various programs for the benefit of older people have been launched a decade ago, but yet to reach the rural elderly population.

The new curriculum has included geriatric medicine in MBBS course. The postgraduate students in clinical subjects must undergo short course training in geriatric care.

The overall care should be promotive, protective, and preventive so that, active ageing is achieved.

The caregiver plays a vital role in providing care.

A holistic approach is need of the hour in providing comprehensive care for the elderly in India.

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CHAPTER

222 Severe Acute Respiratory Infections in Elderly

YS Raju, Y Rahul, Y Sairam

Abstract

Estimates suggest that elderly (above 60 years of age) globally will increase from 12.5% in 2015 to 16.5% in 2030, suggesting need for greater emphasis on health care for elderly population globally. Lower respiratory tract infections (LRTIs) are the most common causes of death among infectious diseases in adults and are among the top ten causes of death in the elderly (aged more than 60 years). Severe acute respiratory infections (SARIs) by definition include a respiratory tract infection with history of fever more than or equal to 38°C and cough; with its onset within 10 days and requiring hospitalization. As the global burden of elderly population is estimated to increase, and older age is an important risk factor associated with increased mortality, there is a need for greater emphasis on health care for elderly population globally. In patients with influenza associated SARI, cough was the most common symptom and the low pulse oximetry (less than 90% on room air) was the most common sign. In elderly, getting admitted with COVID-19 most common symptom was fever followed by cough, fatigue, shortness of breath, and headache. In elderly patients presenting with SARI, empirical antimicrobial treatment should initiated awaiting culture and sensitivity reports; if there is respiratory distress, supplemental oxygen therapy should be initiated immediately. Recognition of severe hypoxemic respiratory failure even with supplementary oxygen mandates institution of ventilatory support. In case of non-invasive ventilation (NIV) failure or in patients with contraindications for NIV, endotracheal intubation and mechanical ventilation should be initiated. In the current situation of COVID-19 pandemic, with no available specific antimicrobial drugs for the treatment, universal hand hygiene precautions, avoiding touching mouth, eyes, and nose, maintaining social distancing likewise preventive measures are the need of the hour.

Introduction

Even after a century following Spanish flu pandemic, with the recent pandemic of coronavirus disease (COVID-19), respiratory tract infections continued to be one of the leading causes of morbidity and mortality among all diseases globally. Lower respiratory tract infections are the most common causes of death among infectious diseases accounting for 3 million deaths in 2016.[1] Severe acute respiratory infections (SARIs) by definition include a respiratory tract infection with history of fever more than or equal to 38°C and cough; with its onset within 10 days and requiring hospitalization.[2] Despite recent advances in the development of antiviral drugs and vaccines, seasonal epidemics of influenza contribute to significantly to workload for practioners, emergency hospital admissions, and deaths as with the case of recent COVID-19 pandemic. Elderly (age ≥60 years)[3] population compared to the young, suffer with several chronic illnesses, and comorbid conditions. In addition to that immune decline with aging makes them more vulnerable to infectious diseases.

Epidemiology

The pace of global population is accelerating and projections indicate that people above 60 years globally will increase from 12.5% in 2015 to 16.5% in 2030 compared to 2.3% increase from 2000 to 2015. By 2030, people above

60 years are expected to account for 25% in Europe and North America, 20% in Oceanica, 17% in Asia, Latin America, and the Caribbean, and 6% in Africa.[4] These projections indicate need for greater emphasis on health care for elderly population globally. Lower respiratory tract infections are among the top ten causes of death in both men and women aged more than 60 years.[4] In a study conducted in United States over 12 years from 1997 to 2009, an annual average of 19,100 deaths were attributed to influenza and 11,300 deaths to respiratory syncytial virus (RSV) taking in to consideration of respiratory broad definition of any respiratory illness with symptoms of cough, breathlessness, and fever, with mortality rates of 6.61 (standard deviation: 2.66) and 3.91 (standard deviation: 0.65) per 1,00,000 population annually for influenza and RSV, respectively. When cardiorespiratory outcome for influenza death was considered, 9%, 14%, and 73% were found in the age groups of 50–64, 65–74, and 75 or more, respectively, indicating increased percentage of deaths associated with respiratory illness as the age advances.[5] India, having the history of highest mortality with nearly 18 million deaths during the second wave of Spanish flu pandemic in 1918, has higher incidence of under five mortality compared to elderly being affected as in high-income countries.[6,7] In the 2009 H_1N_1 pandemic, in a study from 2009 to 2017, revealed most commonly affected age group was 46–60 years accounting for 29.7% of total cases.[8] With the recent COVID-19 pandemic, its strain variability, mutation rate, genetic selection during its interaction with the host population, and transmission across the nations creates a challenging scenario in both diagnosis and management.[9]

Etiology

Etiology of SARI varies with seasonality, region being affected and active infection with virulent organism associated. In a study conducted in Georgia from 2015 to 2017, Influenza was the most common etiology followed by RSV, Coronavirus, and Rhinovirus for SARI in people more than or equal to 65 years.[10] In a study from Lisbon which was conducted on respiratory infections in elderly in 2013–2014, Rhinovirus was the most common etiology followed by influenza and human bocavirus.[11] Viral and bacterial agents can occur as concurrent etiology with viral infections such as RSV, influenza, and rhinovirus along with bacterial causes like *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Klebsiella* species. RSV was the most common viral etiology and *S. pneumoniae* was the common bacterial etiology in those with concurrent etiology **(Table 1)**.[12] In India apart from influenza virus and RSV, human coronavirus was found to be an important cause of SARI in southwestern part, in a study conducted in 2011–2012.[13]

TABLE 1 Etiology of SARI in elderly

Viral etiology
Influenza virus
Respiratory syncytial virus
Rhinovirus
Bocavirus
Human metapneumovirus
Coronavirus
Parainfluenza virus
Bacterial etiology
Streptococcus pneumoniae
Haemophilus influenzae type b
Klebsiella species
Staphylococcus aureus
Escherichia coli

Risk Factors

Risk factors associated with increased mortality were age more than or equal to 65 years, comorbid conditions, virulence of etiological agent, being bedridden, admission to critical care unit, low PaO_2/FiO_2 ratio (<250), low platelet count (<1,50,000/μL), and increased creatinine concentration (>1 mg/dL). Seasonal vaccination has been observed to significantly reduce need for hospitalization in vulnerable population; and lack of seasonal vaccination appear to be one of the important factors in increased morbidity and mortality patients with SARI.[14] In elderly affected with COVID-19, older age and decreased lymphocyte count at admission were found to be the most important factors associated with mortality along with others like presence of hypertension and previous respiratory problems.[15]

Clinical Features

In patients with influenza associated SARI, cough was the most common symptom and the low pulse oximetry (<90% on room air) was the most common sign.[14] In elderly, getting admitted with COVID-19 most common symptom was fever followed by cough, fatigue, shortness of breath, and headache.[16] Anorexia, weight loss, asthenia, and headache were observed in older age group. Running nose and intercostals recession were less common in elderly population.[12] Along with low pulse oximetry, other signs include tachypnea, tachycardia, and those of lobar and bronchopneumonia. Median incubation period was 6.7 days.[16]

Management

Laboratory Investigations

In adults with SARI, laboratory investigations revealed lymphopenia (<1000/μL), low platelet count (<1,50,000), hypoalbuminemia (<3.5 g/L), hyponatremaia (<135 mEq/L), increased plasma lactate dehydrogenase (>250 UI/L), increased blood urea nitrogen concentration (>20 mg/L), increased serum creatinine concentration (>1 mg/dL), and increased serum C-reactive protein (>100 mg/L, 10 times the upper normal value) were evident.[14]

In elderly with COVID-19, lymphocyte count, amino-terminal pro-brain natriuretic peptide, aspartate transaminase, alanine transaminase, cardiac troponin-I, C-reactive protein, D-dimer, and serum creatinine levels were significantly different in survivors compared to non-survivors.[15]

Treatment

Early Supportive Therapy and Monitoring

For the patients presenting with SARI and respiratory distress, supplemental oxygen therapy should be initiated immediately at 5 L/min to maintain percentage saturation of oxygen (SpO_2) ≥ 90%.[17] Conservative fluid management is indicated when there is no evidence of shock with caution to avoid fluid overload as aggressive fluid management may worsen oxygenation. Empirical antimicrobial treatment should be initiated for SARI patients with shock within 1 hour of presentation. Likely choice of empiric antimicrobial treatment is based on the clinical diagnosis, local epidemiology, and susceptibility data. In case of suspected influenza infection neuraminidase inhibitors are to be given based on the travel history or exposure to persons with active infection. Invasive pneumococcal disease following influenza infection is much more common in elderly.[18] Prophylactic broad spectrum antibacterial agents like third generation cephalosporins are considered in suspected cases of influenza to treat secondary bacterial infections, later can be changed according to culture and sensitivity reports.

Comorbid conditions must be appropriately managed along with tailoring the management plan of critical illness for better care of the patient. Signs of clinical deterioration such as rapidly progressive respiratory failure and sepsis must be carefully monitored and timely active interventional supportive therapies are to be considered, which forms the cornerstone of management.

Management of Hypoxemic Respiratory Failure and ARDS

Recognition of severe hypoxemic respiratory failure even with supplementary oxygen is essential in patients with SARI. Hypoxemic respiratory failure may lead to acute respiratory distress syndrome (ARDS) either from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation.

Patients receiving a trial of noninvasive ventilation (NIV) should be carefully monitored and tracheal intubation is indicated in case the patient does not improve after a short trial or acutely deteriorates. Patients with altered mental status, hemodynamic instability, and multi-organ failure should not receive NIV.

In case of NIV failure or in patients with contra-indications for NIV, endotracheal intubation and mechanical ventilation should be initiated with airborne precautions. In patients with sepsis induced respiratory failure who do not meet ARDS criteria, implementation of mechanical ventilation with lower tidal volumes (4–8 mL/kg predicted body weight) and lower inspiratory pressures (plateau pressure <30 cm H_2O) was recommended.[17] In patients with moderate or severe ARDS, higher positive end expiratory pressure (PEEP) is suggested. PEEP has to be titrated considering the benefits like reducing atelectrauma and improving alveolar recruitment and the associated risks, such a, end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance. Ventilation in prone position for a period of

more than 12 hours/day is recommended for patients in severe ARDS. Use of conservative fluid management strategy for patients with ARDS is to be considered without tissue hypoperfusion.[17]

Prevention of Complications

As the patients with SARI are getting treated in intensive care units (ICUs), with requirement of mechanical ventilation in some of them, it is of paramount important to prevent the predictable complications of prolonged ICU care.

Reduction of days of Mechanical Ventilator Support

Use of weaning protocols for readiness of spontaneous breathing trials daily have overall favorable outcome in patients on mechanical ventilator support. Weaning off from continuous to intermittent sedation and minimize the dose of sedation gradually till the point when sedation no longer required is mandatory for early weaning off from ventilator support in patients who have recovery from primary illness.

Reduction of Incidence of Ventilator-associated Pneumonia

Maintaining semi-recumbent position (head of bed elevation 30–45°), using closed suctioning system, periodically draining the condensate in tubing, changing ventilator circuit if it is soiled and changing heat moisture exchanger if it is soiled or once in 5–7 days aids in reducing the incidence of ventilator associated pneumonia.

Reduction of Incidence of Venous Thromboembolism

Pharmacological prophylaxis with low molecular weight heparin in patients without contraindications prevents deep venous thrombosis. Additional factors like intermittent pneumatic compression devices, compressive stockings, and early mobilization of patients prevent deep venous thrombosis.

Reduction of Incidence of Catheter-associated Blood Stream Infections

Using a checklist while inserting a catheter with sterile precautions, regular care of the catheter and daily assessing for the removal of the catheter if no longer needed helps in preventing catheter associated blood stream infections. Following a bundle care serves as a daily reminder for the care of the patients with central venous catheters.

Reduction of Incidence of Stress Ulcers, Gastrointestinal Bleeding, and Pressure Ulcers

Administering proton pump inhibitors or histamine-2 receptor blockers for patients at risk of gastrointestinal bleeding like mechanical ventilation, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities prevents stress ulcers and gastrointestinal bleeding. In addition early initiation of enteral feeding avoids stress ulcers. Frequent change of position of the patient prevents pressure ulcers and their related complications.

Reduction of Incidence of ICU-related Weakness and Psychosis

Active limb physiotherapy and early mobilization of the patient prevent muscle weakness and atrophy in elderly patients. Allowing patients to interact with the family members while following sterile precautions helps in mood elevation and avoids ICU-related psychological problems.[17]

Prophylaxis

In the current situation of COVID-19 pandemic, with no available specific antimicrobial drugs for the treatment, universal hand hygiene precautions, avoiding touching mouth, eyes, and nose, maintaining safe distancing likewise preventive measures are the need of the hour.

In a study from United States over a period of six influenza seasons from 2010 to 2016, vaccination has prevented between 1.6 and 6.7 million illnesses, 39,000–87,000 hospitalizations and 3,000–10,000 deaths related to influenza each season, emphasizing the role of vaccination in influenza related illnesses.[19]

Concept of a universal influenza vaccine with features of being effective against symptomatic influenza virus infection, protective against group I and II influenza A viruses, having durable protection that lasts at least 1 year and through multiple seasons and being suitable for all age groups is yet a farfetched reality.[20]

Conclusion

A century later following Spanish flu, yet with another pandemic of respiratory illness in the form of COVID-19 still poses a greater challenge to humanity affecting both developed and underdeveloped nations alike. With expected increase in elderly population, in developing countries like India where tertiary health care and ICU care facilities are not widely available, preventive measures play a major role in the management of such pandemics. Even with effective preventive measures, the challenge to face such pandemics likely poses the question "Are we yet ready?"

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Section 18

Section Editor: **Shibendu Ghosh**

Poisoning and Toxicology

CHAPTER

223 Management of Organophosphorus Poisoning

Bhupen Barman

Abstract

Poisoning both accidental and intentional is a single contributor to mortality and morbidity throughout the world. The commonest cause of poisoning in developing countries including India is pesticide, the reason being agriculture based economics and organophosphorus (OP) constitute the largest bulk of pesticides. Clinical manifestations result from inhibition of acetylcholinesterase and stimulation of muscarinic and nicotinic receptors and characterized by pinpoint pupil, excessive salivation and sweating, bronchospasm leading to respiratory distress, CNS, and neuromuscular dysfunction. After initial stabilization, atropine should be used in appropriate doses and ventilator support may be required for those who developed respiratory failure due to neuromuscular dysfunction.

Introduction

Poisoning both accidental and intentional is a single contributor to mortality and morbidity throughout the world. The most common cause of poisoning in developing countries including India is pesticide; the reason being agriculture based economics and organophosphorus (OP) constitute the largest bulk of pesticides. According to recent WHO data, it is estimated that deliberate ingestion of pesticides causes 370,000 deaths every year (https://www.who.int/ipcs/poisons/en/). However, these figures are probably an underestimate, especially in developing countries because of insufficient regulatory and surveillance systems, shortage of trained medical manpower, and ineffective utilization of existing facilities. India is a country with about 60–70% rural population, and agriculture is a major component of the economy. Every year, there are about 10,000 reported cases of pesticide poisoning in India with a mortality rate varies between 15% and 30% and is the fourth most common cause of mortality, especially in rural areas.[1] The National Poisons Information Center (NPIC) was established at All India Institute of Medical Sciences, New Delhi, in 1995 to provide toxicological information and advice on the management of poisoned patients across the country. A survey done by NPIC from 1999 to 2002 reported a total of 2,719 poisoning, of which agricultural pesticides represent 12.8% of total cases. On further analysis of the main data, it was found that OP poisoning represents 18.75% cases of all agricultural products.[2]

Pathophysiology

Organophosphorus compounds (OPCs) inhibit the function of acetylcholinesterase (AChE) by binding into the acyl pocket at the active site of AChE. The binding of a phosphate group to the serine amino acid at the active site of AChE changes the configuration of the enzyme molecule and make it dysfunctional. Normally the cholinesterase rapidly hydrolyzes the neurotransmitter acetylcholine into inactive fragments of choline and acetic acid. The neurotransmitter acetylcholine is present in the terminal endings of all postganglionic parasympathetic nerves, at myoneural junction, and at both parasympathetic and

TABLE 1 Clinical manifestations of organophosphorus (OP) poisoning

Muscarinic effects	*Nicotinic effects*	*CNS effects*
• Miosis • Blurred vision • Nausea • Vomiting • Diarrhea • Salivation • Lacrimation • Bradycardia • Abdominal pain • Diaphoresis • Wheezing • Urinary incontinence • Fecal incontinence	• Muscle fasciculations • Paralysis • Pallor • Muscle weakness • Hypertension • Tachycardia • Mydriasis (rare)	• Unconsciousness • Confusion • Toxic psychosis • Seizures • Fatigue • Respiratory depression • Dysarthria • Ataxia • Anxiety

sympathetic ganglia. The inhibition of cholinesterase leads to accumulation of acetylcholine at synapses, causing overstimulation and subsequent disruption of transmission in both central and peripheral nervous system.

Clinical Features

Patients with OP poisoning can become symptomatic within minutes depending on the route and degree of exposure. Most victims become symptomatic within 8 hours of exposure and virtually all within 24 hours. The clinical manifestations can be classified into: cholinergic crisis (muscarinic or nicotinic receptors) **(Table 1)**, CNS effects, and sequelae (Intermediate syndrome).

Intermediate Syndrome

Approximately 10–40% of OP poisoning develop intermediate syndrome which typically manifests after 24–96 hours of exposure. It was first described as type II paralysis. It reflects excessive cholinergic stimulation of nicotinic receptors and is characterized by respiratory and bulbar symptoms as well as proximal muscle weakness, diminished deep tendon reflexes, and respiratory failure. The sensory system remains intake and full recovery is evident in 4–18 days. This syndrome almost never found with carbamate poisoning.

Diagnosis

Diagnosis of OP poisoning is based on the history of exposure to a known OP compound and classic clinical feature like miosis. Two mnemonics which help to remember the clinical manifestations are: **DUMBELS:** *D*iarrhea, *U*rinary frequency, *M*iosis, *B*ronchospasm, *E*mesis, *L*acrimation, *S*alivation; **SLUDGE** and the Killer *B*ees: *S*alivation, *L*acrimation, *U*rinary frequency, *D*iarrhea, *G*astric distress, *E*mesis and *B*ronchospasm, *B*ronchorrhea, and *B*radycardia. For nicotinic effects, think of the days of the week: *M*onday = *M*ydriasis, *T*uesday = *T*achycardia, *W*ednesday = *W*eakness, T*h*ursday = *H*ypertension, *F*riday = *F*asciculation.

Estimation of butyrylcholinesterase activity in plasma (or AChE in whole blood) helps in confirming the diagnosis. However, their importance is limited only for clinical research due to unavailability issues and drawback (use and interpretation). Studies showed that RBC-AChE is a good marker of neuronal function, severity of poisoning, and the need for atropine in patients with OP poisoning, especially initial low plasma/RBC-AChE and high glucose level are good marker for predicting OP induced intermediate syndrome.[3] However, one should not wait for the report to come before starting treatment as normal value of the enzyme does not exclude the diagnosis of OP poisoning.

An atropine challenge test may sometime help in diagnosing OP or carbamate poisoning where history is insufficient to suggest exposure but patients present with findings suggestive of cholinergic poisoning. A test dose of 1–5 mg of atropine (0.05 mg/kg in children) should produce classic antimuscarinic effects like mydriasis, tachycardia, and dry mucus membrane. In contrast, the persistence of cholinergic findings after an atropine challenge strongly suggests OP or carbamate poisoning.

Other ancillary investigations that may help in diagnosis are: leukocytosis, high hematocrit, hyper- or hypoglycemia, anion gap acidosis, and increased serum creatine kinase.

Management

Treatment goals include support of vital signs, preventing the further absorption of the poison (decontamination), administration of specific antidotes, and prevention of re-exposure.

Supportive Measures

- *Check ABC:* Make sure that patient has a patent airway and adequate breathing and circulation. Provide high-flow oxygen with mask. Intubate the patient in compromised airway or breathing.
- *Position of the patient:* Patient should be kept in the left lateral position, preferably with head down position, to reduce risk of aspiration of stomach contents.
- Frequent suctioning is essential as excessive oropharyngeal and respiratory secretion may occlude the airways.
- Obtain intravenous (IV) access and give IV fluid (0.9% NS) to replace loss. Aim is to keep the systolic blood pressure above 80 mm Hg and urine output above 0.5 mL/kg/hr.
- Record pulse rate, blood pressure, size of pupil, presence of sweat, and findings of chest on auscultation at the time of first atropine dose. Prepare atropine chart.
- Continuous monitoring of respiratory function. If tidal volume is less than 5 mL/kg or vital capacity is less than 15 mL/kg, or if they have apneic spells, or PaO_2 < 60 mm Hg on FiO_2 > 60% immediately intubate and ventilate the patient.
- It is important to assess flexor neck strength regularly in conscious patients by asking them to lift their head off the bed and hold it in that position while pressure is applied to their forehead. Any sign of weakness is a sign that the patient is at risk of developing intermediate syndrome.
- The following drugs are contraindicated: Parasympethomimetic, phenothiazine, antihistamine, and opiates. One should not administer Succinylcholine to ventilated patient.
- Treat agitation by reviewing the dose of atropine being given and provide adequate sedation with diazepam. Physical restraint of agitated patients in warm conditions risks severe hyperthermia, which is exacerbated by atropine because it inhibits normal thermoregulatory responses, including sweating. Adequate sedation is therefore important.
- If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with IV bicarbonate guided with arterial blood gas analysis.
- Broad spectrum antibiotics may be required to prevent secondary infection.

External and Gastric Decontamination

Decontamination may be done by removing the contaminated clothes and washing with soap and water. Although there are no evidence based studies; however, this seems to be cost effective and an easy to perform practice by which we can reduce further absorption of the poison into the system. Gastric lavage is a widely used decontamination procedure globally despite the absence of confirmed benefit by randomized controlled trials (RCTs).[4] OP compounds are easily absorbed through mucus membrane and gastric lavage may play a role in the first hour of poisoning. It may be performed, in a patient who is awake, preferably in the left lateral position with tap water (5–10 mL/kg). However, the duration for which the OP compounds remain in the stomach is still unknown and there are concerns for increased risk for aspiration pneumonia and respiratory distress. Activated charcoal has been widely used for absorbing pesticide poisons. The two commonly used regimens of activated charcoal are:

- Single dose of 50 mg
- Multiple doses of 25 mg.

However, no RCT has addressed this issue, especially in OP poisoning.[5]

Antidotes

The three most commonly used classes of antidotes are: Atropine, Oxime (Pralidoxime), and Benzodiazepine.

Atropine: Atropine is an antagonist to muscarinic receptors of Acetylcholine and is the mainstay of treatment of acute OP poisoning. It is used to reverse the cholinergic effect and has no role in neuromuscular junction and

muscular weakness. The five markers indicating atropine requirements are:

- Miosis
- Excessive sweating
- Bronchorrhea and bronchospasm causing difficulty in air entry
- Bradycardia
- Hypotension.

The two commonly used regimens are:

- Bolus dose administration
- Incremental dose administration with rapid escalation.

The aim of therapy is to prevent bradycardia, maintain blood pressure, clear lungs, and dry skin. Bolus dose is defined as 2–5 mg of atropine every 10–15 minutes followed by maintenance using reduced dose or increasing the time interval between the doses. Incremental dose is defined as 1.8–3 mg of atropine by intravenous infusion, repeating the doses every 5 minutes interval, then doubling the doses each time until atropinization occurs, followed by 10–20% of atropine required for atropinization to be given every hour by intravenous infusion. The end points of atropinization are:

- Clear chest on auscultation with resolution of bronchorrhea
- Heart rate of more than 80/minute
- Systolic blood pressure of more than 80 mm Hg
- Dry axillae
- Pupils of more than 2 mm.

Once atroponized, these five parameters should be monitored every 15 minutes initially which can be gradually increased to 1-2-3 hours depending on the state of atropinization **(Table 2)**. Atropine is associated with toxic effects like confusion, agitation, various arrhythmias like multiple ventricular ectopics, atrial arrhythmia, A-V dissociation, raised intraocular pressure, hyperthermia, hallucination, and delirium and ileus. Once atropine toxicity starts, it should be immediately stopped. It may be restarted at 70–80% of the previous rate once the patient settles down. Duration of atropine therapy depends on the severity and response to therapy; usually it is maintained for 24–48 hours and gradually withdrawn over 3–5 days.

Oximes: Oximes reactivate acetylcholinesterase by removing the phosphate moiety from the acetyl pocket. In addition, they also slow the ageing of the phosphorylated enzyme complex and have a direct action in converting OP to a harmless compound. They are effective in counteracting both the muscarinic and nicotinic effects. Pralidoxime (2-PAM) is the only oxime available in India. Despite clear reactivation of red cell AChE, current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute OP poisoning. The WHO recommends a regimen of 30 mg/kg body weight bolus infusion followed by 8 mg/kg body weight/hour intravenous infusion of PAM to all symptomatic patients who need atropine.[6] Pralidoxime is expensive and not free from toxicities. In a recent RCT from India which included 200 patients with moderate OP poisoning stated that high-dose pralidoxime iodide (2 g loading dose, followed by 1 g either every hour or every 4 hours for 48 hours, then 1 g every 4 hours until recovery) associated with reduced case fatality, fewer cases of pneumonia, and reduced time on mechanical ventilation.[7] A Cochrane review including two RCTs reported no clear evidence of benefit or harm from pralidoxime in

TABLE 2 Organophosphorus (OP) observation sheet

Time	*Heart rate*	*Clear lung*	*Pupil*	*Dry axilla*	*BP*	*Bowel sounds*	*Mental state*	*Fever >37.5°C*	*SpO_2*	*Remarks atropine dose*

OP poisoning.[8] Few other meta-analyses combined non-randomized or historically controlled observational studies with RCTs concluded that oximes are harmful.[9,10]

Benzodiazepine: Patients with OP poisoning are often developed agitated delirium due to multiple reasons, viz. atropine toxicity, pesticide itself, brain hypoxia, alcohol ingested along with the poison, and medical complications. Diazepam (5–10 mg IV slowly, every 15 minutes, up to a maximum of 30 mg and for children 0.25 mg/kg IV slowly, every 5–10 minutes, up to a maximum 10 mg) is easily available and best drug to control agitation.[11] It also helps in sedation in ventilated patient and used as first-line drug for convulsion which although rare but may occur especially with organophosphorus nerve agents (such as sarin, soman, and tabun). However, there are no trials evaluating the efficacy of benzodiazepine as a primary treatment for OP poisoning.

Newer Therapies

Magnesium sulfate: Intravenous magnesium sulfate ($MgSO_4$) has a role in the management of acute OP poisoning as it blocks the voltage gated calcium channel, thereby reducing the release of acetylcholine from synapses.[12] It also reduces the NMDA receptors mediated CNS activation. Intravenous $MgSO_4$ (4 g) on first day has shown to decrease hospitalization period and improve outcome.

Clonidine: Clonidine, an alpha-2 receptor agonist, inhibits the release of presynaptic acetylcholine and thereby decreases the cholinergic symptoms.[13] Optimum dose of clonidine regimen is bolus injection of 0.15–0.30 mg followed by infusion rates of 0.5 mg/24 hours.

Alkalization: Alkalization by sodium bicarbonate (blood pH between 7.45 and 7.55) may help in OP poisoning as shown by some studies.[13]

Fresh frozen plasma (FFP): FFP is a cellular component of blood containing clotting factors, proteins, and many enzymes. It is hypothesized that the enzyme butyrylcholinesterase presents in FFP will sequester the free poison present in blood and remove them from circulation.[14]

Removal of OP from blood by using hemodialysis, hemofiltration, or hemoperfusion is not yet clear. However, in a recent report, it was claimed that hemofiltration after dichlorvos poisoning had revealed beneficial therapeutic effect.[15]

Prevention of Re-exposure

Once the patient is fully recovered, he should not be re-exposed again to OPCs for at least few weeks. It has been said that risk for serious harm can happened on re-exposure to a previously harmless product because of alteration in body chemistry of the host due to previous poisoning. In ideal condition and if facility available, following acute poisoning patient should be precluded from further exposure to OPCs until sequential cholinesterase level is available and confirm that cholinesterase level reached a plateau phase. Plateau phase is defined when sequential determination does not differ by more than 10% and it normally takes 3–4 months following acute poisoning. It is important to note that optimization of health education system amongst the agricultural workers regarding procedure of pesticide handling, strictly following the operative and well-maintained spraying equipment and using necessary precautions at all stages of pesticide handling are essential for reducing their exposure to pesticides.

Conclusion

Being cheap and easily available over the counter, OP poisoning is becoming a major health problem, especially in a developing country like India. Acute OP poisoning is a medical emergency leading to severe toxicity and death. It can be diagnosed on the basis of history of exposure to OP compounds and clinical examination. The estimation of RBC AChE can have a role for confirmation of diagnosis. Early initiation of selective decontamination and antidote therapy (particularly atropine) with close monitoring for complications are important in preventing death due to OP poisoning.

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CHAPTER

224 Snakebite

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Abstract

Snakebite is the second deadliest neglected tropical disease. Southeast Asia is the most affected region in the world. Manifestation of envenomation can be either neurotoxic and/or hematotoxic depending upon biting species. Local manifestation can be severe depending upon the species involved in envenomation. In absence of specific definitive diagnostic test, clinical features along with circumstance of bite may help identifying biting species of snake. Snakebite with systemic envenomation is life threatening medical condition and timely administration of antivenom along with supportive therapy can save life. Administration of antivenom can be associated with antivenom reactions including life threatening anaphylaxis. Prophylaxis administration of subcutaneous adrenalin can reduce the incidence of severe adverse reaction related to antivenom.

Introduction

Snake bite is a public health issue with acute and chronic consequences. It mostly affects economically disadvantage population of rural communities in the tropics. South Asia, due to its high human and snake population and agricultural activities, is the world's most affected region. Most of the victims of snakebite die (97% in India and 80% in Nepal) before reaching treatment centers leading to serious misreporting. Community based study has shown that the snakebite figures are alarming.

Snakebite is a life threatening medical emergency. Survival of the victims depends much on immediate transportation of the victim to the nearest health-care center where antivenom can be administered and supportive therapy is available.

Burden and Characteristics of Snakebite

Around the globe snakebite occurs in approximately 5 million people. It is estimated that snakebite causes up to 138,000 deaths and 400,000 disabilities. The Southeast Asia Region has one of the highest snakebite burdens in the world and 70% of all global snakebite deaths occur in South Asia. In India, the direct estimate of deaths attributable to snakebite in 2005 was 46,000 (99% CI 41,000–51,000), or 1 snakebite death for every 2 HIV/AIDS deaths.

The characteristics of snakebite in South Asia are shown in **Table 1**.

Medically Important Venomous Snake of India and Nepal

There are around 300 species of snake found south of the Himalayas. Among them approximately 67 are front fanged venomous species. Medically the most important venomous snakes, also known as "BIG FOUR" are Russell's viper (*Daboia russelii*), Common cobra (*Naja naja*), Common krait (*Bungarus caeruleus*), and Saw scaled viper (*Echis carinatus*). The pit viper species; Malabar (*Trimeresurus malabaricus*), Green pit viper (*Trimeresurus albolabris*), Hump-nosed viper (*Hypnale*

TABLE 1 Characteristics of snakebite in South Asia

Characteristic	*Details*
Age	About three-quarters of the victims belong to 10–40 year age group, with mean age of 30 years.
Gender	Male predominates with 2:1 male female ratio.
Occupation	Farmers account for more than 50%. Students and housewives are also commonly affected.
Time of bite	Krait bites are generally nocturnal. Viper and cobra mostly strike during the daytime.
Bite to treatment delay	Time between bite and treatment delay varies greatly. Very few victims reaches hospital in less than an hour.
First aid methods	Mostly harmful and inappropriate methods are used. Tourniquets use is ubiquities and it is applied by up to 98% of patients.
Mortality	Highly variable (0.5–58%) they are. Most deaths occur before reaching hospital.

hypnale), Bamboo pit viper (Trimeresurus stejnegeri); Sea snakes (*Hydrophiinae*) and others like the King cobra (*Ophiophagus hannah*), Monocle cobra (*Naja kaouthia*), Banded krait (*Bungarus fasciatus*), Sind krait (*Bungarus sindanus*), and *Echis sochureki* are important causes in certain geographical areas.

Clinical Manifestation

Snakebite is a life-threatening medical emergency. Prompt identification of early signs of systemic envenoming is crucial for the optimal management of the victims. Snakebite may have one of the following consequences:

- Dry bite—It may be due to bite from non-venomous snake or bite by venomous snake without envenoming. Fang mark (bite mark) may be present.
- Local effects of venom in parts of bitten site like swelling, bullae formation, necrosis, etc. This may extend to whole limb in viper bite. Secondary infection may lead to abscess formation.
- Absorption of the venom in systemic circulation leading to systemic manifestation. Depending on the biting species the systemic manifestations are neurotoxicity or hematotoxicity.
- Effects of traditional treatment, for example, local gangrene due to tight tourniquet, pain abdomen, vomiting, etc. due to congestion of chilies, herbal medicine, etc. Tight tourniquet/s may cause manifestations that may be confused with local envenoming.
- General manifestation with or without snake envenoming may result in excessive fear, nausea, vomiting, malaise, pain abdomen, weakness, prostration, excessive salivation, etc.

Elapidae Groups of Snakes (Neurotoxic Features)

Elapidae groups of snakes envenoming produce descending paralysis due to neuromuscular blockade. The important neurotoxic features are: Ptosis, diplopia, ophthalmoplegia, pupillary dilatation, inability (or limitation) to open mouth and/or tongue extrusion, inability to swallow, broken neck sign (patients cannot hold his/her neck straight when sitting up from supine position), skeletal muscle weakness, loss of gag reflex, paradoxical breathing (outward protrusion of abdomen during deep inspiration), and respiratory failure. Paralysis of tongue and muscle of deglutition may lead to upper airway obstruction. This may lead to asphyxia due to aspiration of pooled secretions. Hypoxia-associated manifestation like cyanosis and hypoxic brain injury may be secondary to respiratory failure. Abdominal pain may suggest krait envenoming in appropriate circumstance and is likely due to venom induced submucosal hemorrhages in the stomach.

Viperidae Group of Snakes (Hematotoxic and Cytotoxic Features)

Venom of Russell's viper and saw scaled viper manifest as systemic bleeding. Feature of neurotoxicity may also present as added manifestation. Systemic manifestation of coagulopathy can also present in green pit viper envenoming. Malabar pit viper is attributed to cause significant morbidity in India.

Spontaneous bleeding from various orifices and mucosal surface is the major manifestation of viper envenoming. The bleeding is common from venipuncture

site, gums, nose (epistaxis), respiratory system (hemoptysis), gastrointestinal system (melaena, rectal bleeding), genitourinary system (hematuria, bleeding from vagina), bleeding into the mucosae (subconjunctival hemorrhage), skin (petechiae, purpura, ecchymosis), retina (bleeding into tears), bleeding from inflicted wound, if any, bleeding into internal organs like brain and intracranium, lungs or abdomen, acute kidney injury and other organ dysfunction may occur secondary to hypotension following bleeding. Laboratory evaluation reveals prolonged bleeding time (BT) and clotting time (CT), increased prothrombin time and INR. Twenty-minute whole blood clotting test (20 WBCT) is useful bedside test to see incoagulability of the blood and can detect venom induced coagulopathy.

Rhabdomyolysis

Rhabdomyolysis is characterized by muscle pain, and muscle necrosis that releases intracellular muscle constituents into the circulation. Creatine kinase level is highly elevated. Myoglobinuria may be present. All myotoxic snake venoms contain phospholipase A2, which is responsible for the rhabdomyolysis. Russell's viper, saw scaled viper, hump-nosed pit viper, green pit viper, and sea-snake can produce rhabdomyolysis **(Table 2)**.

Long-term sequalae of snakebite: Long-term effects of snake bite may occur. Some known sequelae are as follows:

- Chronic ulceration, bone infection (osteomyelitis) or arthritis
- Physical disability
- Chronic kidney disease due to bilateral renal cortical necrosis and chronic panhypopituitarism may occur in Russell's viper envenoming
- Sequelae of intracranial bleeding in hematotoxic envenoming
- Delayed psychological morbidity like depression and anxiety, impaired functioning, post-traumatic stress disorder, and unexplained residual physical disability as reported from Sri Lanka.

Diagnostic Test for Snakebite Envenoming

Neurotoxic Envenoming

Neurotoxic envenoming is clinical diagnosis and laboratory investigations is rarely of help.

Hematotoxic Envenoming Due to Vipers

- Prolonged BT and CT
- Increased INR
- Incoagulable blood as demonstrated by 20 WBCT (positive 20 WBCT)
- Raised urea and creatinine, if AKI develops
- Leukocytosis indicates systemic envenoming. Hemoconcentration may occur due to systemic bleeding and platelet count may decrease in case of viper envenoming.

Management of snakebite: Management of snakebite involves the following steps:

- First aid and transportation to the hospital
- Immediate clinical assessment and resuscitation

TABLE 2 Summary of the clinical feature of snakebite

Feature	*Cobra*	*Krait*	*Russell's viper*	*Saw-scaled viper*	*Humped nose viper*
Local pain/Tissue damage	Yes	No	Yes	Yes	Yes
Neurological signs	Yes	Yes	No*	No	No
Coagulation abnormality	No	No**	Yes	Yes	Yes
Acute kidney injury	No	No	Yes	No	Yes
Response to neostigmine	Yes	No	No	No	No
Response to antivenom	Yes	Yes#	Yes	Yes	No

* May be seen as added feature to hemostatic abnormality
** May be seen in envenoming with *Bungarus niger* (Greater black krait)
# Response to antivenom in krait envenoming may not be seen. Antivenom currently available is unlikely to neutralized venom of krait species other than common krait (*Bungarus caeruleus*)

- Antivenom treatment
- Supportive/Ancillary treatment
- Treatment of the bitten part

- *First aid and transport to the hospital:* The most of the envenomed patient of our region die before reaching hospital and this is likely due to delay in transport of victim in snakebite causing neuroparalysis. So all means should be applied to transport the patients, as soon as possible, to the hospital or snakebite treatment center, where facilities to administer antivenom exist. The recommended first aid methods are:
  - Reassurance.
  - Immobilization of the bitten limb using a splint or sling. Time should not, however, wasted searching for this materials and delay transport of the patient.
  - Tight fitting ornaments and clothing should be removed. Do not inflict cutting, sucking, electrocautery, etc. of the bite wound.
  - Rapid transport: Transportation of the victims to the nearest health center with facility to treat snake envenoming at soonest possible. Transport using motorcycle is found to save life in snakebite envenoming. The victim is seated and held between driver and pillion rider.
  - Tight (arterial) tourniquet must be discouraged.
- *Rapid clinical assessment and resuscitation:* Snakebite is a medical emergency. A quick clinical assessment to decide whether patient needs antivenom therapy and/or resuscitation should be done upon arrival of the victim. Clinical conditions when snakebite victim may require urgent resuscitation are:
  - Hypotension and shock
  - Respiratory distress and respiratory failure
  - Cardiac arrest
  - Rapid deterioration or development of features of severe envenoming
- *Antivenom therapy:* Antivenom is the only specific treatment from snakebite envenoming. Effective against the four common species of snakes found in India; Russell's viper (*Daboia russelii*), Common cobra (*Naja naja*), Common krait (*Bungarus caeruleus*), and Saw scaled viper (*Echis carinatus*). Antivenom currently is unlikely to be effective against similar sounding species of snakes.

Indications for Antivenom

- Presence of definite evidence of neurotoxicity. Ptosis is the earliest reliable sign of neurotoxicity.
- Evidence of coagulopathy: Abnormal (positive) 20WBT, spontaneous systemic bleeding (gums, hemoglobinuria, myoglobinuria, and mucosa, bleeding).
- Rapid extension of local swelling (more than half of limb) which is not due to pit viper bite or tight tourniquet application.
- Cardiovascular collapse, i.e., shock and hypotension.

Dose of Antivenom

Amount of injected venom during snakebite is similar for children and adults. Therefore, the dose of antivenom for children is same as adult dose.

Initial dose: Neurotoxic/hematotoxic envenoming: 10 vials (100 mL) is further diluted or mixed with dextrose water or saline (100–400 mL). Then it is administered with intravenous infusion at the rate of 2 mL/min (40–60 min at 60–70 drops/min).

When to repeat the dose of antivenom?

Neurotoxic envenoming: If neurological sign/s deteriorates an IV push of 5 vials of antivenom (50 mL reconstituted antivenom) should be administer at 2 mL/min.

Hematotoxic envenoming: Repeat 20WBCT (or other test for coagulation) after 6 hours. If 20WBCT is abnormal (uncoagulable blood) or other coagulation test are abnormal repeat 5 vials of antivenom (50 mL reconstituted antivenom) IV push at 2 mL/min. This can be repeated every 6 hours till coagulation profile is corrected.

Note: Do not use antivenom more than 20 vials or so. Administration of higher dose antivenom is unlikely to be useful, if patient has not responded to initial bolus or around 20 vials of antivenom.

Prevention of ASV Reaction

Prophylactic subcutaneous adrenalin (epinephrine) should be routinely administered before initiation of antivenom treatment to prevent antivenom reaction. However, it should be avoided in older patients with evidence or suspicion of underlying ischemic heart

TABLE 3 Dose of adrenalin

Age (years)	Dose (μg)	Volume (mL)
>13	250	0.25
>10–12	250	0.20
>5–10	125	0.12

disease or cerebrovascular disease. The dose of adrenalin (0.1%) is shown in **Table 3**.

Antivenom reaction: Three types of antivenom reaction can occur.

- *Anaphylaxis:* It usually develops within 3 hours of antivenom initiation. Common features are itching, which may be intense, urticaria, fever, angioedema, dyspnea due to bronchospasm, laryngeal edema, hypotension, etc. Intramuscular adrenalin must be given at first sight of sign of anaphylaxis. Details of treatment of anaphylaxis related to snakebite can be found in national guideline of snakebite management of Nepal and India.
- *Pyrogenic reaction:* Usually develops 1–2 hours after treatment initiation. Features include, chills, rigors, fever, fall of blood pressure, and febrile convulsion may develop in children.
- *Late reaction (serum sickness type):* It can developed 1–12 (mean 7) days after receiving antivenom. Features include fever, itching recurrent urticaria, arthralgia, myalgia, lymphadenopathy, proteinuria, etc.

Supportive therapy: Antivenom treatment alone cannot always prevent respiratory paralysis. Patients with impending respiratory failure artificially ventilated to avoid asphyxiation and hypoxia. Similarly, appropriate measure to be taken to treat hypotension and shock. Patients with acute kidney injury may need dialysis therapy, if indicated. All snakebite patients should receive tetanus toxoid injection at the time of discharge. Neostigmine or may be administer along with atropine, if antivenom is not available for weakness or paralysis secondary to envenomation by a snake capable of causing postsynaptic neurotoxicity. Local wound should be care as like other wound and secondary infection should be treated accordingly.

Conclusion

Snakebite is a true neglected tropical disease that mostly affects the most impoverished people of remote rural area. Immediate transport to health center and timely administration of antivenom, when indicated, along with supportive therapy are key to survival. Local envenomation may need prolonged wound care. Reaction to antivenom, which can be severe, can be reduced by subcutaneous adrenalin prior to antivenom infusion.

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CHAPTER

225 Snakebite in Indian Scenario and Its Management

Vinay Rampal

Abstract

We Indians take pride in Worshipping Vasuki Naag, who being instrumental in Churning of sea for Nectar between the gods and the demons, and, Bhujang who adorns the head of lord Shiva still, the mere imagination of a bite by the smallest of kraits causes perspiration in strongest of human beings. We also take pride in calling ourselves the biggest democracy in the world offering free medical aid to all. Today, when we are thinking of landing at Mars, every year, hundreds of thousands of poor farmers, construction workers, forest employees, trekkers, and migrant laborers lose their precious lives, which can be easily saved by proper timely intervention. Snakes rightly called the sons of soil are as much part of the universe as human beings and created to rid the universe of smaller nuances like rodents and other creepers should be properly taken care of by taking proper precautions with dwellings, footwear, gloves use of stick and light while going to old ruins, fields, forests, and night roaming, especially during summer and monsoons, when the snakes move freely around in tall grass and during floods. Even if bitten, all types of venomous snakebites are amenable to treatment and the hub of treatment the polyvalent anti venin serum (AVS) is available free of cost in all the dispensaries/health centers but what is needed is education and awareness of the populace and the relief givers. In the following pages an effort is being made to bring forth the lessons learnt during last 35 years of treating more than 8,000 snakebite cases, especially the deadliest ones from Kandi area (dry belt of Shivalik Hills).

Introduction

Although snakes constitute an alma-mater of all medical emblems the staff of Aesculapius **(Fig. 1)** and the staff of Appolo, the Cadeceus **(Fig. 2)** still they continue to remain an enigma for not only the human society but the medical profession as well, when it comes to the management of snakebite poisoning. They (snakes) not only find a mention in the Hindu religious books, wherein they are worshipped for attainment of love, health, procreation, wisdom & virtue as "Bhujang" adorning the head of Lord Shiva and "Vasuki" being credited with churning of Ocean for Nectar (Amrit). On the contrary in the Christian mythology, they are treated as backbiters needing pithing. In the developing world most snakebites occur in those who work or sleep outside, such as foresters, farmers, hunters, fishermen, herdsmen, the Army personnel, the trekkers, and the migrant laborers, while in the United States & the Europe, those keeping them as pets are bitten[1] as the famous Aspi of Cloepetra **(Fig. 3)**. Snakes bite both as a method of hunting and a means of protection. The WHO once again lists snakebite as a neglected disease.[2] Out of an average of 5 million snakebites annually, worldwide with around 2.5 million envenomations and 30,000–125,000 deaths, Indian Subcontinent constitutes more than 50% of the share,[3] partly because of the ignorance, prevalence of old practices (Ojha & mantras), and the lack of proper medical facility in far flung areas. There are about 216 species of snakes in India out of which

Fig. 1: Staff of Aesculapius

Fig. 2: Staff of Apollo, Our Emblem

Fig. 3: Cloepetra's famous Aspi

52 are venomous. Broadly speaking there are four major families of venomous snakes:

- Viperidae, with sub class
  - viperinae the old world vipers and
  - crotaline new world and Asian pit vipers
- Elapidae the cobras, kraits, coral snakes, sea snakes, and all venomous Australian snakes
- Lamprophiidae (subfamily Atractaspididae the burrowing asps)
- Colubridae (a large family in which most of species are non-venomous with only a few being dangerously toxic to mankind)[4]

The vipers are mostly hemotoxic and cardiotoxic but occasionally may also be neurotoxic. The Elapidae are mostly neurotoxic but may affect the cardiac as well as the vascular system causing sudden deaths or coagulopathy. Most snake venoms contain multiple toxins ranging from cytotoxins, hemotoxins, neurotoxins, bungarotoxins, cardiotoxins, and myotoxins, which comprise of different types of peptides and proteolytic enzymes, glycoproteins, metal ions and hyaluronidases, phospholipases, etc. The most commonly found examples of viperidae are Russel viper, pit viper, the commonly found elapids are Cobra (Naja naja) and common krait (Bungarus caeruleus).

Poisoning by most viperids and some elapids with necrotizing venoms causes progressive local swelling, pain, ecchymosis, and hemorrhagic bullae or serum filled vesicles. In serious bites tissue loss can be significant. Systemic finding may include change in taste, mouth numbness, persistent severe vomiting and/or abdominal pain, muscle fasciculations, arrhythmias, for example, tachycardia or bradycardia, torsades-de-pointes, ventricular fibrillation, hypotension, shock, pulmonary edema,[5] hemorrhage from any site and renal dysfunction. Poisoning by neurotoxic elapids such as kraits, many Australian elapids (Atractaspis spp.) and tiger snakes (Notechis spp.), cobras and some viperids cause neurologic dysfunction, starting with cranial nerve involvement like ptosis, external ophthalmoplegia, altered mental status progressing to bulbar paralysis, and/or general paralysis involving the muscles of respiration leading to death. Most

often the patient has been brought to us in an unconscious state without any history of snakebite in the absence of any fang marks but a history of having slept on the floor.[6] After elapid bites, the time of onset of envenomation varies from minutes to hours depending upon the species involved, the anatomic location of the bite, and the amount of venom injected.

Management

Basic management at the location of bite: It involves retardation of absorption of venom and neutralization of venom as quickly as possible. The most important management of snakebite of any type remains as ever reassurance, the mere fact of a snakebite frightens the boldest of the persons at times to fainting attacks, so assuring a person that nothing lethal has happened will not only prevent him from collapsing but will also prevent the adrenaline secretion resulting in increased heart rate, and enhanced dissipation of the venom in circulation and its immediate effects. The person should be made comfortable by lying down and placing the part bitten below the level of heart and stabilizing it with a splint so as to cause minimum movement, and hence prevent absorption of the poison. Even if there are no visible fang marks and the snake is apparently non-poisonous the basic management should remain the same, because most of neurotoxic snakebites (common krait) cause minimum pain and little or no visible fang marks. No tourniquets (tight ligatures) to be applied in any case which will result in complication than help, rather remove any rings, watches, bracelets or anything around the bitten part, which may act as a tourniquet once the part swells-up. The person should be made to be fully aware given plenty of fluids and talked to incessantly. If there are minimal fang marks and no ecchymosis or swelling a soft elastic bandage should be applied proximal to the bite through which the little finger can be easily passed (neurotoxic bite, vide-supra). Incising of the wound, applying electric current or suction should be avoided because they can enhance local tissue damage. Similarly, the application of poultices and ice packs should be strongly discouraged. In case of hemorrhagic symptoms the best plan is to stabilize the part with a splint and keep it below the level of heart and wash it with soap and water no pressure or incision to be given in any case. Watch for bleeding from any site and as mentioned above if there are chances of hemorrhagic shock then fluids orally need to be increased and the patient carried on a cot or stretcher to the nearest hospital/dispensary which has the polyvalent anti-venin serum (AVS) available.

Hospital management: The patient should be closely monitored at least for 24 hours even if there are no fang marks and the snake was apparently non poisonous (vide-supra). A care should be taken of airway, blood pressure, respiration, heart rate, and neurological status/deficit, while taking the history and performing a preliminary clinical examination. In case of viper bites the level of swelling of the bitten extremity should be noticed and diameter measured half hourly and the part placed below the heart level till AVS is instituted. The bands or tourniquet if applied should be very slowly removed after a large bore Intravenous access so as to prevent the sudden release of acidotic blood collected in the distal part to the central circulation which may result in bradycardia or hypotension leading to shock and sudden death. A sample of 3–5 mL of venous blood should be immediately drawn and poured in to a dry test tube which should be placed vertically so as to see for 20 minute whole blood clotting time (20 WBCT) and tilted to 45° at 4–6 hours intervals so as to assess for coagulopathy and further institution of AVS.[7] In addition other blood chemistry and measurements like thrombocyte count, renal and hepatic functions, coagulation studies, and urine for fibrin degradation products to diagnose consumptive coagulopathy and for blood and myoglobin should be carried out. If the bitten part is swollen due to intra-compartmental bleed the part should be raised above the heart level after starting AVS and if it does not respond to conservative measurements then Mannitol (1 gm/kg fast) should be infused to release the pressure. Arterial blood gas (ABG) studies, electrocardiography, and chest radiography may be carried out in severe envenomation when there is no active bleeding going on. In case of neurotoxic poisoning a care should be taken about ptosis, drooling of saliva, respiratory insufficiency, or other types of neurodeficiency.

The hub of treatment of venomous snakebite, resulting in significant envenomation is the administration of specific AVS. These sera are obtained from the sera of animals after, either by the injection of the venom of common varieties of snakes obtained by milching them **(Fig. 4)** or by giving them a direct bite. The AVS

Fig. 4: Russell's viper snake

available in our country is a polyvalent one, which acts as an antidote to the most of the types of snake venoms involved in our country. Produced either at Haffkine's Institute, Mumbai, or National Serum Institute Kassauli (Himachal Pradesh). The goal of AVS administration is to allow antibodies (or antibody fragments) to bind up circulating venom components before they can attach to target tissues and cause deleterious effects. Because the hemotoxic snake venom due to its procoagulants and anti-coagulants causes venum induced consumptive coagulopathy[8,9] through its toxins exerting effect on the platelets, coagulation factors, coagulation products and blood vessels, the administration of AVS should be strictly according to the nature of the clot, that is, if no clot forms within 20 minutes full dose of AVS to be instituted (100 units stat) and firmer the clot lesser the dose of AVS. Some studies have also mentioned the role of liver gene regulation in hemostasis.[10]

Since the heterologous sera, obtained from any source, being a foreign body carry their own risks like acute, non-allergic/allergic anaphylaxis and delayed type hypersensitivity reactions (serum sickness) skin testing for potential allergy is a must although our practice has been to administer 100 mg of hydrocortisone IV before starting AVS even if the intradermal test was ambiguous or in the alternative 0.01 mg/kg, up to 0.3 mg of epinephrine subcutaneous or intramuscularly. The indications for administration of AVS to victims of bites by viperids or elapids depend upon:

- Presence of systemic symptoms or signs (vide-supra), persistent and severe vomiting and/or abdominal pain and/or laboratory abnormalities and significant progressive local findings (massive local necrosis, soft tissue swelling crossing a joint or involving more than half the bitten limb or continuous bleeding from any site, internal or external). In case of neurotoxic poisoning the administration of AVS is indicated at the first sign of any neurotoxicity (ptosis, difficulty in swallowing or signs of peripheral neuropathy).
- Modest expansion of patients' intravascular volume with crystalloids also may blunt acute adverse reactions, hence their administration should be concomitant with IV administration of AVS, which should be started in the presence of a doctor and closely monitored by him for any adverse reactions like acute bronchospasm or cardiovascular collapse.

Specific Treatment

- *Hemotoxic/Cardiotoxic bite:* The patient presenting with a local swelling or bleed or ecchymosis or signs of bleeding from any part (mouth, gums, hematemesis/melaena) signs of cardiovascular failure and apprehension.
  - Reassurance.
  - Administration of tetanus toxoid.
  - Establish two large bore IV lines with normal saline/crystalloid starting with a bolus 20–40 mL/kg body weight if the patient is hypotensive, if in shock treat it.
  - Maintenance of proper airway, breathing, blood pressure, and raise the swollen part above the level of heart once AVS is started.
  - Urgent clotting time estimation (CT) vide-supra 4–6 hours (Reid criteria).
  - Intradermal test of AVS and thereafter 100 mL (ten vials of lyophilized/liquid polyvalent AVS) in 500 mL of normal saline over a period of 4–6 hours to be preceded by 100 mg of hydrocortisone (in case of doubtful test).
  - The above dose to be repeated after 6 hours if the blood remains non-clotting (>20 minutes depending upon the quality of clot) (Reid criteria).
  - If the swelling in the bitten extremity points toward subfascial muscle edema impeding tissue perfusion (muscle compartment syndrome) IV

mannitol (1 gm/kg) may be administered in a hemodynamically stable patient. However, if the response is not proper, fasciotomy of the limb may be needed after orthopedic consultation.[11] AVS must be administered in all cases presenting in an acute form with active bleeding even if presenting after 3–4 weeks of bite.
  - Antibiotics effective against staph like cloxacillin/cephalexin 500 mg 8 hourly. In case of massive necrosis and skin and muscle damage metrogyl should be added.
  - The amount of AVS administered depends upon the clinical response and is inversely proportional to the quality of the clot (i.e., poor clot, more AVS and good clot less AVS. Watch the clot for 4 hours because at times the clot may redissolve). No fixed dose of AVS has been calculated so far.
- *Neurotoxic bites:*
  - Reassurance
  - Maintenance of proper airway, breathing, blood pressure, and watch for signs of neurodeficiency like altered mental status, ptosis, drooling of saliva, difficulty in swallowing, diplopia, difficulty in breathing or signs of peripheral neuropathy, paralysis, or unconsciousness.
  - Intradermal test of AVS and thereafter 100 mL (ten vials of lyophilized/liquid polyvalent AVS) in 500 mL of normal saline over a period of 4–6 hours to be preceded by 100 mg of hydrocortisone (in case of doubtful test).
  - Atropine 0.6 mg IV (children, 0.02 mg/kg; minimum of 0.1 mg) follow with:

Edrophonium: 10 mg IV (children, 0.25 mg/kg)
Or
Neostigmine 1.5–2 mg IM (children, 0.025–0.08 mg/kg)

Continue neostigmine at a dose of 0.5 mg (children, 0.01 mg/kg) IV or S/C every 30 minutes as needed, with continued administration of atropine by continued infusion of 0.6 mg over 8 hours (children 0.02 mg/kg over 8 hours). Stop this regimen if no relief is evident after three doses because in that case the bite is that of a krait.

Maintain vigilance regarding aspiration risk and secure the airway with endotracheal intubation as needed and put on ventilator if still not responding.
  - Continue to repeat the AVS dose till substantial relief or death of the patient.
- In case of an acute reaction to AVS the infusion should be temporarily stopped and the reaction immediately treated with intramuscular epinephrine 0.01 mg/kg up to 0.03 mg, antihistamines (diphenhydramine, 1 mg/kg to a maximum of 100 mg and cimetidine, 5–10 mg/kg to a maximum of 300 mg and glucocorticoids (200 mg IV). Once the reaction is controlled if the severity of poisoning warrants additional AVS, the dose should be diluted further in isotonic saline and restarted as soon as possible. Rarely in recalcitrant cases desensitization needs to be done with hydrocortisone (starting from 400 mg hourly and tapering till normalization or a concomitant IV infusion of epinephrine may be required to hold allergic sequelae at bay while further AVS is administered). The patient must be monitored very closely, preferably in an intensive care setting, during such therapy.
- Blood and blood products are rarely necessary in the management of a hemotoxic bite, although these bites can cause a drop in platelet count or hematocrit and depletion of coagulation factors these usually rebound within hours after administration of adequate amount of AVS. Even if there is a great need for these products they should be given only after adequate AVS administration to *avoid adding fuel to the fire of ongoing coagulopathy*.[4,8,9]
- Patients who develop acute renal failure due to rhabdomyolysis or hemolysis should be managed in a conventional fashion, as the insult is one of acute tubular necrosis and is frequently reversible and if not responding should be referred to a nephrologists for hemodialysis or peritoneal dialysis.
- A dry, sterile dressing should be applied to the wound while splinting with padding between the digits. Pain control should be achieved with paracetamol or codeine. Salicylates and other non-steroidal anti-inflammatory agents should not be used because of their effect in prolonging clotting of blood.
- After full care of the wound and normal clotting of blood, physiotherapy should be instituted for return to a functional state. The victim should keep contact with the treating physician even after discharge and be made aware about signs and symptom of wound infection, AVS related serum sickness and long-term sequelae like pituitary insufficiency, with central diabetes insipidus[12] in Russel viper bites and the late onset of coagulopathy after 2–3 weeks of bite and to

avoid elective surgery or activities involving high risk of trauma. The serum sickness should be treated with prednisone (1–2 mg/kg daily) until all findings resolve and then tapered over 1–2 weeks, besides oral antihistamines and analgesics.

Morbidity and Mortality

The mortality in India is high because of religious beliefs (witchcrafts and mantras) lack of connectivity and ignorance in both, the treater and the treated (vide-supra). Similarly, the incidence of morbidity (permanent functional loss in a bitten extremity) is also substantial due to muscle, nerve, or vascular injury or to a scar contracture with resulting inability to work and earn a proper living.

Future Aspects

In the biggest democracy of the world which boasts of free-medical care for all and when we are planning to land at Mars, a substantial portion of the population either losses life or is mauled permanently due to a preventable cause. The following main points which need to be addressed are:

- Education of the masses about the prevalence of the types of snakes and their proliferation at a particular time of the year (summer and monsoon) and at specific places (farmland, mudhouses, ruins, forests) and use of proper gear (covering the lower limbs up to knees and the upper limbs up to elbows with long boots and thick gloves or in the alternative with thick wrappings like jute, etc. and use of a lathi and torch/lamp when going to fields/forests or working at extremes of times makes it easily preventable). Digging of a shallow ditch around the Jhuggis as the defense personnel do around their tents. Special care needs to be taken during floods, which not only bring the snakes out of their burrows but also from far off places.[13]
- Availability of proper amount of AVS (which is available) and qualified persons at subcenters of the health department which already exist to orientate them and to make them more conscious about envenomation and its management because the ultimate treatment of any type of snakebite poisoning is only timely administration of AVS besides other remedial measures.
- Since this is mainly a problem of developing countries only, a combined research should be oriented toward production of a snake venom vaccine/venom toxoid for those people who are prone to snakebite poisoning like the farmers, the foresters, the trackers, and the migrant laborers who sleep on the ground.
- Some trials are being given to the use of PLA2 inhibitor Varespladib[14] as an alternative to AVS because of its effective inhibition of snake phospholipase. Some local people have also used Citrus peels locally but again it is firmly stressed to follow only the above standard guidelines because human life is invaluable and does not need to be experimented with.

Conclusion

Snakes, an essence of the Universe, have been created by the almighty, like human beings to take care of the rodents and other insects, which otherwise would cause immense loss to the mankind. Worshipped in some civilizations and hated in others, the Snakes find an important place in our Medical emblems. In the West they are being nurtured as pets as well since the Roman Empire. Still a word of caution is essential when dealing with them, especially in certain seasons like rains and floods which cause a surge in their population and activity. For the defense personnel, forest employees, trackers, and explorers like archaeologists a proper gear needs to be worn and a lathi and torch for the house holder are a must and only antidote of snake bite poisoning the AVS though available liberally needs to be used judiciously. Similarly, a lot of old remedies like laceration, tourniquet, and application of electric current need to be discarded. Neurotoxic snake bite should be ruled out in all unconscious patients in the planes, especially during rainy sessions. New drugs are in the pipeline but till their confirmed benefit AVS should be the hallmark of treatment.

Since a neglected problem, especially of the developing countries a combined effort to develop an anti-toxin or vaccine of universal usage is the need of the hour and may be the answer as has been very fortunately carried out in the case of COVID-19 in less than a year.

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Section 19

Section Editor: **Sudhir Mehta**

Hematology and Oncology

CHAPTER

226 Hemolytic Anemias: Diagnostic Approach

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Abstract

Hemolytic anemias are an important type of anemia in which destruction of RBCs occurs. Manifestations occur in the form of development of anemia along with sign and symptoms of hemolysis. Usually the diagnosis is made by good clinical history relating the cause of anemia and evidence of hemolysis in laboratory evaluation. Therefore, a general approach for making etiological diagnosis of the hemolytic anemia is always needed for classification and management of anemia. In this chapter an effort has been made to provide a relevant approach for the evaluation of hemolytic anemia.

Introduction

Anemia is defined as decrease in hemoglobin (Hb) level, according to reference ranges specific for age, gender, and race. For men Hb <13 g/dL and for women Hb <12 g/dL is considered as anemia as per World Health Organization (WHO).

The mean life span of Red Blood Cells (RBCs) is 120 days. Taking a good history followed by proper clinical examination along with laboratory investigations is still considered as the best approach for any case of anemia.

In hemolytic anemias, there is premature destruction of RBC, that is, in less than 120 days (which defines the hemolytic disorder) which in turn to compensate, there is increase in the production capacity of RBCs by bone marrow. When the rate of destruction of red blood cell exceeds the capacity of producing more red cells by bone marrow, the hemolytic disorder will manifest as hemolytic anemias.

Usually the diagnoses of hemolytic anemia are made through the laboratory investigations but a clinical history along with physical examination is also helpful for providing useful information about presence of hemolysis and its probable etiology.

Causes of anemia that can be treated (anemia due to nutritional deficiencies, gastrointestinal bleed, anemia of renal origin, and hemolysis) should be looked for carefully, so that it is not missed.

Classification

- On the basis of etiology, hemolytic anemia can be classified as:
  - Inherited or
  - Acquired.
- According to the site of hemolysis **(Table 1)**, it is divided into:
  - Intravascular, where RBCs destruction is in the circulation or
  - Extravascular, where destruction occurs in the spleen or liver (within macrophages).
- From the clinical perspective, hemolytic anemia can be
  - acute or
  - chronic.
- According to mechanism (location of the abnormality) **(Table 2)**, there may be
  - intrinsic (intracorpuscular) defect or
  - extrinsic (extracorpuscular) defects.

TABLE 1 Classification according to site of hemolysis

Intracorpuscular factors (Red cell abnormality)	*Extracorpuscular factors*
Hereditary • Membrane defect (spherocytosis, elliptocytosis) • Metabolic defect (Glucose-6-Phosphate-Dehydrogenase (G6PD) deficiency, Pyruvate kinase (PK) deficiency) • Hemoglobinopathies (unstable hemoglobins, thalassemias, sickle cell anemia) **Acquired** Membrane abnormality-paroxysmal nocturnal hemoglobinuria (PNH)	**Immune hemolytic anemias** • utoimmune hemolytic anemia – caused by warm-reactive antibodies – caused by cold-reactive antibodies • Transfusion of incompatible blood **Nonimmune hemolytic anemias** • Chemicals • Bacterial infections, parasitic infections (malaria), venons • Hemolysis due to physical trauma – hemolytic-uremic syndrome (HUS) – thrombotic thrombocytopenic purpura (TTP) – prosthetic heart valve – Hypersplenism

TABLE 2 Classification according to the location of the abnormality

	Intracorpuscular defects	*Extracorpuscular factors*
Hereditary	• Hemoglobinopathies • Enzymopathies • Membrane-Cytoskeletal defects	• Familial (atypical) hemolytic uremic Syndrome
Acquired	• Paroxysmal nocturnal hemoglobinuria (PNH)	• Mechanical destruction (microangiopathic) • Infectious • Autoimmune • Toxic agents • Drugs

Mechanisms involved in anemia include:

- *Inadequate production:* Stem cell damage or defective red cell maturation.
- *Excessive destruction (hemolysis):* Intrinsic defect in red cell leading to shortened lifespan or external factors in blood or blood vessels destroy red cells.
- *Blood loss (bleeding)*

Causes of hemolytic anemia include:

- *Inherited red blood cell membrane abnormalities:* There is change in the shape of cell due to membrane defects and this change in shape is identified as abnormal by spleen and destroyed it.
- *Inherited enzyme deficiencies in red blood cells:* Abnormalities in enzyme levels makes the red blood cell fragile, which makes red blood cell prone to get destroyed easily.
- *Hemoglobin disorders:* Abnormal hemoglobin is because of inherited gene in some people. Abnormal hemoglobin can lead to easy destruction of red blood cells. Disorder includes sickle cell anemia and the thalassemias.
- *Physical damage to RBCs:*
  - During heart-lung surgery
  - In patients with artificial heart valves (as blood flows near devices)
  - In a patients with severe burn (exposure to extreme heat)
- *Physical damage to RBCs:*
  - During heart-lung surgery
  - In patients of artificial heart valves
  - In patients with severe burn due to exposure to extreme heat
  - *Autoimmune hemolytic anemia:* It can occur in autoimmune conditions like lupus, certain types

of infections, and use of some drugs. This happens when the red blood cells of the body gets destroyed by immune mechanism of its own body.

– *Hypersplenism:* The spleen is enlarged and becomes overactive. It traps the circulating red blood cells and destroys it.

General Features of Hemolytic Disorders

Hemolytic anemias can be differentiated from other anemias by presence of signs and symptoms arising because of hemolysis.

General examination: Jaundice, Pallor, Bossing of Skull

Physical findings:

- Enlarged spleen (as a preferential site of hemolysis) leading to neutropenia and/or thrombocytopenia
- Enlarged liver (in some cases)
- Skeletal changes, because of bone marrow over activity (seen in severe congenital forms)
- Hemoglobin—From normal to severely reduced
- MCV—Usually increased
- Reticulocytes—Increased (sign of the erythropoietic response by the bone marrow)
- Bilirubin—Increased (mostly unconjugated)
- LDH—Increased
- Haptogloin—Reduced to absent

Two main principles for diagnosis:

- First is to confirm the diagnosis of hemolysis
- Second is to determine its etiology

The etiology of hemolytic anemia can be determined by:

- A good clinical history
- The peripheral blood film

Clinical Presentation

- New onset pallor or anemia
- Hemolytic faces—Chipmunk facies
- Jaundice
- Splenomegaly, bossing of skull (in severe congenital cases)
- Gall stones
- Dark colored urine
- Leg ulcers

Features of Hemolysis

- Hemoglobin—Normal to severely reduced
- MCV, MCH—Usually increased
- Bilirubin is raised (mostly unconjugated)
- LDH is raised (up to 10 times of normal with intravascular hemolysis
- Reticulocytes, n-RBC—Raised
- Haptoglobins are reduced to absent
- Urinary hemosiderin, Urobilinogen are +ve

↓

Blood Smear

↓

- Spherocytes—
  - DCT +ve (Autoimmune hemolysis)
  - DCT –ve (*H. Sherocytosis*, malaria, clostridium)
- No spherocytes—Hereditery enzymopathies
- Fragmentation—Microangiopathic, Traumatic

Laboratory Evaluation of Hemolysis

See **Table 3**.

Metabolic Manifestations of Increased Red Cell Turnover

There is significant iron loss (requiring treatment), due to persistent hemoglobinuria because of chronic intravascular hemolysis. If frequent blood transfusions are needed or if erythropoiesis is massively increased then iron overload is very common. This iron overload leads to hemochromatosis affecting liver and heart muscles eventually leading to cirrhosis and heart failure respectively.

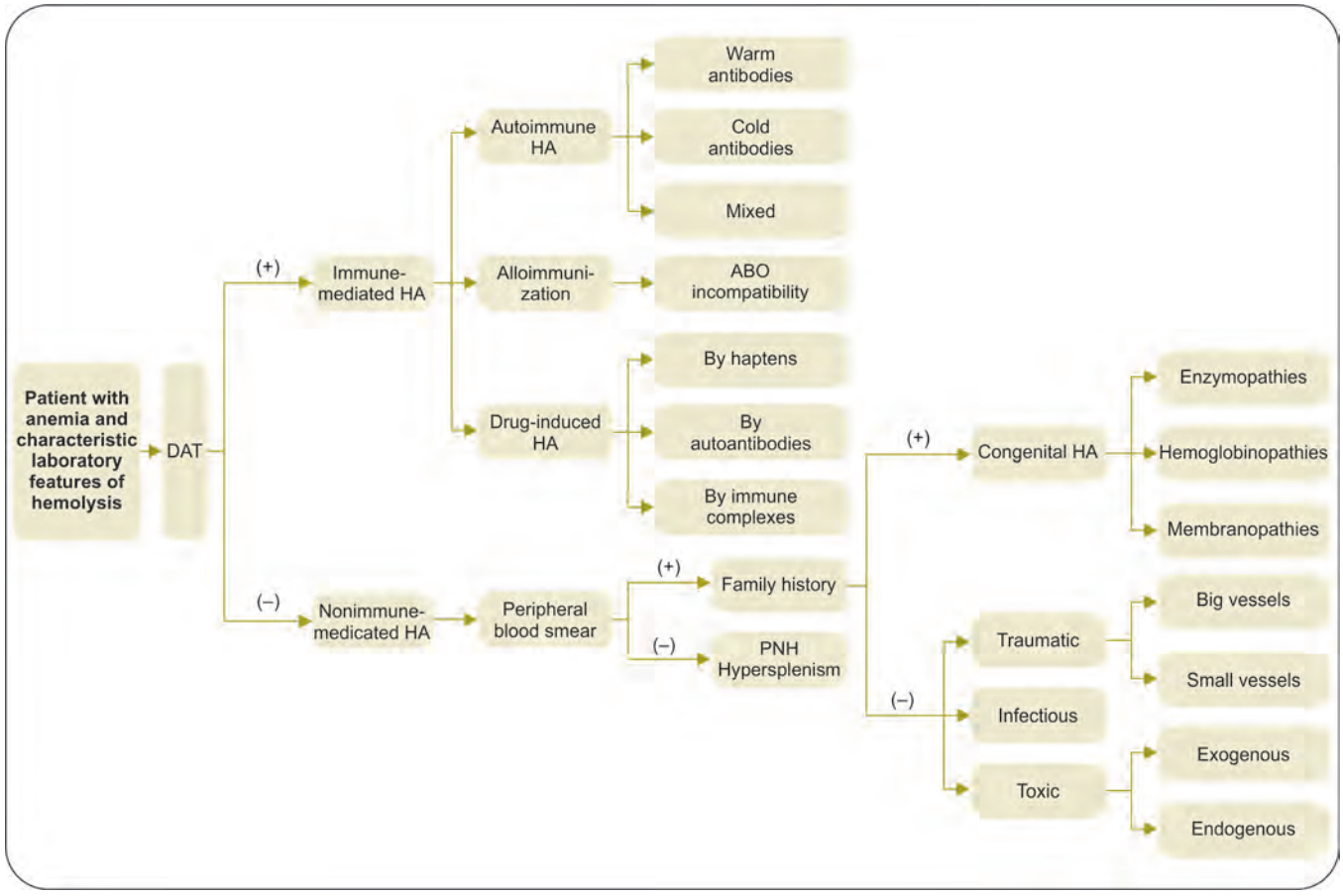
Morphological Abnormalities of RBCs in Hemoltyic Anemias

- Schistocytes—thrombotic microangiopathies or cardiac prosthetic valves
- Spherocytes—hereditary spherocytosis, immune hem. anemia, burns, chemical injury to RBC
- Sickled cells—sickle cell disease
- Elliptocytes—hereditary elliptocytosis
- Echinocytes—pyruvate kinase deficiency
- Heinz bodies—G6PD deficiency
- Basophilic stipplings—thalassemia, Wilson's disease, and lead poisoning

TABLE 3 Laboratory evaluation of hemolysis

	Extravascular	*Intravascular*
Hematologic		
• Peripheral blood film • Reticulocyte count • Bone marrow examination	• Polychromatophilia • Raised • Erythroid hyperplasia	• Polychromatophilia • Raised • Erythroid hyperplasia
Plasma or serum		
• Bilirubin • Haptoglobin • Free hemoglobin • Lactate dehydrogenase	• Unconjugated decreased • Absent • N/increased (Variable)	• Unconjugated • Absent • Increased • Increased (Variable)
Urine		
• Bilirubin • Hemosiderin • Hemoglobin	0 0 0	0 + + → severe cases

Flowchart 1: Approach to identify and classify hemolytic anemias



Red Cell Survival Study

To prove that the life span of RBC is reduced than normal (about 120 days), then the study labeling the red cells with 51Cr can be done and fall in radioactivity over days to weeks can be measured. Nonradioactive isotope 15N can also be used now in place of radioactive substance.

Algorithm for the Evaluation and Diagnosis of Hemolytic Anemia

Anemia—present
Indirect hyperbilirubinemia—present
Reticulocytosis—present

↓

Then look for hemolysis: CBC, reticulocyte count, LDH, indirect bilirubin, haptoglobin, and peripheral blood smear

↓

- *If negative:* Consider alternative diagnosis (other causes of normocytic anemia like chronic kidney disease, hemorrhage, chronic disease)
- *If positive:*
  - Spherocytes, positive DAT **(Flowchart 1)**—Immune hemolysis: lymphoproliferative disorder/malignancy, autoimmune diseases, drugs, infections, transfusion.
  - Spherocytes, negative DAT, family history—Hereditary spherocytosis.
  - Schistocytes—Microangiopathic hemolytic anemia PT/PTT, LFT, KFT, Blood Pressure TTP, HUS, DIC, Eclampsia, Preeclampsia, malignant hypertension, prosthetic valve.
  - Hypochromic microcytic anemia Thalassemia-Hemoglobin electrophoresis.
  - Sickle cells-Sickel cell anemia—Hemoglobin electrophoresis.
  - Infection/drug exposure—G6PD activity.
  - Fever/recent travel—Thick and thin smears, Babesia serology, bacterial cultures.

Conclusion

Hemolytic anemias can be diagnosed on the basis of detailed history, general and physical examination. Laboratory investigations and peripheral smear are helpful to confirm the hemolysis and to guide further tests to look for etiology.

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CHAPTER

227 Thalassemia in Adults—Management Issues

Ramesh Aggarwal, Anupam Prakash

Abstract

Beta-Thalassemia can be broadly classified into transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT). The primary management in these patients is regular blood transfusion and adequate iron chelation. Some patients may require splenectomy and hematopoietic stem cell transplantation (HSCT). Majority of the complications arise because of transfusion related iron overload and include cardiac failure, arrhythmias, endocrine complications like hypogonadism, hypoparathyroidism, diabetes, hypothyroidism, delayed growth, osteoporosis, renal complications, and infections. Early initiation of chelation therapy can reverse the process of iron deposition in tissues and salvage or prolong the development of complications. This chapter highlights the challenges which arise in managing patients of beta-thalassemia and summaries the clinical approach in preventing various complications which arise out of iron load in these patients.

Introduction

The disease β-Thalassemia includes many different conditions like β-thalassemia major, β-thalassemia intermedia, and HbE/β-thalassemia. They can be broadly classified into transfusion-dependent thalassemia (TDT), which includes severe forms of HbE/β-thalassemia and β-thalassemia major and non-transfusion-dependent thalassemia (NTDT), which includes thalassemia intermedia and milder forms of HbE/β-thalassemia **(Fig. 1)**. TDT are patients who require regular transfusion of blood to survive whereas NTDT will require blood transfusions in certain conditions like pregnancy, surgery, and infections.[1]

Management

The management of TDT requires regular blood transfusion and adequate iron chelation. In some patients, splenectomy and hematopoietic stem cell transplantation (HSCT) are required. **Table 1** summarizes the current therapies available for TDT.

Complications and Management Issues

Majority of the complications in TDT arise because of transfusion related iron overload and include cardiac failure, arrhythmias, endocrine complications like hypogonadism, hypoparathyroidism, diabetes, hypothyroidism, delayed growth, osteoporosis, renal complications, and infections. Some complications like silent cerebral infarction and pulmonary hypertension are more common in patients with NTDT.

Cardiac Complications

They include cardiomyopathy congestive heart failure, arrhythmias, peripheral vascular disease, and pulmonary hypertension. Persistent hypoxia, high levels of abnormal hemoglobin, and high iron levels in tissues along with

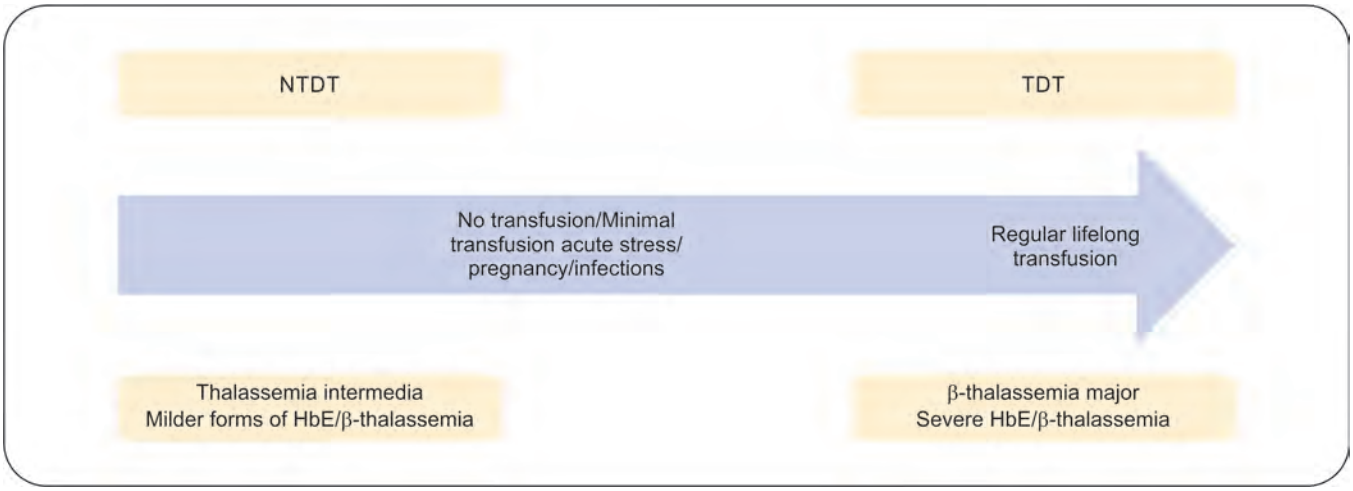

Fig. 1: Classification of thalassemia based on transfusion dependence

TABLE 1 Treatment options for beta thalassemia[2]

Treatment modality	***Merit***	***Demerit***
Blood transfusion	Helps by suppressing ineffective erythropoiesis, prevents bone marrow expansion	• Every 2–4 weeks' transfusion required for life long • Transfusion associated complications like infections, iron overload, and alloimmunization
• Iron chelation • Deferoxamine: Parenteral • Deferasirox: Oral • Deferiprone: Oral	• Decreases iron overload in myocardium, liver, pituitary, etc. • Improves endocrine functions and cardiac health	• May not be effective in every patient • Side effects are common • Parenteral formulation often lead to non-compliance • Cost of therapy is high
Hydroxyurea (It is a cytotoxic antimetabolite that helps to increase fetal hemoglobin levels)	• Some hematological parameters may improve in NTDT patients • Cost of therapy is low	• Lack of clear evidence of its use in TDT
Splenectomy	• The quality of life and growth may improve • It may improve hemoglobin concentration • The frequency of transfusions may decrease	• Risk of infection and sepsis increases • The risk of venous thrombosis and pulmonary hypertension increases • It also reduces the ability to scavenge toxic-free iron species
HSCT	• Treatment of choice for patients younger than 14 years • Others may benefit depending on donor availability and iron load after this age • The survival rate is up to 90% and the disease-free survival rates reaches up to 80% • The quality of life is improved • Long-term cost-effective	• May not be useful for all patients, only a subset of patients qualify for this treatment • Young age • Donor should be a compatible sibling • Risk of 5–10% mortality • Preparation for this treatment requires myeloablative conditioning and can cause impairment of fertility • Highly trained centers are required • Very high cost

HSCT, hematopoietic stem cell transplantation; NTDT, non-transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia

infection with cardiotropic viruses contribute to initiation and progression of cardiomyopathy in these patients. Presenting features are dyspnea, fatigue, or palpitations.

Cardiomyopathy in thalassemia presents with two different phenotypes:

- Dilated cardiomyopathy where the left ventricle is dilated and contractility is reduced. This progresses to congestive heart failure.
- Restrictive cardiomyopathy where the left ventricle filling is restrictive. This phenotype can lead to pulmonary hypertension, dilatation of right ventricle, and subsequent heart failure.

Measurement of amino-terminal pro-B-type natriuretic peptide is more reliable in early diagnosis than Doppler echocardiography.[3] Cardiac MRI provides better estimate of iron burden than serum ferritin and it has been found to be a better predictor of heart failure and arrhythmia in different studies.[4]

Rhythm Disturbances

They are atrial fibrillation, atrial flutter, intra-atrial re-entrant tachycardia, ectopic atrial tachycardia, and ventricular arrhythmias. Prolonged QT interval and repolarization abnormalities occur because of iron overload leading to torsades de pointes and sudden cardiac death (SCD).[5]

Management

As aggressive iron chelation therapy can restore the functions of myocardium, it should be the goal:

- Asymptomatic patients with no cardiac dysfunction and no deposition of iron in heart: healthy lifestyle and adequate chelation therapy
- Iron deposition in heart but no cardiac dysfunction: healthy lifestyle and intensification of chelation therapy including use of combination therapy
- Cardiac dysfunction with or without symptoms:
  - Healthy lifestyle and intensification of chelation therapy including use of combination therapy
  - Slower transfusion of blood with use of diuretics
  - Use of ACE inhibitors, or ARII blockers
  - Cardioselective beta-blockers like bisoprolol and carvedilol
  - Digitalis if atrial fibrillation is present along with anticoagulation

Endocrine Complications

They include hypogonadism, growth retardation, diabetes mellitus, hypoparathyroidism, and hypothyroidism.[6]

Gonadal Axis

Hypogonadism can be primary (hypergonadotropic hypogonadism) due to iron deposition in gonads or secondary (hypogonadotropic hypogonadism) due to iron affecting the gonadotrophs in anterior pituitary. Secondary hypogonadism is more common in patients with TM. Primary amenorrhea precedes secondary amenorrhea in most women with thalassaemia major. Screening for hypogonadism should be done annually. Careful history should be taken which includes erectile function, libido, spontaneous erections in males and libido, vasomotor symptoms, and menstrual history in females. The patient's genitalia should be examined and loss of secondary sexual characters should be noted.

Investigations:

- Serum fasting testosterone, SHBG, LH, FSH, and hCG in males and estradiol, LH, and FSH in females.

Management:

- *Females:* Treatment is given to relieve from symptoms of estrogen deficiency like sweats, hot flushes, mood changes and vaginal atrophy. Hormone replacement therapy (HRT) is helpful to overcome them and prevent osteoporosis.
- *Males:* Testosterone replacement in the form of transdermal gel or intramuscular injections every 2 weekly helps to improve libido, erectile dysfunction, and may improve bone mineral density and muscle mass.

Growth Hormone Axis

Many factors contribute to delayed growth in patients, which are iron overload, chronic anemia, hypersplenism, hypothyroidism, hypogonadism, chronic liver disease, malnutrition, stress, and growth hormone (GH) deficiency. GH deficiency is common in patients with TM and results in short stature and delayed growth. GH deficiency can have varied presentations like classic GHD, GH resistance or a combination of both.[7] Clinical Assessment should

be done preferably at regular interval of 6 monthly. It includes:

- Patient's height (standing and sitting) and weight
- Measurement of upper/lower segment ratio and calculation of BMI and annual growth velocity (GV)
- Recording of parental heights at the first visit (calculate mid-parental height)
- Accurate measurement of standing and sitting heights, weight, and head at each visit; measurement of the head circumference especially during the first 2 years of life
- Plotting growth data on ethnically adjusted charts or international (WHO) adjusted charts
- Calculating annual growth velocity (GV), body mass index (BMI), and upper/lower segment ratio at every visit
- Assessment of pubertal status as per Tanner stage (development of breast in girls and testicular volume in boys)
- Assessment of bone age

Investigations:

- Serum IGF-1, Serum TSH, and free T4, LH, FSH, and sex steroids along with X-ray of wrist and hand for bone age.

Treatment:

- Children who are short with low IGF-1 levels and normal GH secretion to stimulation tests may benefit from IGF-1 or GH-IGF-1 treatment.
- If the bone age is 10 years or greater, then priming with sex steroids is done before initiating any treatment for GH deficiency.
- Treatment of other diseases like diabetes and hypothyroidism has to be done simultaneously.
- There must be psychological evaluation and support for conditions that are non-treatable like constitutional delay of puberty and growth, familial short stature, etc.
- Treatment with rhGH should start with low doses and then titrated according to IGF-1 levels and growth rate.

Adrenal

Patients with thalassemia are often asymptomatic for adrenal insufficiency and may have only biochemical evidence. A study of 56 children suffering from thalassemia had shown presence of adrenal insufficiency in about 37.5% asymptomatic patients.[8] Acute stress can precipitate adrenal insufficiency and symptoms can be feeling of lack of energy, fatigue, decreased appetite, and muscular weakness. Adrenal androgen deficiency can sometimes lead to decreased pubic and axillary hairs.

Investigations:

- Serum cortisol level, adrenocorticotropic hormone (ACTH) stimulation test or rarely insulin stimulation test (ITT) can be done to assess adrenal insufficiency.

Treatment:

- Acute adrenal crisis is not common in these patients, and hence steroids should not be used routinely to cover asymptomatic individuals. Glucocorticoids can be used in acute stressful conditions.[9]

Thyroid

Primary hypothyroidism is present in 4–29% of patients with TDT and is much common than central or secondary hypothyroidism.[10] Prevalence of hypothyroidism is directly proportional to iron load. With the increase in serum ferritin the prevalence of hypothyroidism increases. Also hypothyroidism is more frequent in splenectomized patients than non-splenectomized patients. The reason may be because of the fact that intact spleen acts as reservoir of excess iron and functions as a scavenger for free iron fraction.

Classification of hypothyroidism:

- *Sub-biochemical hypothyroidism:* The response to TRH test is exaggerated and TSH and FT4 are normal.
- *Subclinical hypothyroidism:* The TSH is high (>4.2 mIU/L and <10 mIU/L) and FT4 levels is normal.
- *Overt (clinical) hypothyroidism:* The TSH is high (TSH >10 mIU/L) and FT4 is low.

Investigations:

- Assessment of serum-free T4 and TSH should be done annually from the age of 9 or earlier if hypothyroidism is suspected. For early diagnosis, TRH stimulation test can be used. In patients with iron overload, there is exaggerated TSH response to TRH, which may evolve into subclinical or clinical hypothyroidism. In clinical hypothyroidism, there are the FT4 and basal TSH gradually decrease over time.

Treatment:

- Early detection and adequate chelation therapy may reverse the thyroid dysfunction. Patients with overt hypothyroidism are treated with L-thyroxine.

Hypoparathyroidism

It is an uncommon and a late complication in TM patients. Deposition of iron in parathyroid glands results in hypoparathyroidism. Hypocalcemia and paraesthesia occur in mild cases and severe cases may present with tetany and seizures.

Investigations:

- Measurement of calcium, phosphate and parathyroid hormone (PTH) levels should be done. In hypoparathyroidism there is low serum calcium, high phosphate, and low PTH levels.

Treatment:

- Supplementation with calcium and vitamin D is done. Calcitriol 0.25 μg twice daily brings the calcium and phosphate levels to normal. In some patients with high phosphate levels, phosphate binders may be used. In severe hypocalcemia, tetany, and cardiac failure, intravenous calcium has to be given.

Thalassemia Bone Disease

Patients with thalassemia can suffer from bone diseases, which include osteopenia, osteoporosis, bone deformity and fractures.[11] Risk factor for bone disease in these patients includes concurrent presence of hypogonadism and deficient growth hormone. Other contributory factors include chronic anemia and marrow expansion, chelator toxicity, hypercalciuria, and renal dysfunction from deferasirox, liver disease, and advancing age.

Investigations:

- Serum calcium, serum phosphorus, alkaline phosphatase, and 25-hydroxy vitamin D
- PTH, LH, FSH, testosterone levels
- Osteocalcin
- C-terminal telopeptide
- 24-h urinary calcium
- X-ray of spine (AP and lateral views)
- MRI spine: to exclude an intervertebral disc degeneration
- Dual-energy X-ray absorptiometry (DEXA) scan for assessing bone mineral density (BMD)

Treatment:

- Treatment with calcium and vitamin D can be started although there is not much evidence of improvement in BMD.
- Bisphosphonates like zoledronic acid have the advantage of intravenous administration and longer duration of action lasting more than 12 months and should be initiated earlier.
- Other drugs helpful in bone disease include teriparatide, denosumab, and zinc.

Glucose Intolerance and Diabetes Mellitus

Patients with thalassemia are susceptible to develop diabetes. The etiology is multifactorial including genetic predisposition, β-cell destruction because of iron overload, insulin resistance, insulin deficiency, chronic liver disease, and viral infections. Initially patients may present with impaired glucose tolerance because of insulin resistance and later develop insulin deficiency. Some characteristics of insulin dependent diabetes in thalassemics are:

- Ketoacidosis is an uncommon presentation
- Islet cell antibodies are usually negative
- HLA haplotypes like DR4, B8-DR3, and BW15 have no association

Investigations:

- Fasting blood sugar levels, 2-h oral glucose tolerance testing (OGTT) and measurement of insulin levels should be started at the age of 10 years. HbA1c is altered in hemoglobinopathy and cannot be used as a reliable marker for monitoring. Instead serum fructosamine levels may be used for monitoring long term glycemic control.

Treatment:

- Dietary counseling and weight reduction in metabolically obese patients.
- Chelation therapy should be more intensive. There is increase in insulin secretion and decrease in insulin resistance with intensive chelation therapy.
- Data on use of oral antidiabetic drugs is limited. Insulin is needed in late presentation and complications.

Conclusion

The management in thalassemia requires a team effort and a multidisciplinary involvement. Management of TDT mainly depends on lifelong transfusion therapy. The complications arise because of the iron deposition in various organs and infections from frequent blood transfusions. It has been proven in studies that early initiation of chelation therapy can reverse

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the process of iron deposition in tissues and salvage or prolong the development of complications. Pregnancy, fertility, and psychosomatic stress are other associated issues in managing patients of thalassemia and require treatment for enhancing quality of life in these patients.

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CHAPTER

228

Approach to Thrombocytopenia

Avinash Kumar Singh, Divya Krishna, Gautam Kumar Rakesh, Bhupendra Kumar

Abstract

Thrombocytopenia is a common medical problem encountered by physicians in their day-to-day OPD as well as IPD practice. Anxiety is at peak for patients as well as young physicians when dealing with case of severe thrombocytopenia. Thorough history, physical examination, and directed investigations lead to correct cause and resolution of thrombocytopenia. Causes range from benign disease like ITP and megaloblastic anemia to serious diseases like leukemia, lymphoma, and TTP. Drugs are culprit in many cases and sometimes misleading drug history leads to unnecessary battery of tests. Once properly diagnosed, correct and timely treatment can resolve thrombocytopenia. Platelet transfusion is not always required and should be reserved for severe thrombocytopenia or with bleeding patients.

Introduction

By the time you shall be reading this chapter, we hope that world will be on the path of recovery from COVID pandemic crisis and message like "stay safe" will be less frequently used.

Thrombocytopenia is a common medical problem encountered by physicians in day-to-day practice. It creates panic among general people as well as practicing physicians, which is not always justified.

We will describe how to approach a case of thrombocytopenia with brief about treatment options of common diseases.

Thrombocytopenia is defined as a platelet count below the 2.5th lower percentile of the normal platelet count distribution. Results of the third US National Health and Nutrition Examination support the traditional value of 150×10^9/L as the lower limit of normal; however, counts between 100×10^9/L and 150×10^9/L do not necessarily indicate disease if they have been stable for more than 6 months, and the adoption of a cut-off value of 100×10^9/L may be more appropriate to identify a pathologic condition.[1-3]

Low Platelets—How Serious It is?

Platelets play an important role in vessel wall integrity and so low platelet leads to primary hemostatic defects. Its relevance in an individual patient is variable and depends upon the clinical presentation.

Clinically significant bleeding does not occur unless platelets are less than $10–20,000 \times 10^9$/L, while mild to moderate thrombocytopenia becomes significant when there is additional bleeding risk like surgery, trauma or when higher cut-off to be met as when treatment for hepatitis C or chemotherapy is indicated.

In some situation, finding of thrombocytopenia points toward serious disease like HIV or Myelodysplastic syndrome and also sometimes it indicates disease activity like in thrombotic thrombocytopenic purpura (TTP).

How Important is Setting of Thrombocytopenia?

In OPD settings, mostly thrombocytopenia is isolated and asymptomatic and diagnosis is straight forward while in inpatient, or in ICU settings, multisystem

TABLE 1 Clinical scenario and most common causes of thrombocytopenia

Outpatient	*Inpatient*		
ITP	***Multisystem illness/ICU***	***Cardiac***	***Pregnancy/Postpartum***
DITP	Infections	HIT	GT
Infections: HIV, Hep C, CMV, H. Pylori, Dengue, and other recent viral infection	DITP	Cardiac bypass	ITP
Connective tissue disorder	TTP/HUS	GP IIB/IIIA inhibitors	HELPP syndrome
Vaccinations	DIC	DITP	Pre-eclampsia
Congenital thrombocytopenia	Liver disease/BM disorders	Dilutional	TTP/HUS
Common variable immunodeficiency disease	HIT		
MDS	MAS		
	CIT		

CIT, chemotherapy-induced thrombocytopenia; DITP, drug-induced ITP; MAS, macrophage activation syndrome; MDS, myelodysplastic syndrome.

involvement leads to thrombocytopenia and diagnosis and management is sometimes challenging **(Table 1)**. Pregnancy with thrombocytopenia has to be approached differently as it has significance in the care for mother as well as the newborn.

A structured approach involves clinical details and support of lab along with other medical disciplines.

Mechanism of Thrombocytopenia

Major mechanism of thrombocytopenia is reduced production as in aplastic anemia, Myelodysplastic syndrome (MDS), or chemotherapy induced thrombocytopenia and platelet destruction as in disseminated intravascular coagulation (DIC) or TTP.

Less common mechanism is platelet sequestration as in congestive splenomegaly and hemodilution as in excessive fluid or platelet poor component transfusion.

There are conditions like ITP and hepatitis C, where multiple mechanisms play role.

History and Physical Examination—How does it Help in Evaluation?

As for any medical disorder history is very important for thrombocytopenia evaluation and question should be directed toward bleeding history, associated symptoms like fever, jaundice, joint pain, medication history, dietary habits, addiction and history to rule out autoimmune disease and malignancy.

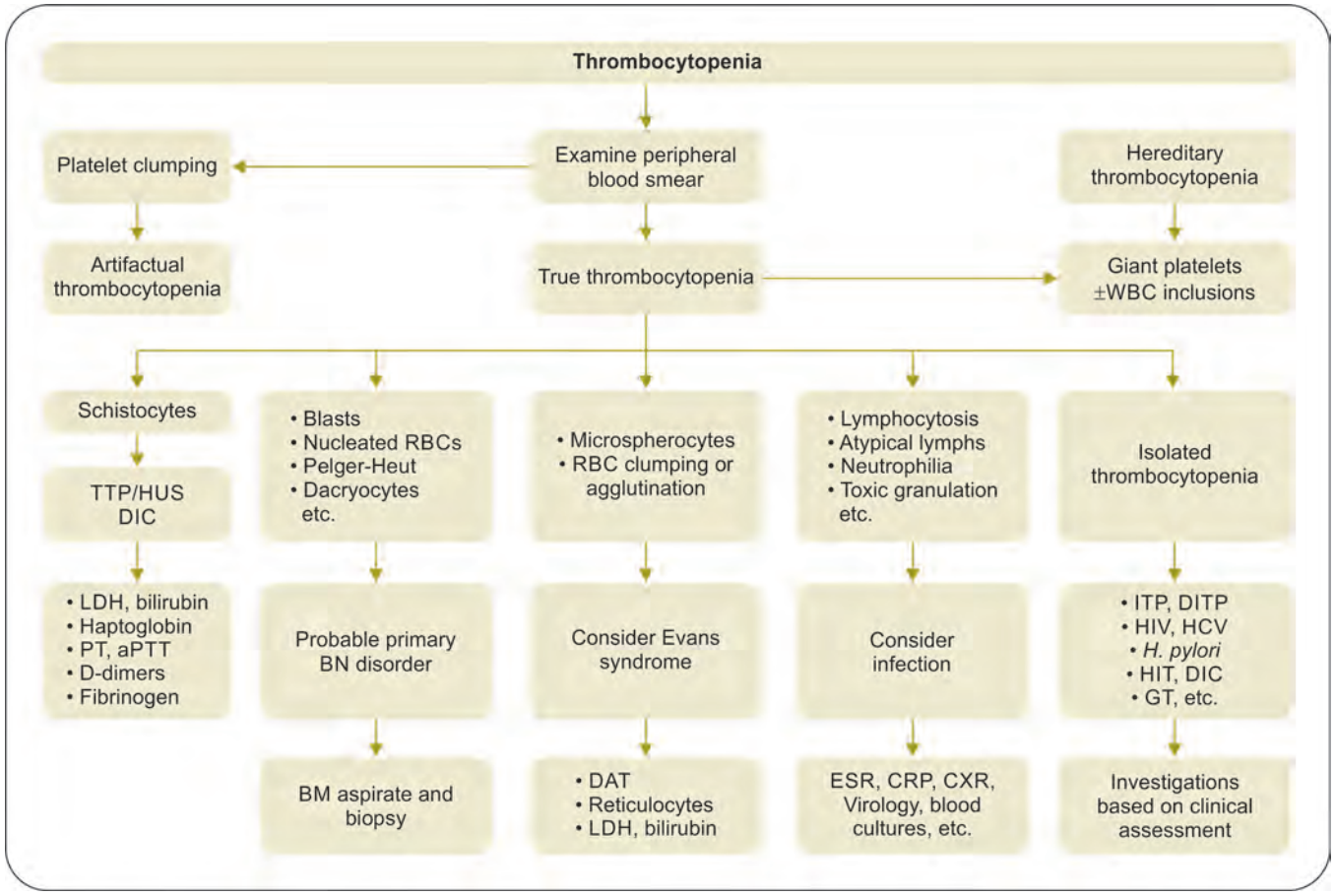
Physical examination should be directed to look for bleeding, organomegaly, or skeletal abnormality.

Lab Investigations—What Battery of Tests Required?

Even today, initial and basic investigation for thrombocytopenia evaluation is complete blood count (CBC) and peripheral smear. Routine tests, like liver function and renal function test, are always required. Chest X-ray is required to look for focus of infection and mediastinal mass and USG abdomen is done to look for any evidence of chronic liver disease or lymphadenopathy. Autoimmune workup is required in suspected cases to rule out SLE/APLA syndrome. Infective workup is required in patients who present with classical features. Immature platelet fraction or reticulated platelets help in differentiation from bone marrow failure (low percentage) and hyper-destructive thrombocytopenia (higher percentage).[5,6] **Flowchart 1** shows algorithm for thrombocytopenia on the basis of peripheral blood smear findings.[7]

Artefactual thrombocytopenia and conditions like Harris platelet syndrome are not so rare problem encountered in our clinical practice and it has huge psychological impact on the patient, their immediate care giver, and physicians.[8] They need only counseling that they should not worry and need no intervention. We will discuss common conditions leading to thrombocytopenia in our practice.

Flowchart 1: Algorithm for the workup of thrombocytopenia based on peripheral blood smear finding



Isolated Thrombocytopenia

It is defined as thrombocytopenia in the absence of RBC or WBC abnormality and without signs or symptoms of systemic illness. Common examples are ITP and D-ITP.

Immune Thrombocytopenia (ITP)

(terms idiopathic and pupura have been removed)

Even being the commonest cause of isolated thrombocytopenia, there is no single test, which confirms ITP as diagnosis and it remains a diagnosis of exclusion. **Box 1** lists all blood investigations in a suspected case of ITP. Antiplatelet antibody assay is not very sensitive, but specificity approaches 90%. **Table 2** enumerates morphologic features and pointers towards different causes of thrombocytopenia. Bone marrow is not required unless patients are more than 60 years or with atypical features.

BOX 1 List of basic tests required as per international consensus report[4]

- Complete blood count
- Peripheral blood smear
- Reticulocyte count
- Quantitative Ig level measurement
- BM examination (in patients >60 years)
- Blood group (Rh)
- Direct antiglobulin test
- *H. pylori*
- HIV
- HCV

ITP patients are divided into newly diagnosed (thrombocytopenia is of less than 3 months duration), persistent (thrombocytopenia extends from 3 months to

TABLE 2 Showing morphological findings on PBS in different causes of thrombocytopenia

Platelets
• Platelet clumping – Platelet clumping caused by EDTA-dependent platelet autoantibodies is a common cause of artifactual thrombocytopenia. It occurs in about 1 in 1000 nomral adults and is not associated with bleeding or thrombosis
• Platelet size and granularity – Consistently large platelets suggest hereditary macrothrombocytopenia. Large platelets with a gray color on Wright-Giemsa stain define the gray platelet syndrome, an autosomal-dominant macrothrombocytopenia associated with bleeding tendency due to absent or greatly reduced α-granules – In thrombocytopenia due to peripheral destruction, large platelets or giant platelets are often seen in addition to platelets of normal size – When thrombocytopenia is due to reduced platelet production (e.g., after chemotherapy), platelets are of normal size. In myelodysplasitc syndromes, platelets have variable size (giant platelets may be seen) and are frequently hypogranular. In Wiskott-Aldrish syndrome, and X-linked thrombocytopenia, both cuased by mutations of the WAS gene, platelets are smale
WBCs
• Leukemic cells – Malignant hematological disorders (leukemias and lymphomas) are often associated with thrombocytopenia, which is almost never an isolated finding – Other abnormalities of WBCs, including leukocyte inclusions ♦ A constellation of nonspecific abnormalities of WBCs are common to many conditions (e.g., neutrophilia, lymphocytosis, leukopenia, etc.) and may be associated with thrombocytopenia. The presence of hypolobulated neutrophilis (Pelger-Huet anomaly) suggests a myelodysplastic syndrome. Dark coarse granules (toxic granulations) found in neutrophils suggest sepsis. Atypical lymphocytes suggest viral infection. The presence of WBC inclusion (Dohle-like bodies) should be investigated carefully when platelets are mostly large (MYH9-related congenital macrothrombocytopenia)
RBCs
• Schistocytes – The presence of RBC fragments known as schistocytes is indicative of a thrombotic microangiopathy (TTP/HUS) or DIC
• Size and other morphological features. – Microspherocytes may suggest Evans syndrome, but may also be present along with chistocytes in thrombotic microangiopathies. Macrocytosis (and hypersegmentation of neutrophils) suggest vitamin B12 or folate deficiency. Dacryocytes (teardrop-shaped cells) suggest myelofibrosis. Nucleated RBSc suggest hemolytic anemia, myelofibrosis, or an inflitrative process of the BM
• Parasites – The presence of intracellular parasites (e.g., in malaria) is diagnostic of infection

12 months), and chronic when thrombocytopenia is for more than 1 year.

In ITP patients with emergency (intracranial bleed, massive GI bleed) IVIG, High dose methylprednisolone, and anti D (in Rh positive patients) are options.

For asymptomatic or patients with minor bleeding, observation and local bleeding control are best options, as most of the morbidity in ITP patients are due to treatment than due to low platelet count. Good counseling can reduce need of drugs and give better quality of life to patients. It is important to explain to patients that even with very low platelets, severe or life threatening bleeding is rare in ITP.

Options in symptomatic patients are steroid (short course), immunosuppressants (azathioprine, MMF), Dapsone, MAB (rituximab), Thrombopoietin mimetic (wltrombopag, romiplostim), and splenectomy. Other less commonly used options are danogen, vincristine, cyclosporine, and cyclophosphamide.

Drug-induced Immune Thrombocytopenia (D-ITP)

The list of drugs leading to thrombocytopenia is ever increasing one. The pathophysiological mechanism of D-ITP is due to formation drug dependent antibody against epitope of platelet glycoprotein created by their interaction with the drug.

Sometimes D-ITP can be confused with ITP, and only good history can help to differentiate.

Diagnosis often is difficult as sometimes not only drug but even food and beverages can lead to thrombocytopenia.

Diagnosis is mostly empirical with recovery of platelet count after discontinuation of drug. Lab diagnosis is by demonstration of drug dependent antibody by various methods.

An overall score of 5 or more is compatible with overt DIC. A score less than 5 is suggestive of non-overt/low-grade DIC.

Thrombocytopenia in Hospitalized Settings

Approximately 1% of admitted patients in acute care hospital are thrombocytopenia but only 30% of them have bleeding manifestation.[9] As expected it is more common in ICU, where 8–68% are thrombocytopenic on admission and 13–44% during stay in the unit.[10] Many potential etiologies like sepsis, DIC, drugs, CABG coexist and it is often difficult to elucidate cause of thrombocytopenia ITP should always be considered as it is seen in about 20% of these and antibiotics are the major culprit.[11,12] Discontinuation of such drug should always be based on clinical criteria.[13]

Disseminated Intravascular Coagulation

DIC is a consumptive coagulopathy characterized by activation of intravascular coagulation with microvascular thrombi formation, thrombocytopenia, depletion of clotting factors, bleeding complications, and end organ damage. It can be acute or chronic. International society on thrombosis and hemostasis divides DIC into overt (decompensated hemostatic system) or non-overt (compensated coagulopathy).[14]

Acute DIC is seen in sepsis, septic shock, after trauma (neurotrauma), after surgery, after obstetric complications and in APML. Chronic DIC is seen in solid tumors and large aortic aneurysm. **Table 3** enumerates factors and scoring to diagnose overt or non-overt DIC.

Thrombocytopenia in Cardiac Patients

Open heart surgery is an important cause of thrombocytopenia in cardiac patients. Nadir is typically seen on days 2–3 and recovery starts rapidly thereafter. Causes of low platelet after surgery are multiple.

Severe thrombocytopenia has been observed in 0.1–2% of patients after exposure to gp IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide). Peculiarity is sudden onset, usually within hours after surgery, and used to resolve by day 10. This has been attributed to presence of naturally occurring antibody to neoepitopes exposed by gp IIb/IIIa inhibitors.[15]

HIT—It occurs in 1–3% of patients receiving heparin beyond the first postoperative week and in 10% of patients after ventricular assist device implantation.[16,17] 4T described in **Table 4** helps in diagnosis of heparin induced thrombocytopenia.[18]

Pregnancy with Thrombocytopenia

About 6–15% of women develop thrombocytopenia (<1.5 lakhs/mm^3) at the end of pregnancy but platelets less than 1 lakh/mm^3 are seen in only 1% of patients. Most common cause of thrombocytopenia is gestational thrombocytopenia (GT) (70%), preeclampsia (21%) ITP (3%).[19,20]

Gestational Thrombocytopenia (GT)

GT is seen in mid second to third trimester of pregnancy and it is extreme variation of normal physiological fall of platelet count. Platelet count usually remains above 70 k/mm^3 and if falls to lower than 70 k, then alternative diagnosis should be considered. Diagnosis is

TABLE 3 Diagnostic score of DIC

Parameters	*0*	*1*	*2*	*3*
Platelet count	>100 × 10^9	50–100 ×10^9	<50 × 10^9	
Elevated fibrin degradation products	No increase		Moderately increase	Strong increase
PT more than ULN	<3S	>3S	>6S	
Fibrinogen	>1 gm/L	<1 gm/L		

TABLE 4 The 4Ts pretest probability of heparin-induced thrombocytopenia

	*Points**		
4Ts	***2***	***1***	***0***
Thrombocytopenia	Platelet count decrease >50% and platelet nadir >20 × 10^9/L	Platelet count decrease 30–50% or platelet nadir >10–19 × 10^9/L	Platelet count decrease <30% or platelet nadir <10–19 × 10^9/L
Timing of platelet count decrease	Clear onset between d 5 and 10 or platelet decreases ≤1 d (prior heparin exposure within 30 d)	Consistent with d 5–10 decrease, but not clear (e.g., missing platelet counts); onset after d 10; or decreases ≤1 d (prior heparin exposure 30–100 d ago)	Platelet count decrease <4 d without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post intravenous	Progressive or recurrent thrombosis; non-necrotizing erythematous) skin lesion; Suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Pretest probability socre: 6–8, high; 4–5, intermediate; 0–3 low.
*0, 1, or 2 for each category with a maximum possible score of 8.

by excluding other causes and there may similar history of thrombocytopenia in previous pregnancy and fetus/newborn remains unaffected (normal platelet) and recovery takes 1–2 months after delivery.

ITP in Pregnancy

ITP in pregnancy is seen in about 1–2 of 1,000 pregnancies. It is the most common cause of thrombocytopenia in first and early second trimester. One third of patients are diagnosed first time during pregnancies and rest has history of ITP.

Differentiating GT from ITP is difficult and it is more important for neonatal management as 9–15% of neonates of ITP mother can have thrombocytopenia and 1–2% can have intracranial hemorrhage.[21]

Whenever platelet is less than 50 k/mm^3, diagnosis is ITP by default, though as in medicine always it should be correlated in clinical context.

COVID-19 and Thrombocytopenia

SARS-CoV-2 leading to present COVID-19 pandemic present commonly with fever, cough, and breathlessness. Common abnormality in hematological parameters includes leukopenia, lymphocytopenia, and thrombocytopenia. Thrombocytopenia is seen in about 5% of patients at admission and overall about 36% of patients showed thrombocytopenia, most of which are significant in severe cases. The proposed mechanism is multifactorial due to cytokine storm, direct hematopoietic stem cell injury, increased autoimmune destruction and lung injury.[22-25]

Bleeding due to thrombocytopenia is rarely seen.

What are the Indications, Dosing of Platelet Transfusion?

- Any patient with bleeding due to thrombocytopenia or severe thrombocytopenia (less than 30 k/mm^3 even without bleeding) or patient with moderate thrombocytopenia (30 k to 1 lakh/mm^3) and due for surgery or has other associated bleeding risk need platelet transfusion.
- Higher threshold (more than 1 lakh/mm^3) is required for patients with life threatening bleeding (ICH) or planned for neurosurgery or ophthalmic surgery.
- Exact cut-off depends upon primary disease leading to thrombocytopenia.
- In aplastic anemia and acute leukemia, platelet transfusion should be done when platelet count is less than 10 k/mm^3 without fever and less than 20 k with fever, for APML threshold is higher due to excess bleeding risk.
- Disease like TTP and HIT are conditions where platelet transfusion is always avoided and common disease like ITP rarely needs platelet transfusion.
- Physicians should think twice before ordering for platelet transfusion in asymptomatic thrombocytopenia patients.

- Dose for adult patient is single donor platelet or 6 unit random donor platelet (1 RDP per 10 kg). One SDP leads to increase of platelet by 40–50 k and RDP increase platelet by 5–10 k unless reasons for platelet refractoriness are absent.

Conclusion

Thrombocytopenia is a common problem encountered by physicians in day-to-day in IPD as well as OPD practice. Common causes are ITP, D-ITP, and infections. Good history, physical examination, and directed investigations can lead to correct diagnosis of thrombocytopenia.

Delay in diagnosis and blind treatment leads to unnecessary intervention in many patients, which should always be discouraged. Platelet transfusion is required in emergency cases and should not be misused, just to overcome fear and anxiety of low platelet.

We thank our patients for having faith on us and giving us opportunity to understand "thrombocytopenia" and all supporting staff including nurses who help us in patient management.

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CHAPTER

229 Management of CML in Resource-limited Settings

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Abstract

After the development, testing and global availability of BCR/ABL targeted tyrosine kinase inhibitors (TKIs), the prognosis of patients with CML in the chronic phase has improved to point that the majority of patients can expect a multi-decade survival which is now close to that of age and sex matched subjects without the disease, at least in the developed world. However, the situation in the low- and middle-income countries (LMIC), like India, may not be as encouraging. Many hematological cancers in developing countries, including CML, have subtle and not so subtle differences in incidence, age of onset, stage at presentation, phenotype, stage-for-stage response rates, and prognosis as compared to their counterparts in the developed world. Several reasons have been postulated for this and these include; socioeconomic factors, genetic differences, environmental factors (infections, particularly, viral infections, exposure to pesticides, etc.), nutritional factors and factors related to availability of drugs, means for monitoring the disease and option for the use of second generation agents. Generic first generation TKIs (imatinib) and also second generation ones are available in many parts of the world but several challenges still remain in providing optimal treatment to the patients with CML in resource-poor countries. These include availability of optimal and high-quality BCR/ABL testing, availability and cost of second and third generation TKIs (nilotinib, dasatinib, bosutinib, and ponatinib) and hematopoietic stem cell transplantation, compliance and toxicities of drugs and ensuring minimal standard-of-care treatment and monitoring for each and every patient diagnosed with CML. Some of these issues will be reviewed and highlighted in this article.

Introduction

Chronic myeloid leukemia (CML) is a clonal hematopoietic disorder of a pluripotent stem cell that leads to increased proliferation of cells of the myeloid lineage. Its hallmark is the presence of reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11), which brings the BCR (breakpoint cluster region) gene into proximity to the ABL1 (Abelson murine leukemia viral oncogene homolog 1) gene, forming a new fusion chimeric gene—BCR-ABL1—which is the oncogene responsible for the pathogenesis of the disease.[1] The truncated chromosome so formed is termed the Philadelphia chromosome, owing its name to the city where it was first described.[2]

Our understanding of the pathophysiology of this disease led to the development of targeted therapies in the form of tyrosine kinase inhibitors, which have a specific action to inhibit the BCR-ABL1 fusion oncogene. The agents were rightly dubbed "magic bullets" and revolutionized the practice of oncology. They have led to a paradigm shift in the management of CML, and now most patients with newly diagnosed disease can look forward to a multi-decade survival as opposed to the 4–5 years survival in old times.

In this chapter we have discussed the practical aspects of usage of these agents with special focus on optimum use in a setting of resource constraints.

Clinical Features, Diagnosis, and Risk Stratification

A significant proportion of patients are nowadays detected in asymptomatic stage with incidentally detected leukocytosis. Patients in more advanced stages of the disease present with signs and symptoms of gross splenomegaly (abdominal fullness and discomfort with feeling of early satiety), symptomatic anemia, and constitutional symptoms like fever, fatigue, or weight loss. Hemogram shows leukocytosis, which may be accompanied with thrombocytosis and/or anemia. The differential leukocyte count shows prominence of immature precursors of the granulocytic series, like myelocytes and metamyelocytes. Circulating blasts are also seen. Basophilia is a consistent feature. The absolute eosinophil and monocyte counts are usually increased, although the percentages are not elevated. Small numbers of nucleated red blood cells and mild reticulocytosis may be seen. Clinical chemistry may reveal hyperuricemia and hyperuricosuria, elevated serum lactate dehydrogenase (LDH), increased serum vitamin B12-binding capacity, and increased serum B12 levels. Low or absent neutrophil alkaline phosphatase activity is seen in 90% of patients.

Bone marrow (BM) examination usually shows marrow hypercellularity up to 75–90% with marked increase in myeloid precursors. Blasts usually represent less than 5% of cells in CP CML. Presence of more than 10% blasts indicate transformation to AP. Megakaryocytes may be hypolobated and typically dwarf forms are seen.

The definitive diagnosis of CML is established by demonstrating the presence of the characteristic translocation and its resultant transcript. This can be done by conventional cytogenetics, fluorescence in situ hybridization (FISH) or by polymerase chain reaction (PCR).

The disease has a triphasic clinical course through chronic phase (CP), accelerated phase (AP), and blast phase (BP).[1] Without treatment, the disease inevitably progresses from CP to AP/BP, which have high morbidity and mortality. Risk stratification helps in predicting survival and it can be done using the Sokal score[2] or ELTS score.[3]

Treatment

The standard goals of therapy were relief of symptoms and prevention of progression of the disease. The classical understanding was that treatment has to be continued lifelong for continued suppression of the BCR-ABL1 transcript. But with tyrosine kinase inhibitors (TKIs), we have managed to achieve such deep suppression of the disease activity that it is possible in a certain cohort of patients to discontinue TKI after a few years and attain a state of treatment-free remission (TFR) and in fact, TFR has now become one of the standard goals of therapy.[4,5]

Tyrosine Kinase Inhibitors

TKIs are orally administered agents, which act by binding to the ATP binding site in the BCR-ABL1 protein and inhibit its kinase activity. These agents are able to provide much deeper and sustained responses and can provide near normal life expectancy in a large proportion of patients. Imatinib was the first TKI approved for the use in CML after showing markedly better results than the previous standard therapy of interferon plus low dose cytarabine in the pivotal IRIS trial.[6] Acquired mutations in the kinase domain can render imatinib ineffective in certain proportion of cases. Second generation TKIs, which include nilotinib, dasatinib, and bosutinib, can be effective in such a setting. These agents are also approved as first line agents where they have demonstrated superior activity than imatinib with respect to rapidity and depth of response, although survival outcomes are similar (ENESTnd,[7] DASISION,[8] and BFORE[9] trials). The T315I is a unique mutation that renders the disease resistant to all four of these TKIs. The 3rd generation TKI ponatinib is effective in such cases.[10] These TKIs are summarized in **Table 1**.

Monitoring Response to Therapy

Initiation of therapy leads to resolution of symptoms, splenomegaly, and normalization of blood counts. Complete blood count (CBC) needs to be monitored every 2 weeks till a state of complete hematological response is noted. Subsequent depth of response is monitored using techniques that detect the characteristic chromosomal translocation using karyotyping or FISH or by detecting the BCR-ABL1 transcript using PCR. Monitoring using PCR based assays is the current gold standard as it allows for detection of minute quantities of the transcript, and hence responses can be monitored to a degree of depth, which is not possible by any of the other techniques.

There can be dramatic variations in the absolute transcript value across laboratories and standardization

TABLE 1 Tyrosine kinase inhibitors for CML

Generation	***Imatinib***	***Nilotinib***	***Dasatinib***	***Bosutinib***	***Ponatinib****
	1st	***2nd***	***2nd***	***2nd***	***3rd***
Dose (1st line/ 2nd line)	400 mg OD	300 mg BD/400 mg BD	100 mg OD/70 mg BD	400 mg OD/500 mg OD	45 mg OD (May initiate at lower dose)
Adverse effects	• Myelosuppression • GI intolerance • Fatigue • Edema • Skin changes • Muscle cramps	• Myelosuppression • Hyperglycemia • Hepatotoxicity • Cardiotoxicity • Pancreatitis	• Myelosuppression • Pleural effusion • Pulmonary hypertension	• Diarrhea • Myelosuppression • Raised ALT	• Thrombotic events • Hypertension • Arrhythmias
Sensitive kinase domain mutations	None	F317L/V/I/C, T315A, V299L	Y253H, E255V/K, F359V/I/C	F317L/V/I/C, T315A, Y253H, F359V/I/C	All mutations including T315I

*Not available in India at the time of writing.

TABLE 2 Response definitions

Test	***Frequency of monitoring***	***Definition of response***
Clinical examination and complete blood counts	Every 15 days until CHR, then every 3 monthly unless otherwise required	Complete hematological response: • Platelets ≤450 × 10^9/L • WBC count ≤10 × 10^9/L • Differential without immature granulocytes and with ≤5% basophils and • Non-palpable spleen
BCR-ABL1 quantitative PCR (ratio of transcript/ housekeeping gene expressed on IS)	Three monthly	• Major Molecular Response (MMR): ≤0.1% • MR^4: ≤0.01% • $MR^{4.5}$: ≤0.0032% • MR^5: ≤0.001% • Deep molecular response (DMR)—MR^4 or deeper • Molecularly undetectable leukemia—Undetectable BCR-ABL1 mRNA transcripts
Cytogenetics (chromosome banding analysis of bone marrow metaphase cells)	Alone not sufficient for monitoring To be done in patients with atypical translocations, atypical transcripts of BCR-ABL1 not quantifiable by PCR, at failure or progression to document ACA	• Complete (CCyR): No Ph^+ chromosome • Partial (PCyR): 1–35% Ph^+ metaphase • Minor (mCyR): 36–65% Ph^+ metaphase

techniques are employed in order to homogenize the results. The BCR-ABL1 transcript value is described as a ratio of the transcript value to that of a housekeeping gene like ABL1 or GUSB. This ratio is further converted to the International scale (IS). The baseline 100% was defined as the median transcript value measured in 30 pooled samples of patients of newly diagnosed CML CP enrolled in the IRIS trial. Reference materials were generated using this pool of samples and laboratories can use this to generate specific conversion factors to convert their results into IS values.[11] The results are defined on a log scale; 1%, 0.1%, 0.001%, 0.0032%, and 0.0001% correspond to 2, 3, 4, 4.5, and 5 log reductions respectively from the baseline value of the IRIS trial. BCR-ABL1 quantitative PCR is recommended to be performed every 3 months.[5] The standard response definitions are described in **Table 2**.

Effective therapy leads to progressive decline in the BCR-ABL1 IS and target values at different timepoints are defined in order to ascertain the efficacy of treatment. The

TABLE 3 Molecular targets of treatment (BCR-ABL1 IS values)

	Optimal	*Warning*	*Failure*
Baseline	NA	High risk ACA, high risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Anytime	≤0.1%	>0.1–1% Loss of MMR	>1%, resistance mutations, high risk ACA

molecular timepoints as per the European LeukemiaNet 2020 guidelines are described in **Table 3**.[5] In case of suboptimal response or failure of therapy there is a need to determine if any mutations are present in the kinase domain. Detection of these mutations serves as a guide for choosing the most optimum second line therapy. Mutation analysis was conventionally done using Sanger sequencing but Next-generation sequencing has proved to be more sensitive and has become the recommended technique.[12]

Imatinib was the first TKI to be approved for use in CML based on the results of the IRIS trial. The starting dose is 400 mg once a day but higher doses of 600 mg and 800 mg have also been tried. The second generation TKIs were compared with imatinib as the frontline agent in newly diagnosed CML CP in various trials and were found to induce faster and deeper responses as compared to imatinib, but there was no significant superiority in progression-free and overall survivals in any of these studies. No head-to-head comparison is available for any of the 2G-TKIs. Hence, the choice of frontline TKI depends on a combination of various factors including risk stratification, cost, availability, adverse effect profile, comorbidities, and individual preferences of the physician and the patient. The choice of agent for second line use also depends on similar factors but also take into account mutation status.

Treatment of patients with failure of two previous TKIs is not so straightforward. Allogeneic stem cell transplant should be considered in this setting. TKIs (2G and 3G) can be used but responses are seldom durable. If effective, TKIs can be used as an effective bridge to transplant.

Advanced phase CML (AP and BP) can present either de novo or as progression from CP. TKIs are effective in TKI-naïve patients with de novo AP. Imatinib at higher dose of 600 mg or any of the 2G TKIs may be considered in this setting. Patients with AP who have additional cytogenetic abnormalities or who have progressed after TKI failure respond poorly with second line TKIs and allogeneic stem cell transplant should be considered. CML BP can be either myeloid-type or lymphoblastic-type and this should be determined by immunophenotyping. The outcomes of CML BP remain poor and the only modality that can provide long-term cure in setting of BP is allogeneic stem cell transplant. Patients are usually treated with TKI along with acute myeloid leukemia (AML)-like or acute lymphocytic leukemia (ALL)-like chemotherapy to bring the disease into chronic phase or hematological remission prior to proceeding with transplant.

When TKIs were first introduced two decades ago it was thought that they have converted CML into a chronic disease with near normal life expectancy and lifelong treatment. But long-term experience with TKIs showed that it is possible to go even a step further. These drugs are able to achieve sustained deep molecular responses when used over a period of few years and it is possible to discontinue the drug in selected patients, providing them with the equivalent of a "cure." This concept of TFR was initially explored with the use of the older agent interferon.[13] The STIM1[14] and TWISTER[15] trials demonstrated that TFR can be achieved in patients on long-term imatinib. Subsequently a large number of trials have been done with both first line and second line TKIs demonstrating the utility and feasibility of TFR.[16] Although all studies have used different criteria for patient selection, a few common criteria have emerged. Ideally the patient should be in first CP, on first line TKI for prolonged duration (5 years or more), having achieved optimal response at all milestones and having achieved a sustained deep molecular response (DMR) for 2 years or more. Patients on TFR should be motivated and have access to regular monitoring (monthly for initial 6 months, 2 monthly for next 6 months, and subsequently 3 monthly for life).[5] The success rates of TFR in almost all trials have been in the range of 40–50%.[16] Failure of TFR is considered when there is a loss of MMR. Most failures occur in the initial 6 months but thankfully nearly all patient regain MMR following reinitiation of TKI. The success of TFR has led to its incorporation as one of the standard goals of therapy.

Managing CML in Resource Poor Settings

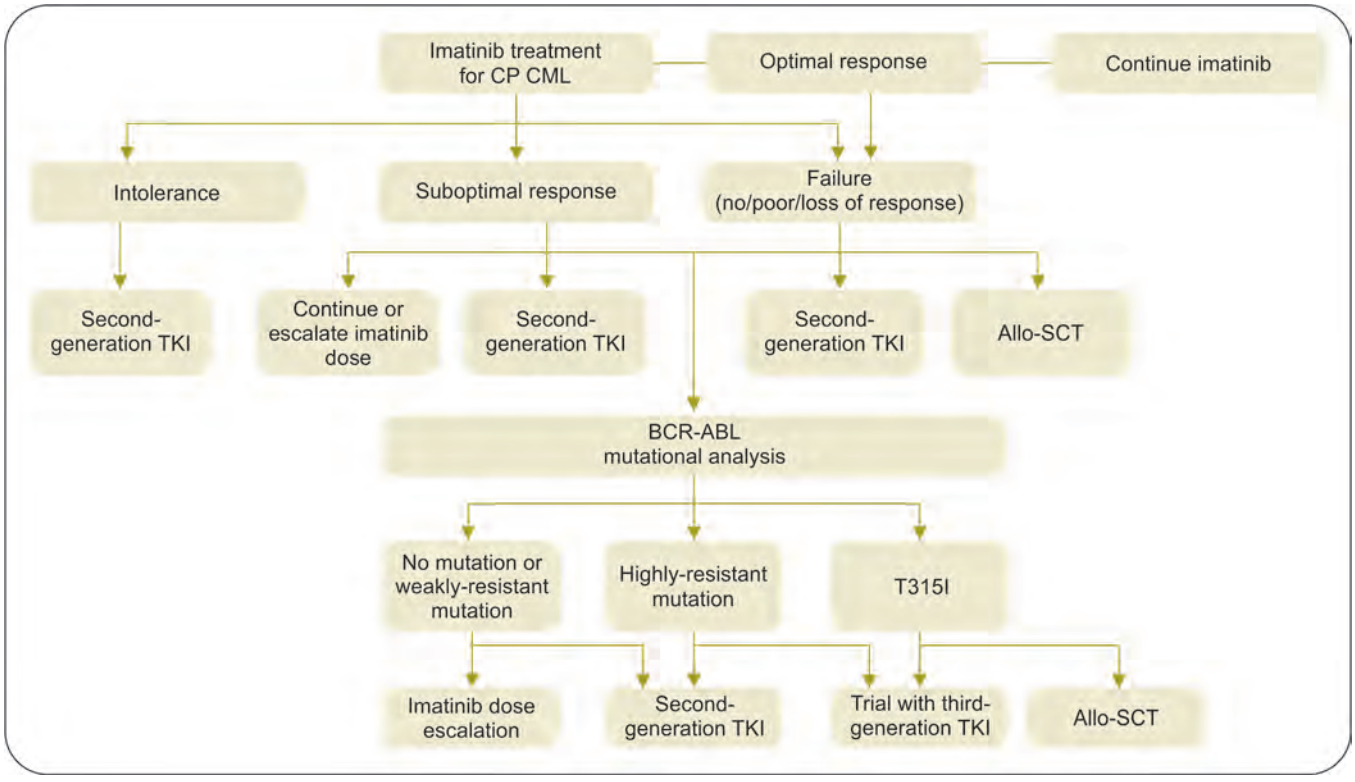
Although major advances have been made in our understanding, treatment, and monitoring of CML, these advances have not universally permeated into clinical practice, and this is particularly true for low and middle income countries. Patients and physicians in these regions of the world face unique challenges at every step of disease management. Efforts are needed to ensure that our patients are able to obtain similar benefits of treatment as those in developed nations.[17]

An algorithm for guidance in resource-limited setting is provided in **Flowchart 1**.

Specific Issues Related to CML Treatment in Resource-limited Settings

- *Delays in diagnosis:* A majority of CML patients in India are diagnosed late and have a higher disease burden and higher risk score at the time of diagnosis.[18,19] This is related to poor awareness of the disease and inadequate access to diagnostic modalities in peripheral centers. Presentation with a higher risk score leads to inferior survival outcomes.
- *Age at diagnosis:* Patients of CML in Asian countries present a decade earlier than those in the west.[20] This translates to a longer course of the disease and subsequently a longer need for TKIs and monitoring, which adds to the overall financial burden.
- *Investigations:* Molecular and cytogenetic methods for diagnosis and monitoring are not readily available in smaller cities. Even with availability, the cost of these investigations ends up posing a hindrance to their usage. The standard recommendations on the monitoring frequency (once in 3 months) are seldom, if ever, followed in India. Clinicians have to devise their own modifications to these guidelines in order to ensure that the patient remains well monitored yet not be overburdened by the cost.
- *Drugs:* The cost of imatinib at the time of launching was prohibitively expensive, but three major developments have ensured that today they are within the reach of nearly every patient who needs it. In this regard,

Flowchart 1: Algorithm for CML-CP treatment in resource-limited settings



Allo SCT, allogenic stem cell transplantation; CP CML, chronic phase CML; TKI, tyrosine kinase inhibitor

massive strides have been made in the last two decades. Firstly, the Glivec International Patient Assistance Program (GIPAP), in association with the Max Foundation, which sought to make imatinib available free of cost to patients particularly in low and middle income countries.[21] India has been the largest beneficiary of this program, and GIPAP has provided free of cost imatinib to more than 12,000 patients (25% of all GIPAP beneficiaries) from 2002 onward. The program stopped enrolling new patients in 2016. Secondly, a large number of Indian pharmaceutical companies started production of generic imatinib, which is available to patients at a much cheaper rate. Thirdly, several public funded institutions provide generic imatinib free of cost. These benefits are not restricted to imatinib alone. Nilotinib is available at a concessional cost as a part of a patient assistance program. Generic formulations of Dasatinib and Bosutinib were launched in early 2020. These have ensured that even the 2G TKIs are much more accessible to patients than what they were previously and have led to increased use of these agents both as first line and second line.

- *Adherence to treatment:* Poor adherence to treatment is a major barrier to obtaining favorable long-term outcomes.[22] Various factors non-adherence relevant to the Indian context are financial constraints, lack of social support, and poor patient awareness about the disease and treatment. Treating clinicians must pay adequate attention to addressing these issues. Adequate counseling at diagnosis and reinforcement of the same at each hospital visit is essential. Various government and non-government aid regarding provision of TKIs go a long way in ensuring uninterrupted treatment.

Conclusion

CML is a chronic myeloproliferative neoplasm characterized by t(9;22)(q34;q11) and the resultant chimeric BCR-ABL1 oncogene. Effective targeted therapy is now available in the form of TKIs, which can induce deep and prolonged molecular responses in a large number of patients. TFR has shown moderate success and has become one of the major goals of treatment. Challenges remain in low and middle income countries related to accessibility and affordability of investigations and treatment. Various governmental and non-governmental schemes along with availability of generic medications have gone a long way in ensuring our goal of providing treatment for all.

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CHAPTER

230 Disability-free Hemophilia in India—Myth or Reality

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Abstract

Hemophilia is a rare X-linked genetic disorder where a patient bleeds because of lack of clotting factors essential for coagulation. Based on the type of clotting factor deficiency, hemophilia is classified into hemophilia A, which is deficiency of factor VIII and deficiency of a clotting factor IX is called hemophilia B. Currently, replacing the deficient clotting factors with plasma derived and recombinant clotting factor is the widely accepted treatment modality for hemophilia. In many countries, advanced treatment prophylaxis is the accepted modality of treatment, which allows persons living with hemophilia (PWH) to lead a disability-free life. According to recent survey, India has 10% of all the PWH in the world.[1] Yet most of the patients have not been adequately treated because of various factors. A void in awareness, unavailability of clotting factors, high treatment costs, poor economic status, and lack of home therapy along with low frequency of physiotherapy exercises are causing big dent in the Indian PWH's aspiration in achieving a disability-free life. In India, access to prophylaxis and optimal dosages of CFCs is still not up to the established standards of care. This review describes the current scenario of hemophilia care and the challenges faced by PWH in India.

Introduction

Hemophilia is a mostly inherited genetic bleeding disorder, first found in the literatures of 2nd century's Jewish-Talmud (Jewish religious script). A more detailed explanation was given by the 11th century physician Albucasis. The word "hemophilia" is derived from the Greek word "haima" which means "blood" and "philia" which means "love or attraction." In the late 18th and early 19th century, the understanding of hemophilia evolved and conceptualized. The European royal families suffered during the same period, and it led the world to recognize the disease and brought it into prominence. The two types of hemophilia, that is, Hemophilia A and Hemophilia B (Christmas disease) were recognized in the mid-20th century. Hemophilia is transmitted as X-linked recessive pattern where males are usually affected and females remain as asymptomatic carriers. The lack of heterogeneous transformations of the coagulating factor qualities because of the mutation *F8C* gene and *F9* gene causes Hemophilia A and B, respectively. Hemophilia A constitutes to about 80–85% of the hemophilia patients **(Table 1)**.[1]

Clinical Features

Hemophilia is X-linked recessive disease where male is clinically affected and women are almost asymptomatic. Family history is absent in ~30% of the cases, attributing to de novo mutation. Severe the hemophilia earlier the presentation of first bleeding episode, which can present as early as at birth and majority of them are spontaneous bleeds. New born can present as cephalohematoma, central nervous system (CNS) bleed, or excessive bleeding during medical intervention like venipunctures and circumcision. As child starts walking, joint bleed, bruising

TABLE 1 Hemophilia clinical classification[2]

Hemophilia type	*FVIII/FIX activity (% of normal)*	*Pattern of bleeding episodes*	*Clinical manifestation*
Mild	6–40	Uncommon	Major trauma, Surgery
Moderate	1–5	4–6 per year	Minor trauma
Severe	<1	24–48 per year	Spontaneous

and musculoskeletal bleed becomes more common. In older children and adult, presentation is mainly joint and muscle bleed. Hemarthrosis can affect every joint but commonly involves knee, elbow, ankle, shoulder, and hips. However CNS, oropharyngeal, and retroperitoneal bleed are life threatening and require immediate therapy.

Complications

Hemophilic arthropathy: Most common and develops in ~50% of patients with severe hemophilia. Mechanism of arthropathy is multifactorial including chronic or episodic synovitis, loss of cartilage, subchondral cyst formation, bone cysts, erosion and joint space narrowing leading to contractures, pain, and limitation of motion.

Infection: Found relatively more in plasma-derived products compare to recombinant factor products and elimination of Parvovirus B19, hepatitis A and prion diseases like Creutzfeldt-Jakob disease is still a challenge.

Pseudotumor: Unique to hemophilia, pseudotumor is a potentially disabling condition that results from inadequately treated soft tissue bleeds usually in muscle adjacent to bone, which can be secondarily involved.

Inhibitors: The cumulative incidence (i.e., lifetime risk) of inhibitor development in severe hemophilia A is in the range of 20–30%, approximately 5–10% in moderate or mild disease and hemophilia B has 1–5% lifetime risk of inhibitor development.[3,4]

Inhibitors are neutralizing alloantibodies developed following the host immune response to the infusion of clotting factor concentrate, seen by host immune system as foreign protein. Inhibitors development is highest during the first 20 exposure days (ED) to factors. Frequent screening is required during initial exposure days, screening every 5ED until 20ED are reached and after 150ED frequency of screening can be reduced. Inhibitors are detected either during routine screening or it is suspected when patient fails to respond to replacement of CFC. High titer inhibitor (HTI) and low titer inhibitor (LIT) are inhibitor classes quantified by Bethesda units (BU).

High titer inhibitor (≥5BU) and low titer inhibitor (<5BU) behave differently and consequently are managed differently. LTI may be transient and disappear spontaneously without specific treatment but significant proportion of it gets converted into HTI; hence, demands close monitoring. Treatment of bleed in LTI include factor infusion at higher dose, porcine rFVIII, which is not quickly inactivated unlike human FVIII and Desmopressin (DDAVP) in mild hemophilia A, which releases endogenous FVIII.[5]

HTI are persistent and completely resistant to factor concentrates; hence, their management requires avoidance of further FVIII exposure until immune tolerance induction (ITI) is commenced where infusions of variable doses of FVIII and FIX given over a period of time to tolerize the immune response. Use of bypassing agents (rFVIIa and aPCC) and monoclonal antibody emicizumab can be opted.[1,5] Emicizumab (Hemlibra) is registered in over 50 countries around the world for prophylactic use for hemorrhagic episodes in adult and pediatric hemophilia A patients with inhibitors.[6] In addition, this drug has recently been approved by FDA for prophylaxis in patients with hemophilia A without FVIII inhibitors.[6]

Treatment Modalities

Hemophilia is treated by replacing the deficient clotting factors. Based on source, there are plasma derived clotting factors concentrates (PDCFCs) and recombinant clotting factors (rFVIII/rIX). Recombinant clotting factors are inherently safer as the risk of transfusion transmitted diseases is much less compared to plasma derived CFCs. There are two modalities in treatment based on timing of the therapy, i.e., episodic/on demand therapy and prophylaxis therapy.[7]

TABLE 2 Dose required in hemophilia[2]

Type	*1 unit/kg factor VIII/IX*	*Dose required (in units)*
Hemophilia A	Raise the plasma FVIII level approximately 2%	[Body weight × Desired level]/2
Hemophilia B	Raise the plasma FIX level approximately 1%	[Body weight × Desired level]

TABLE 3 Desired level of factors in different sites of bleed in hemophilia A & B[4]

Site of bleed	*Desired level (IU/dL)*
Muscle/joint	40
Iliopsoas bleed	60
Throat	50–80
Neck	
GI bleed	
Genitourinary bleed	
Surgery (Postoperative)	
Surgery (Preoperative)	100
Intracranial bleed	

On Demand Therapy

Assuming the baseline factor of persons living with hemophilia (PWH) as 0%, the therapy should raise the clotting factor to a certain minimum level in order to stop the bleeding. Although on demand, treatment can stop bleeding, reduce the pain to an extent and restore joint movement. It will not protect the PWH from arthropathy. The target dose of CFC is calculated with the help of bleeding site specific desired levels and approximate raise of plasma factor levels **(Tables 2 and 3)**.

Prophylaxis Therapy[7]

Here the treatment is given by intravenous injection of factor concentrate to prevent anticipated bleeding. It prevents life threatening bleeding, joint destruction and preserves normal musculoskeletal function. Prophylaxis has been a standard of care in developed countries. Two well-studied and documented clinical protocols for prophylaxis are being followed across the world:

- *Malmo protocol:* (high dose: 25–40 IU/kg/dose)[1]
- *Utrecht protocol:* (intermediate dose: 15–30 IU/kg/dose)[1]

For hemophilia A, the factors are administered thrice a week and for hemophilia B, the factors are administered twice weekly. In countries with resource constraints lower dose of prophylaxis maybe given as an interim measure.

On Demand versus Prophylaxis Therapy

Manco-Johnson et al. conducted a randomized controlled study and found prophylaxis is more effective in preventing hemarthrosis and is also efficacious in decreasing bleeding and joint damage compared to on demand therapy.[8] Another randomized controlled study, ESPRIT study, concluded by saying prophylaxis was more effective when started at age 36 months or less with PWH having fewer joint bleeds and no radiologic signs of arthropathy versus patients treated on demand.[9] The MUSFIH study concluded, on demand therapy failed to preserve musculoskeletal functions in PWH.[10] All these studies are stressing the importance of prophylactic replacement of clotting factors over the on-demand therapy. Even in India, several pilot studies conducted across India have shown the evidence of the advantage of prophylaxis over on-demand.[11,12]

Hemophilia Scenario in India

India has currently 20,321 registered PWH. 17,606 with hemophilia A and 2,715 with hemophilia B.[1] Majority of Indian PWH fall into 19–44 years of age. However, as per the incidence and prevalence estimates, India should have had approximately 100,000 PWH. Many of the patients go undiagnosed or unregistered because of lack of awareness and lack of diagnostic facilities.

Among the registered patients, a significant percentage of them suffer from joint disease due to recurrent joint bleed. In a study of 148 severe hemophilia A patients from 5 centers across India, Kar et al. found that about 94% had some form of disability. Patients from the age group 25+ were the most affected with 0% of them being free from disability.[13] This pervasive disability has turned hemophilia from a mere bleeding disorder to a chronic musculoskeletal disorder. Many of these patients in India do not complete education, are not gainfully employed and become a burden to their families and the society. In

contrast, in most developed countries, PWH enjoy good joint health, are not burdened with disability and lead a normal and productive life.

This stark contrast among the quality of life led by PWH in India and other countries may be ascribed to several factors:

- *Lack of optimum management of bleeds:* Bleeds are not treated with optimum dosages in many cases. In India, mean per capita factor VIII and IX usage is 0.230 and 0.063 IU/population while global mean is 2.40 and 0.37 IU/population.[1] Also the time from onset of bleed to factor administration is rarely less than 2 hours. This leads to increased blood in the joint space, increased inflammation and increased time to recovery and in the long-term results in joint arthropathy.
- *Lack of prophylaxis:* Only about 13% of Indian PWH have access to prophylaxis.[1] Some of the reasons could be lack of awareness, difficulty in venous access in young children, training the parents of PWH and in some cases inadequate supply of clotting factors. Moreover, psychosocial barriers like handling the myths, misconception, apprehensions about prophylaxis and willingness to endure repeated venipunctures play a vital role.
- *Lack of home therapy:* Self-administration at home setting demands skills and expertise with proper training of the family members. Lack of motivation among patients and administrative hurdles reduce the efficiency of home therapy.
- *Lack of diagnostic facilities:* Only a few laboratories across the country can perform factor and inhibitor assays. This may be one of the reasons why only small portion of the PWH are identified.

However, there has been a significant improvement in the hemophilia care in India in the recent years. Out of all the genetic disorders and hemoglobinopathies hemophilia have attracted a fair share of support and funding from the government. Over the last few years treatment of hemophilia in India has evolved from whole blood transfusion, fresh frozen plasma and cryoprecipitates to plasma derived and recombinant clotting factor concentrates. It is also encouraging to note that hemophilia is now listed in "The Rights of Persons with Disabilities Act, 2016". The government is allocating funds, purchasing good quality clotting factors and bypassing agents. Many hemophilia treatment centers (HTCs) are opening across the country to help PWHs. Most HTC have well qualified treating physicians, nurses, lab technicians and physiotherapists with adequate experience of handling PWH.[14] HTCs are mainly supported by respective State Governments and in some cases by Central Government as well.[14] Some hospitals also serve as tertiary care centers for hemophilia care where advanced management for inhibitors and even surgeries are provided. However, the number of such surgeries is abysmally low. Some of the tertiary centers have started prophylaxis and home therapy as pilot projects, albeit at smaller scale.

The Hemophilia Federation of India (HFI) is a patient support group, working to help PWH in India in various ways. It also performs a vital task of maintaining a national hemophilia registry for all PWH.

Conclusion

Persons living with hemophilia (PWH) in India still face many issues in terms of comprehensive care, inhibitor management, optimum dosage in acute bleeds and optimum prophylaxis regimen. Paving our way toward WFH's vision of "Treatment for All". *Awareness*, *access* to *safe factors*, *prophylaxis* and *home therapy* should be the focus areas for all the concerned stakeholders to work in a coordinated fashion and make the treatment accessible to all the PWH. With such an approach of comprehensive hemophilia care and tireless efforts of medical experts, government, health administrators, and even patients, we can aspire for a disability-free hemophilia in India.

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CHAPTER

231 Immunotherapy in Clinical Practice

Vineet Talwar, Amrith BP

Abstract

Cancer immunotherapy is rapidly evolving and is gaining a major role in current oncological practice. Advances in understanding of immune surveillance and tumor biology have opened up new therapeutic strategies that can be used for the treatment of many cancers. Immune evasion is a hallmark of property of cancer and cancer immunotherapy uses strategies to augment body's immunity against cancer. A subset of cancer patients dramatically benefit from this approach and identifying a right patients through a biomarker is need of the hour. In addition, knowledge on tumor response to immunotherapy and toxicity profile of these agents are important as they differ from traditional cytotoxic chemotherapies by virtue of its unique mechanism of action.

Introduction

Advances in understanding of the interlink between immune surveillance and tumor biology have opened up new therapeutic strategies that can be used for treatment of many cancers.[1] Nobel prize for physiology/medicine in 2018 was awarded to James P. Allison for the discovery of cytotoxic T-lymphocyte associated protein (CTLA-4) and to Tasuku Honjo for programmed cell death protein 1/programmed cell death protein ligand 1 (PD-1/PD-L1), a landmark discoveries in the field of immunotherapy.[2] Cancer immunotherapy is based on the principle of strengthening the host immune system to combat against the cancer.

Evasion of Immune Surveillance

Evasion of the immune surveillance is one of the hall marks of cancer.[3] Adaptive immunity directed at the cancer antigens is one of the defense mechanism which helps to fight against the cancer. There are several mechanisms by which the cancer cells escape this natural defense known as "immune evasion."[4] Immune evasion helps in tumor growth despite having a normally functioning host immune system. Various mechanisms for immune escape include:

- Up regulation of immune checkpoints such as PD-1 and PD-ligand 1 (PD-L1)
- Alteration of antigen presentation mechanism by loss of MHC class 1 expression or cellular mechanisms that help in transportation of tumor antigens for T cell recognition
- Promotion of immune tolerance by alteration of cytokines like IL-6, IL-10, and TGF-beta

Proper understandings of these mechanisms have been exploited as the basis of immunotherapy in current clinical practice.

Approaches to Cancer Immunotherapy

A number of therapeutic approaches are in practice or under investigation to strengthen the body's immune system fight against cancer. Various immunotherapy approaches in current practice are enumerated in the **Box 1**.

BOX 1 Immunotherapy approaches in current practice

Modalities of immunotherapy
Check point inhibitors • PD-1 and PD legend (PD-L1) inhibitors • CTLA-4 inhibitors
Manipulation of T cells • Chimeric antigen receptors • Bispecific T cell engagers
Cancer vaccines
Cytokines
Oncolytic viruses

Checkpoint Inhibitors

Programmed Cell Death 1 (PD-1) and PD-Ligand 1/2

Programmed cell death-1 (PD-1), a transmembrane protein expressed on immune cells like T cells, B cells, and NK cells. Ligand of PD-1 (PD-L1) is usually expressed on many tissues including tumor cells. Interaction of the PD-1 with its ligand acts as check point and resists the cell death by inhibition of apoptosis.[5] Up regulation of PD-L1 expression is seen in many tumor cells and drugs targeting PD-1/PD-L1 pathway known as check point inhibitors are an important class of immunotherapy in current oncological practice. The interaction of the PD-1 with its ligand is depicted in the schematic **Figure 1**.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another immune check point, which helps in down regulation of the immune responses against tumor cells.[6] Monoclonal antibodies targeting CTLA-4 can also clear these "breaks" in immune surveillance. Ipilimumab, an anti-CTLA-4 antibody was the first immune checkpoint inhibitor to be approved in patients with malignant melanoma.[7]

The various check point inhibitors currently in use are listed in **Table 1** with the approved indications and doses.

Immunotherapy Response Criteria

The pattern of response to immunotherapies mainly checks point inhibitors that can differ from that of classical cytotoxic chemotherapeutic agents by the virtue of difference in mechanism of action of these agents.[8] Unlike chemotherapy the responses may take longer time to become apparent. The immune infiltration of the tumors can lead to an apparent increase in the size of the lesion

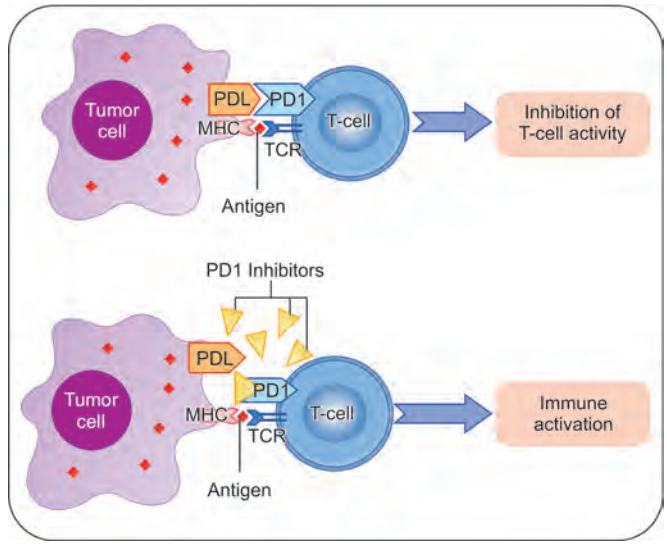

Fig. 1: PD-1/PD-L1 pathway and check point inhibitors

initially known as immune confirmed progressive disease (IUPD) commonly known as pseudoprogrssion.[9] In such situations the clinical status of the patient should be taken into consideration in deciding the further course of action.

To address these issues many response criteria have been developed like immune-related response criteria (irRC), immune response evaluation criteria in solid tumors (iRECIST),[10] immune-modified response evaluation criteria in solid tumors (imRECIST).[11] Detailed description of these criteria is beyond the scope of this chapter.

Toxicities Associated with Checkpoint Inhibitor Immunotherapy Immune-related Adverse Events (IRAEs)

The toxicities depend on the class of immunotherapeutic agents. Check point inhibitors are the most commonly used class of immunotherapy in clinical practice. Though these drugs are well tolerated in most of the cases they are known for unique side effects related to their mechanism of action. These are known as immune-related adverse events (irAEs).[12] Virtually these can affect any organs. However, the important organs affected and the manifestations are depicted in the **Figure 2**. The usual timeline of appearance of these side effects are shown in the **Figure 3**.

The management of irAEs depends on the severity of manifestations. It varies from close monitoring,

TABLE 1 Check point inhibitors with approved indications

Drug	*Target*	*Dose*	*Approved indications*
Nivolumab	PD-1	240 mg once every weeks Or 480 mg once every 4 weeks	• Head and neck squamous cell carcinoma • Hepatocellular carcinoma • Hodgkin lymphoma • Melanoma • Lung cancer • Renal cell cancer • Urothelial cancer
Pembrolizumab	PD-1	200 mg once every 3 weeks	• Cervical cancer (recurrent or metastatic) • Esophageal cancer (recurrent locally advanced or metastatic) • Gastric cancer (recurrent locally advanced or metastatic) • Head and neck cancer, squamous cell • Hepatocellular carcinoma • Hodgkin lymphoma, classical (relapsed or refractory) • Melanoma • Microsatellite instability-high cancer • Non-small cell lung cancer • Renal cell carcinoma • Urothelial carcinoma
Cemiplimab	PD-1	350 mg once every 3 weeks	• Cutaneous squamous cell carcinoma, metastatic or locally advanced
Atezolizumab	PD-L1	Breast cancer: 840 mg Day 1 and Day 15 every 4 weeks Others: 1200 mg every 3 weeks	• Breast cancer (triple-negative) • Lung cancer • Urothelial carcinoma
Durvalumab	PD-L1	10 mg/kg every 2 weeks	• Lung cancer • Urothelial carcinoma
Avelumab	PD-L1	800 mg once in every 2 weeks	• Merkel cell carcinoma • Renal cell carcinoma • Urothelial carcinoma
Ipilimumab	CTLA-4	1–10 mg/kg (depending on the indication)	• Melanoma • HCC • RCC

interruptions in treatment, dose reductions, and other pharmacological management. The pharmacological agents like steroids, infliximab, may be used in the management of irAEs.[13]

Other Forms of Immunotherapy

Manipulating T Cells

Immune enhancement by manipulating the T cells is another emerging mode of immunotherapy.

Chimeric Antigen Receptors (CAR) T Cells

CAR-T cell therapy involves the modification of the patient's own T cells to recognize the cancer cells more effectively and to destroy them. Chimeric antigen receptors (CARs) are the engineered proteins that give T cells this new acquired ability. These proteins are chimeric as they are engineered by combining antigen-binding and T cell activating functions into a single receptor.[14] So CAR-T cell therapy utilizes these T cells engineered with CARs as a therapeutic strategy.

CAR-T cells are studied in various solid and hematological malignancies and have shown a great result in B-cell acute lymphoblastic leukemia (B-ALL). Tisagenlecleucel and axicabtagene-ciloleucel were the first two CAR-T cell therapy receiving FDA and EMA approval for ALL (tisagenlecleucel) and diffuse-large B-cell lymphoma – DLBCL (tisagenlecleucel and axicabtagene ciloleucel).[15]

CD3-Directed Therapies—Bispecific T-cell Engagers

Bispecific T-cell engager antibodies (BiTEs) act as linker between T cells and specific target antigens. These consist of a protein, which contains two separate variable regions,

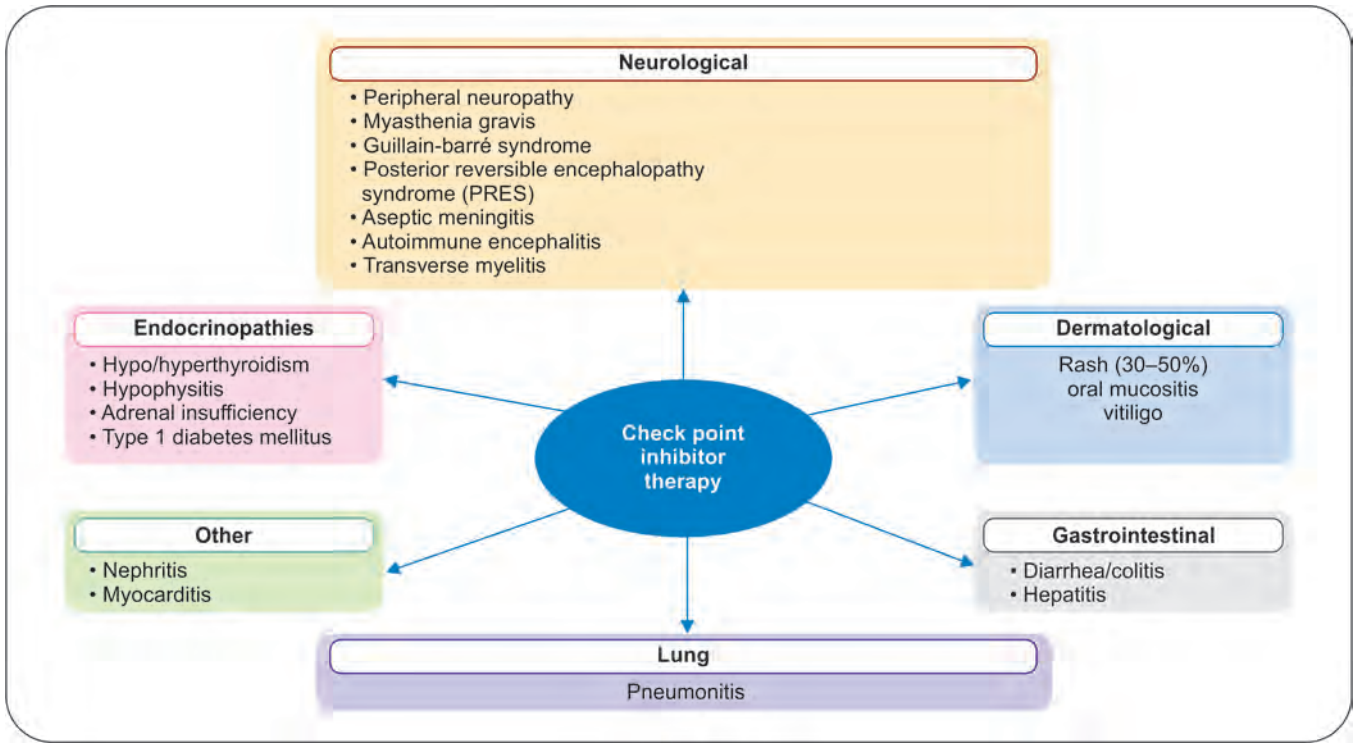

Fig. 2: Immune-related adverse events (irAEs)

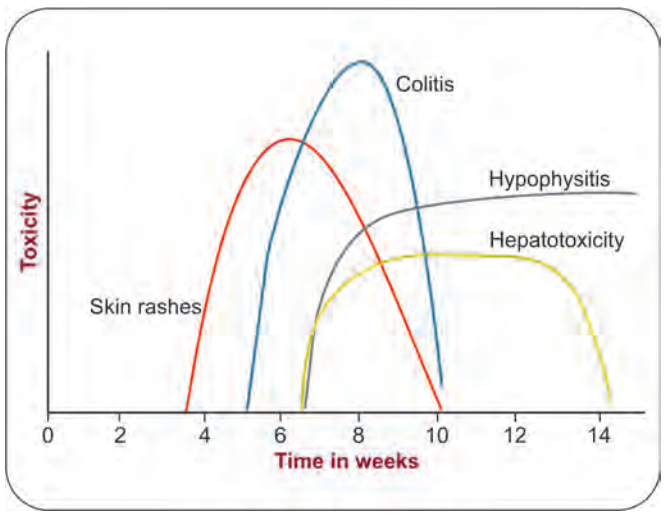

Fig. 3: Timeline of immune-related adverse events (irAEs)

one recognizing CD3 on T cells and the other recognizing target antigen. Thus, activating cytotoxic T cell-mediated tumor damage. BiTEs functioning in an MHC independent manner and don't require patient specific processing enabling it to administer to all the patients irrespective of human leukocyte antigen (HLA) type.[16]

Blinatumomab is a BiTE having specificity for CD19 found on B cells and the Fc region of the CD3 receptor on T lymphocytes and is approved for Philadelphia-chromosome negative B-ALL.[17]

Oncolytic Viruses

Several viruses are genetically engineered to infect the cancer cells preferentially and to present the tumor associated antigens to immune system. Many virus backbone like attenuated herpes simplex virus 1, adenovirus, reovirus have been studied in clinical trials. talimogene laherparepvec (T-VEC) uses an attenuated HSV-1 to over express granulocyte macrophage colony-stimulating factor (GM-CSF) and mediates the antigen presentation through dendritic cells. Intratumoral injections of T-VEC have shown durable responses in Melanomas.[18]

Therapeutic Cancer Vaccine

Therapeutic cancer vaccines are a form of immunotherapy, which educates the immune system about how cancer cells look like so that it can fight against it. Vaccine antigen is the most important component of a cancer vaccine,

which can be tumor-associated antigen or tumor-specific antigen. There are mainly three types of vaccine platforms that are being investigated for cancer therapy. These includes cellular vaccines (autologous or allogeneic), virus vector vaccines, and molecular vaccines comprised of either peptides, DNA, or RNA.

The first US Food and Drug Administration approved therapeutic cancer vaccine is sipuleucel-T (Provenge).[19] It was used for metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T was developed by enriching the patient derived DCs and their activation ex vivo with a chimeric protein, GM-CSF fused to the antigen PAP.

Cytokines

The initial approaches of immunotherapy were mainly based on alteration of cytokines that influence the immune system.

- Interleukin-2(IL-2):
  - IL-2 plays an important role in activation of immune system and is an approved treatment for renal cell carcinoma and melanoma.[20]
  - Immunomodulators like lenalidomide and pomalidomide are an established therapy in multiple myeloma act by destruction of Ikaros family proteins, which results in inhibition of IL-2 secretion.[21]
- Interferon (IFN) alfa-2b has also been used in malignant melanoma.

Conclusion

The immune-oncology has transformed the care of cancer patients. These act in a targeted manner minimizing the side effects. Checkpoint inhibitors are the mainstay of current immunotherapy practice in oncology. CAR-T cell therapies and personalized cancer vaccine have limited utility at present, which will be added to the immune-oncology armamentarium for wider use in near future.

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CHAPTER

232 PNH—A Great Masquerader: When to Suspect?

Asish Rath, Jasmita

Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal disorder characterized by partial or complete deficiency of glycophosphatidylinositol anchored proteins (GPI-AP). PNH can present with varied clinical manifestations. PNH can masquerade as an intravascular hemolysis or thrombosis. It can be associated with acquired bone marrow failure. Early diagnosis of PNH is crucial for appropriate clinical management. However, the rarity and diverse clinical manifestations complicate an early diagnosis. Though various tests are available, flow cytometric PNH analysis is considered the gold standard because of its rapidity and high sensitivity. A high index of suspicion and choice of appropriate high sensitivity assay helps in timely diagnosis and prevention of fatal complication in patients.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder of hematopoietic stem cells caused by a somatic mutation in X-linked PIGA gene resulting in partial or absolute deficiency of all glycophosphatidylinositol (GPI) linked proteins.[1,2] The GPI anchored proteins (GPI-AP) have different functions as enzymes, receptors, adhesion molecules, or complement regulators.[3] Examples of GPI-AP, which inhibit the complement are CD55 (decay accelerating factor-DAF) and CD59 (membrane inhibitor of reactive lysis-MIRL). PNH can cause myriad manifestations ranging from the expected intravascular hemolysis to presentation with thromboses or bicytopenia/ pancytopenia due to bone marrow failure.[4] In addition, some patients of PNH present with abdominal pains and leg cramps with compensated hemolysis.

Clinical Manifestations and Pathogenesis[2,5]

Complement-mediated Intravascular Hemolysis

PNH red cells are vulnerable to complement mediated lysis due to reduction or absence of CD59 and CD55. CD55 (DAF) accelerates destruction of membrane bound C3 convertase where as CD59 (MIRL) inhibits membrane attack complex (MAC) induced lysis. In PNH there is low-level continuous activation alternate complement pathway, which in association with GPI-AP causes chronic intravascular hemolysis. Classically patients have paroxysms of hemolysis at night, a morning dark colored urine and gradual resolution over the day. It is primarily the CD59 molecule that is responsible for inhibiting complement mediated lysis.

Thromboses

- NO (nitric oxide scavenging)—Free hemoglobin released into plasma following intravascular hemolysis scavenges NO. This leads to endothelial dysfunction and platelet activation. NO depletion can manifest in abdominal pain, dysphagia, erectile dysfunction, and thrombosis.
- Platelet activation by procoagulant microparticles released from GPI-AP deficient cells.
- Deficiency of GPI-AP like u-PAR (urokinase like plasminogen activator receptor) and TFPI (tissue factor

pathway inhibitor) that lead to reduced inactivation of the thrombotic pathway.

Bone Marrow Failure

Approximately 30–45% of PNH patients have associated aplastic anemia or myelodysplastic syndrome (MDS). A second hit following PIGA mutation causing immune destruction of normal stem cells and clonal selection of PNH stem cell may explain coexistence of PNH clones in acquired aplastic anemia.

PNH has been subclassified by *International PNH interest group*[1] into three categories:

- The classical PNH—clinical and laboratory signs of intravascular hemolysis without evidence of other diseases of bone marrow failure
- PNH associated with AA/MDS
- Subclinical PNH with a minor PNH clone usually less than 1%

We will discuss three case scenarios **(Table 1)** to elucidate the manifestations of the disease and identify patients who should be tested for PNH.

TABLE 1 Details of the three clinical cases

Case details	*Case 1*	*Case 2*	*Case 3*
Age/Sex	21/Male	28/Female	31/Male
Primary complaints	symptomatic anemia, intermittent jaundice, leg cramps	Jaundice Abdominal pain	Petechiae Anemia requiring transfusions
Duration of illness	2 years	1 month	2 months
Hb (g/dL)	8.1	10.2	5.1
TLC ($\times 10^9$/L)	5.08	8.2	1.2
Platelets ($\times 10^9$/L)	150	99	18
MCV (fL)	115.3	96.5	91.5
Reticulocyte (%)	13.4	3.2	0.9
Additional information	-	-	ANC-120/µL
Bilirubin total/Indirect (mg/dL)	5.2/4.8	2.2/1.9	0.8/0.2
LDH (U/L; Normal reference 220–420)	890	550	230
Peripheral blood smear	Macrocytes, polychromasia, hypersegmented neutrophils	Normocytic normochromic; mild polychromasia; Normal platelets	Pancytopenia with normocytic normochromic red cells
Bone marrow aspirate	Megaloblastic erythroid hyperplasia; giant myeloid forms	Normoblastic erythroid hyperplasia with adequate megakaryocytes	Paucicellular with predominantly lymphocytes and plasma cells
Perl's stain	Absent iron stores	1+	4+
Bone marrow biopsy	Hypercellular; megaloblastic erythroid hyperplasia	Normocellular with normoblastic erythroid hyperplasia	Cellularity 10% consistent with hypoplastic anemia
Other lab tests	Negative G6PD, incubated osmotic fragility test, Direct Coombs test	AST>ALT, Negative Direct Coombs test; Thrombophilia workup normal including Antiphospholipid antibody syndrome and JAK2V617F mutation	Chromosomal fragility test negative
Radiology	-	Hepatic vein thrombosis, mild hepatomegaly and mild ascites	-
Summary	Unexplained hemolytic anemia with secondary folate deficiency	Hepatic vein thrombosis with evidence of hemolysis	Aplastic anemia

When to Suspect PNH?[5-10]

The rarity and diversity of clinical manifestations complicates the early diagnosis of PNH. Patients may present with anemia, fatigue, dyspnea, chronic kidney disease, abdominal pain, pulmonary hypertension, erectile dysfunction, dysphagia, thrombosis or hemoglobinuria. Many of these signs and symptoms are so common that every patient with anemia or thrombosis cannot be screened for PNH. Thus, PNH testing should be advised when some clinical or laboratory findings raise a suspicion.

A PNH test should be ordered in any patient who presents with:

- Intravascular hemolysis (~25% patients present with hemoglobinuria) as evidenced by hemoglobinuria, elevated LDH, reticulocytosis, and elevated plasma hemoglobin.

  Significant hemoglobinuria is usually present in classical PNH, whereas in cases associated with AA or MDS it may be absent due to a small PNH clone.
- Evidence of unexplained hemolysis with accompanying iron-deficiency, or abdominal pain or esophageal spasm, or thrombosis, or neutropenia and/or thrombocytopenia.
- Other acquired Coombs' negative, non-schistocytic, non-infectious hemolytic anemia.
- Thrombosis with unusual features:
  - Unusual sites—Hepatic veins (Budd-Chiari syndrome)/Other intra-abdominal veins (portal, splenic, splanchnic)/Cerebral sinuses/Dermal veins
  - With signs of accompanying hemolytic anemia
  - With unexplained cytopenia
  - Young patients

  PNH is the second most common cause of intra-abdominal vein thrombosis after myeloproliferative neoplasms. Thrombosis is the leading cause of mortality in PNH. About 29–44% of PNH cases experience at least one thromboembolic event during course of the disease. An early diagnosis and management of PNH associated thrombosis is paramount.
- Evidence of bone marrow failure:
  - Suspected or proven aplastic or hypoplastic anemia: Up to 70% patients with acquired AA have a PNH clone and 40% PNH evolves from AA. Mahapatra et al. in their extensive study at AIIMS New Delhi of 1501 AA patients, detected PNH clone in 39.7% cases at diagnosis.[9]

    Various studies have mentioned an excellent response of AA to immunosuppressive therapies in presence of minor PNH clones. Emergence of PNH clones and expansion of pre-existing PNH clones post ATG is known. However, clinically relevant PNH clones are seen in less than 5% cases of AA post ATG causing significant hemolysis.
  - Refractory cytopenia with unilineage dysplasia, hypoplastic MDS: Up to 50% patients with MDS test positive for a PNH clone. Testing for PNH in MDS is recommended in cases with refractory anemia subtype, MDS with evidence of hemolysis, or evidence of bone marrow failure such as hypoplastic MDS.
  - Other cytopenias of unknown etiology after adequate workup.

Diagnosis

Diagnosis of PNH is done by detection of the PNH clones. Different methods can be adapted.

Complement-based Test—Modified Ham's Test, Sucrose Lysis Test[5,11,12]

These tests are based on the sensitivity of PNH cells to activated complement proteins. Though inexpensive, these tests are laborious, technically challenging, and not accurate quantitatively. As these tests are RBC based, spurious results may be obtained during hemolytic episodes and post-blood transfusion. Also, autoimmune hemolytic anemia and congenital dyserythropoietic anemia may give false positive reports. Hence, these tests are no longer recommended as tests of choice for the diagnosis of PNH.

Gel Card-based Tests[5,11,13]

Gel card-based test is based on antigen-antibody reaction. If GPI linked proteins, like CD55 and CD59, are not present on RBCs there will be no reaction with anti-CD55 and anti-CD59. Minor clones and subclinical clones cannot be identified using this technique. This test is non-quantitative. Just like complement-based tests, this test also has limited ability to detect PNH clone during hemolytic episodes and in post-transfusion samples.

Flow Cytometric (FCM) Detection of PNH Clones[5,13-15]

This is a rapid, highly sensitive assay. FCM for PNH is the gold standard test for detection of PNH clones. FCM can pick up subclinical clones and can delineate type I, type II, type III RBCs with normal expression, partial deficiency, and complete deficiency of GPI linked protein, respectively. Patients with more than 20% type III red cells are likely to manifest as hemolysis whereas patients with majority type II clone without significant type III cells usually do not show hemolysis. Unlike previous tests, PNH can detect PNH clones in RBCs and neutrophils. As in multiparametric FCM one can acquire more events/cells and analyze multiple antigen characteristics of a cell, it can help detecting clones as low as 0.01%. More importantly monitoring of patients can be done by highly sensitive technique like FCM.

However, a proper knowledge of monoclonal antibodies to be used, their expression, sample requirement, gating strategy, and sensitivity of the assay is required.

Sample Requirement[14,16]

Most preferred specimen is peripheral blood in EDTA. Bone marrow sample is not recommended as immature myeloid cells may have changes in GPI-linked protein expression and in MDS patients there may be altered expression of some GPI-linked proteins in neutrophils and monocytes.

A minimum of 1 mL sample is required. But in cases with pancytopenia sample as much as 3 mL is required for higher cell acquisition to detect small subclinical PNH clones.

Though sample can be stored for 7 days at 4°C for RBC analysis, it is preferable to process sample within 48 hours as alteration in scatter and antigen expression in neutrophils over time is known.

Any commercial lysing agent with fixative can be used for WBC analysis (ammonium chloride with fixative may be used).

RBC or WBC[5,14,16]

Goal of RBC analysis is to diagnose and quantify cells lacking GPI-linked protein (type I/II/III cells). However, testing only RBCs may not be adequate in cases having active hemolysis or in case of transfusion where it underestimates clone size. So, determining WBC clones is more important for appropriate quantification of PNH clones.

Choice of Antibodies[5,14,16,17] (Table 2)

GPI-linked protein—simultaneous two GPI-linked proteins for two lineages are recommended.

CD55 and CD59 analyses in neutrophils are not recommended as they give a higher false positivity rate for PNH.

FLAER directly binds to GPI anchors and detects wide range of GPI-linked structures in different WBCs.

CD157 is brightly expressed on both neutrophils and monocytes and can replace two different antibodies for neutrophils and monocytes and is cost effective.

Testing for lymphocytes is not recommended because of their longer life span, which may give erroneous results in new onset PNH.

TABLE 2 Antibodies and panels used for the diagnosis of PNH by flow cytometry

Lineage of cells		*Gating marker*	*Lineage marker*	*GPI-AP*
RBC		CD235a		CD55, CD59
WBC	Neutrophils	CD45	CD15	CD24, CD157, FLAER
	Monocytes	CD45	CD64	CD14, CD157, FLAER
PANELS	RBC	3-color CD235a/CD55/CD59		
	WBC	6-color CD45/CD15/CD64/CD24/CD14/FLAER 5-color CD45/CD15/CD64/CD157/FLAER		

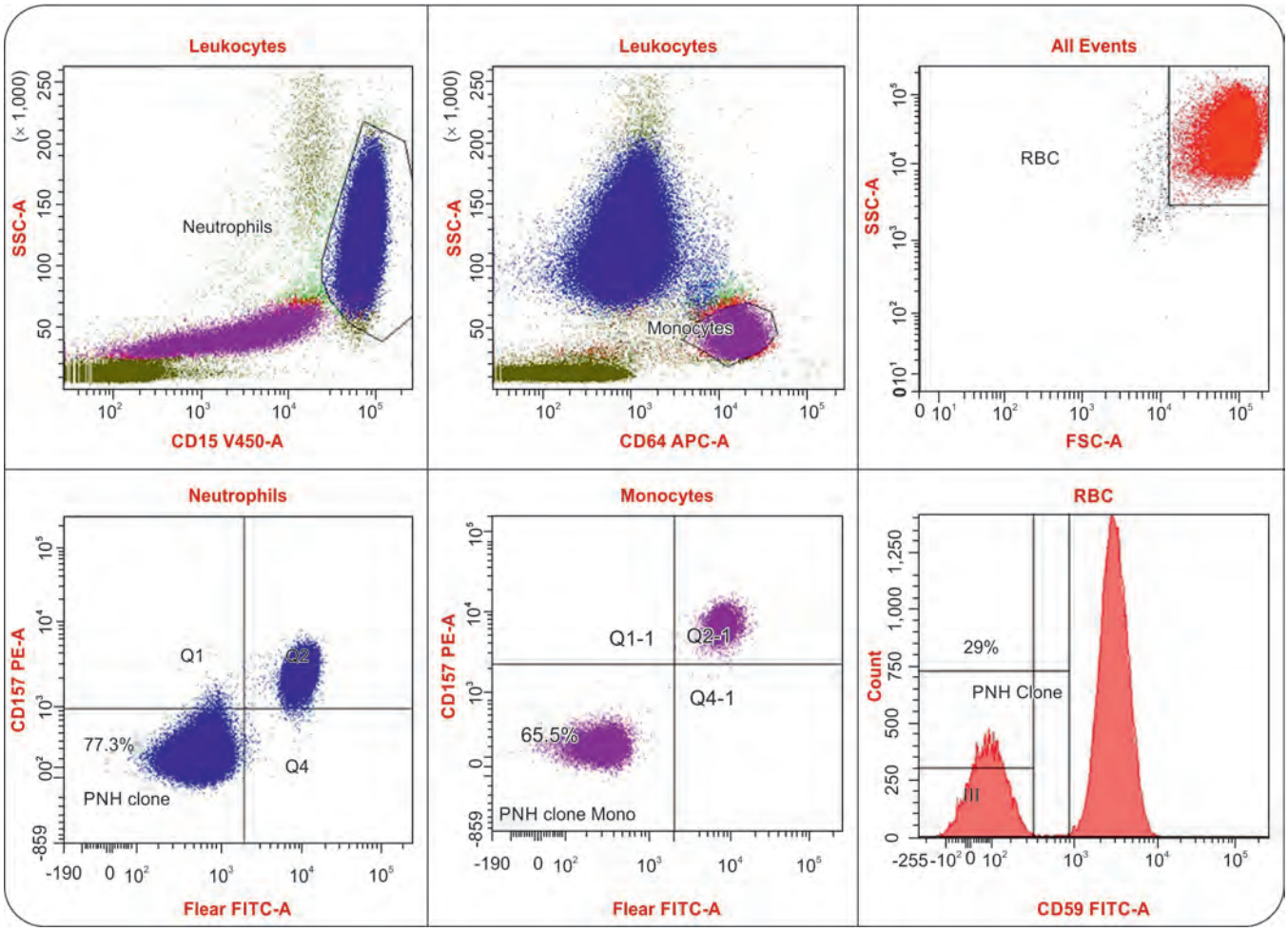

Fig. 1: Case 1. Neutrophils gated on the CD15-SSC plot after refinement of initial gate on CD45-SSC plot show a 77.3% PNH clone while monocytes gated on CD64 vs. SSC plot show a 65.5% PNH clone at diagnosis using a high-sensitivity assay. Red cells had a 29% PNH clone primarily type III with complete absence of GPI linked proteins. The clone size was smaller in red cells due to brisk hemolysis

- *Quantification*[14,16]—A laboratory specific lower limit of detection and lower limit of quantification should be established. In a high-sensitive FCM-PNH assay, minimum 50 PNH cells should be obtained to appropriately quantify. A minimum of 1,00,000 RBCs, 50,000 CD15 positive cells, and 10,000 CD64 positive cells are recommended to be acquired for sensitivity of 0.05%, 0.1%, and 0.5%, respectively in high sensitive assays. High sensitivity assays are not required for classical PNH but small clones in AA/MDS.
- *Interpretation*[14]—
  - >1% clone—PNH clone
  - 0.1–1%—Minor PNH clone
  - <0.1%—Rare cells with PNH phenotype
- *Monitoring/Retesting*[7,18]—Monitoring of PNH clones may be done annually or more frequently if there is worsening of symptoms. Frequent monitoring may also be needed in eculizumab therapy.

Patients with aplastic anemia need serial monitoring as minor clone can progress to a hemolytic PNH. Patients with no detectable clone should be screened every 6 months, decreasing to yearly if no clone appears in the first 2 years. If a clone is present or appears, patients should be screened every 3 months until the clone size is shown to be stable for 2 years.

Outcome of the three Cases

See **Table 3**.

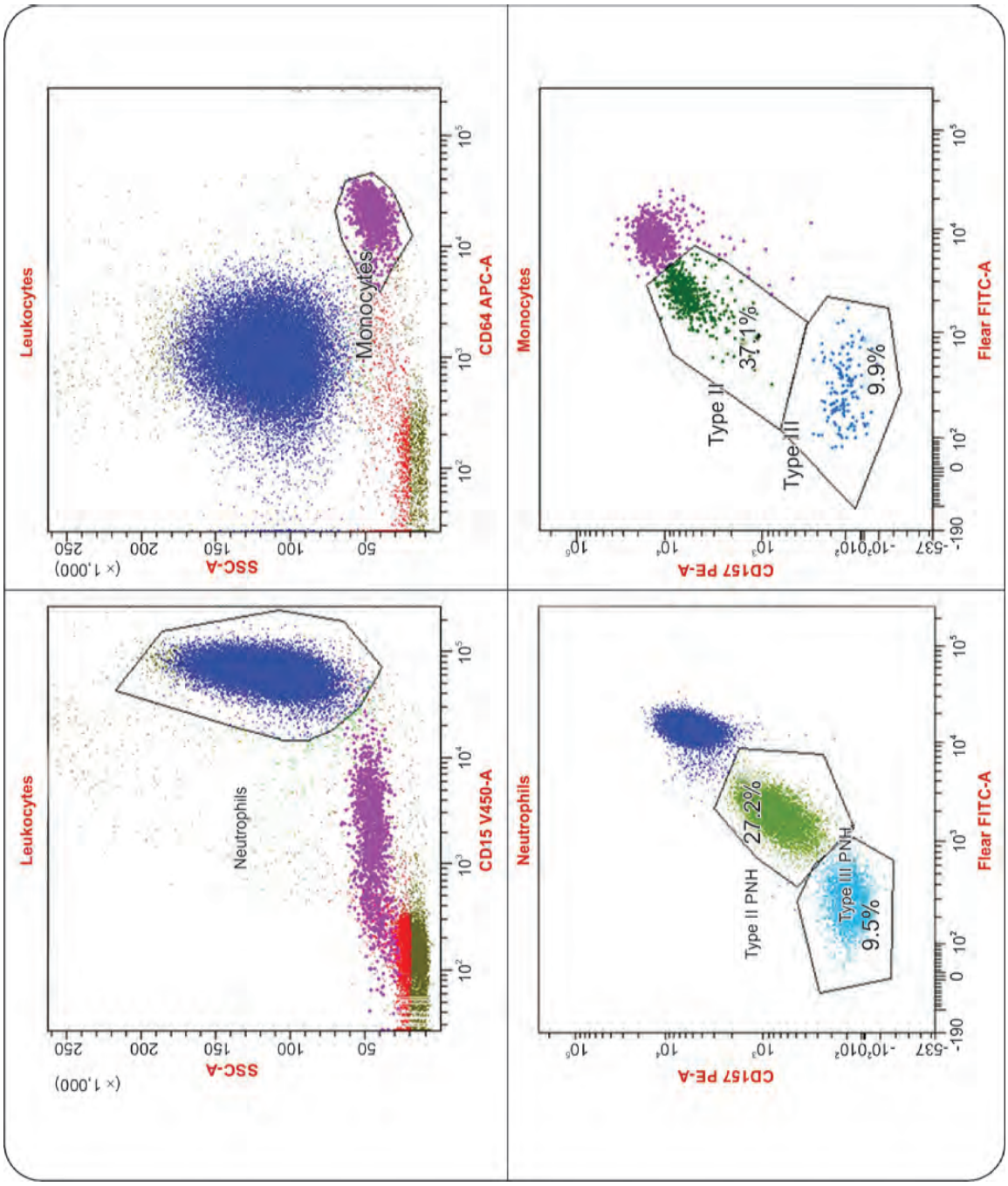

Fig. 2: Case 2. Both neutrophils and monocytes exhibit predominant type II PNH clones with reduced expression of GPI anchor and related proteins. Type II clones are sometimes clearly apparent on the CD157-FLAER plots in neutrophils and monocytes

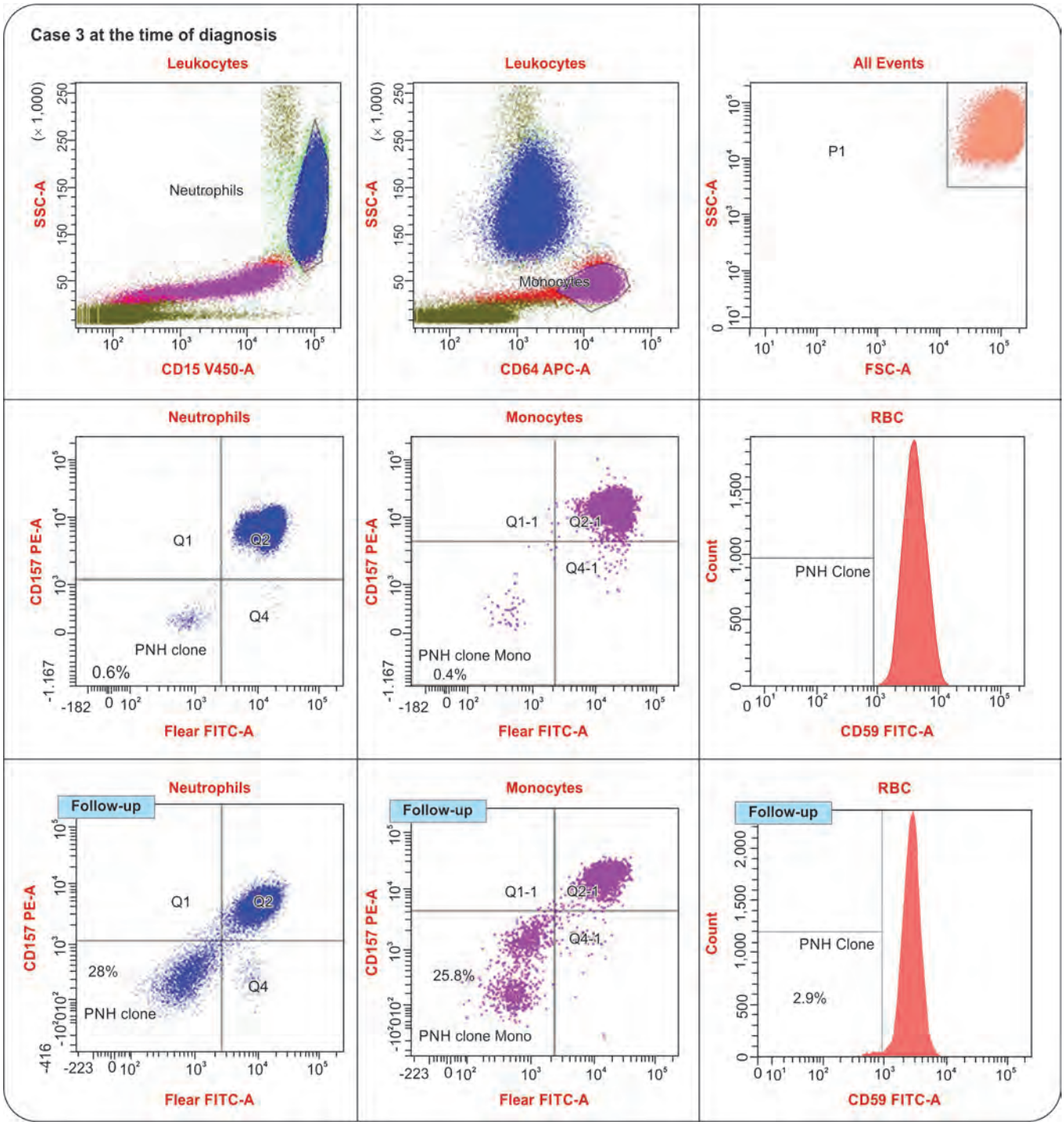

Fig. 3: Case 3 at the time of diagnosis and follow up. Neutrophils gated on the CD15-SSC plot after refinement of initial gate on CD45-SSC plot show a 0.6% PNH clone while monocytes gated on CD64 vs. SSC plot show a 0.4% PNH clone at diagnosis using a high-sensitivity assay. Red cells do not show any PNH clone on a routine sensitivity assay. After 5 years, PNH immunophenotyping was repeated when cytopenias recurred. PNH clone in neutrophils and monocytes had increased to 28% and 25.8%, respectively while a small clone of 2.9% was seen in red cells, mostly type II. The reason for lower red cell clone was attributed to ongoing packed cell transfusions and mild hemolysis

TABLE 3 PNH clones and clinical course in the three cases

	Case 1	*Case 2*	*Case 3*
Summary	Unexplained hemolytic anemia with secondary folate deficiency	Hepatic vein thrombosis with evidence of hemolysis	Aplastic anemia
PNH flow cytometry Neutrophil clone Monocyte clone Red cell clone	**(Fig. 1)** 77.3% 65.5% 29%, Type III: 28%	**(Fig. 2)** 36.7%, type II: 27.2% 47%, Type II: 37.1% Not done	**(Fig. 3)** 0.6% 0.4% 0.1%
Clinical course	Due to unavailability of eculizumab in India and lack of response to steroids, the patient underwent matched sibling donor transplant; remains asymptomatic 2 years post-transplant	Patient was treated with full anticoagulation but succumbed to death due to a second thrombotic episode	Patient responded to immunosuppressive therapy (ATG + cyclosporine) and attained hematological recovery. However, the patient relapsed with cytopenias 5 years later. Repeat bone marrow revealed hypoplasia with Monosomy 7. PNH-FCM showed increasing PNH clones

Conclusion

PNH is a rare and life-threatening disorder, has varied presentation like hemolysis, thrombosis at abnormal locations or bone marrow failure. Knowledge of different presenting symptoms and high index of suspicion is needed for an early diagnosis. Reliable testing and reporting procedures matter. Laboratory testing for high sensitivity PNH analysis by FCM in WBCs and RBCs should be preferred.

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CHAPTER

233 JAK2 Mutation—What Physicians Should Know?

Tulika Seth

Abstract

Myeloproliferative disorders include polycythemia vera, primary myelofibrosis, and essential thrombocytosis. These disorders have an increased risk of thromboembolic complications and may progress post fibrotic state or transform into acute myeloid leukemia. Understanding of the molecular pathogenesis has resulted in newer targeted therapies and better risk stratification of patients.

Introduction

We are entering an era of molecular medicine. All of us were earlier taught about the variability of disease presentation, severity, and varied responses to treatment. We are now aware that variability even in infectious diseases and much more so in non-infectious diseases has a genetic basis. We know that different mutations, polymorphisms of genes, and even the allele burden are implicated in diseases. Knowledge about JAK2 mutation associated diseases is increasing. The classic JAK2 diseases are myeloproliferative conditions—polycythemia vera (PV), essential thrombocytosis (thrombocythemia) (ET) and primary myelofibrosis (PMF).[1] But the JAK2 mutation has been found in many other conditions and to make things more complicated the classic conditions of PV, ET, and PMF may also occur without JAK2.[2]

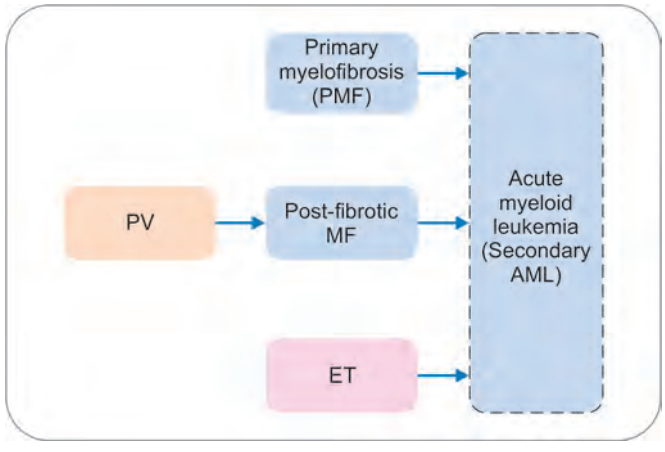

Fig. 1: Different myeloproliferative disorders and their risk of transformation

JAK2 Mutation

When we speak of JAK2 mutation we commonly refer to JAK2 (V617F) mutation **(Fig. 1)**. This mutation is acquired, and is present in the myeloid lineage of the hematopoietic cells. JAK2 mutation has been associated with a wide variety of myeloproliferative/myeloid disorders—such as PV, PMF, chronic myelomonocytic leukemia (CMML), myelodysplastic syndrome (MDS),[3] etc. **(Table 1)**. The presence of the mutation is not diagnostic of any disorders; it has to be taken in context with other clinical and laboratory abnormalities. To make a diagnosis we need to evaluate the clinical presentation and hematological parameters. Many of the conditions typically associated with JAK2 can also arise without JAK2 mutation.

TABLE 1 Conditions associated with JAK2 V617F mutation

Conditions associated with JAK2 V617F	*Frequency of JAK2*
• Polycythemia vera (PV)	PV: >90% JAK2 exon 12 = PV: 2–3%
• Essential thrombocytosis/ thrombocythemia (ET)	ET: 60%
• Primary myelofibrosis (PMF)	PMF: 60%
• Systmemic mastocytosis (SM)	25%
• Chronic neutrophilic leukemia (CNL)	17–33%
• Hypereosinophilic syndrome (HES)	0–2%
• Myelodysplastic syndrome (MDS)	1.5–5%
• Chronic myelomonocytic leukemia (CMML)	3–13%
• Unclassified MPD (UN)	20%
• HVOTO/ Budd-Chiari Syndrome (BCS)	Varied

Blood. 2005;106(6):2162-8; Blood. 2005;106(10):3370-3; Blood. 2005;106(4):1207-9.

Abbreviations: CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia; ET, essential thrombocythemia/thrombocytosis (ET); HES, hypereosinophilic syndrome; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; PV, polycythemia vera; SM, systemic mastocytosis; UN, unclassified MPD.

What are the Implications of JAK2?

JAK2 associated diseases are a wide variety of chronic diseases in the myeloproliferative neoplasms (MPN) or MDS group of diseases. They are characterized in MPN by increased production of red blood cells, platelets, or one type of white blood cell; or in MDS by increased production of dysplastic hematopoietic cells, resulting in cytopenias.[3,4] They are associated with constitutional symptoms, high symptom burden, poor quality of life, and decreased life expectancy and risk of transformation to acute myeloid or other leukemia **(Fig. 1)**.

Why Do Various Conditions Evolve from the Same Mutation?

The JAK2 gene is a signaling molecule for many cytokines including: INF-γ, erythropoietin (EPO), prolactin, thrombopoietin, G-CSF, GM-CSF, and IL-3 via activating many signaling pathways like: MAPK, PI3, ERK20, and importantly STAT. JAK2 abnormalities present with different genetic alterations **(Table 2)**, the interplay of various genetic and cytokine abnormalities results in the clinical disease state and its severity.[3-5]

TABLE 2 Types of JAK2 abnormalities and pathogenesis

Rearrangements
JAK2 can be rearranged with other genes: • TEL/ETV6: t(9;12) (p24;p13) reported in myeloproliferative neoplasm (MPN), also in T-cell ALL • BCR: t (9;22) (p24;q11.2) reported in few MPN • PCM1: t (8;9) (p22;p24) reported in MPN, also in AML and ALL • NF-E2: der (9) t(9;12) (p24;q13) reported in MDS
Point mutations
V617F G >T at nucleotide 1849 on exon14, the classical MPNs T875N reported in AML (M7)
Deletions/Insertions
Exon12: In 4% PV patients there are >8 reported mutations including deletions and insertions in codon 538 to 543
Numerical
It can present as trisomy (+9) or be overexpressed due to amplification.

What is JAK2?

The JAK2 gene is a member of a family of genes that includes four Janus kinases 1, 2, 3, and tyrosine kinase 2. The protein group was named Janus kinases after the Roman God Janus with two faces, as the non-receptor kinases have two similar "active" and "inactive" domains.

The JAK gene has domains, which binds to type 1 cytokine receptor, it plays a role in trafficking of the (erythropoietin) EPO receptor (EPOR).

The JAK2 protein in contact with the cytoplasmic domain of the receptor catalyses tyrosine phosphorylation and leads to activation of signal transducer and activator of transcription (STAT) molecules that act as transcription factors and modifies other key regulatory pathways and cytokine signaling[3-5] (diagram illustrating functional JAK STAT pathway—**Fig. 2**).

The V617F mutated JAK2 spontaneously activates downstream STAT mediated transcription, and activation of ERK/MAP kinase and P13K/AKT pathways. The wildtype JAK2 has an autoinhibitory activity, and does not mediate such events. The hematopoietic stem cells in patients of myeloproliferative/myeloid disorders are extremely sensitive to growth factors; proliferation is

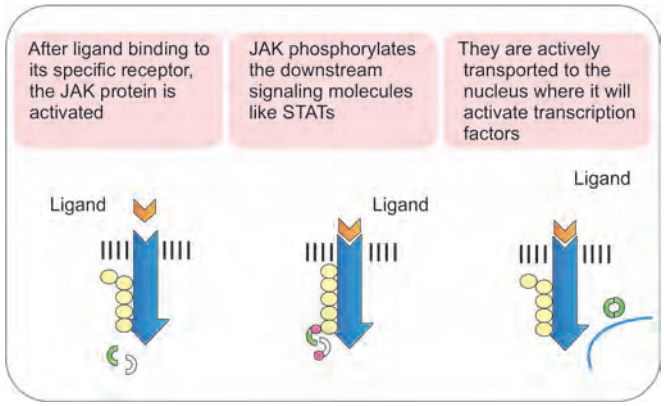

Fig. 2: Steps of JAK-STAT pathway

triggered by JAK2 signaling. Patients who are homozygous for JAK2 mutation have advanced disease and increased risk of progression to secondary myelofibrosis compared to heterozygous patients.[3-6]

Types of JAK2

JAK2 V617F occurs more frequently in a specific JAK2 haplotype, named JAK2 46/1 or GGCC, which is tagged by rs10974944 (C/G), rs12343867 (T/C), and rs4495487 (T/C). Other JAK2 mutations are more commonly associated with Budd Chiari and other disorders.[6-9]

Allele Burden and Disease

Allele burden has different implications in different diseases, a high V617F allele burden in PV is associated with a more aggressive phenotype, but a low allele burden in myelofibrosis is associated with reduced survival.[10]

JAK2 as a Target for Therapy

We now have agents, which are targeted inhibitors JAK2, and also has inhibits JAK1. This is approved for therapy of patients with intermediate- or high-risk MF, including primary MF (PMF), post-polycythemia vera MF (PPV-MF), and post-essential thrombocythemia MF (PET-MF), and PV patients with hydroxyurea (HU) failure or intolerance. Newer more specific JAK2 inhibitors are in phase 3 trials—fedratinib.

Clinical Features of MPN

The MPN are characterized by increased counts and constitutional symptoms **(Table 3)**. These may occur secondary to other conditions, so exclusion of renal, pulmonary causes of increased hemoglobin, or causes of reactive thrombocytosis etc. are necessary. Myelofibrosis is often missed or under diagnosed as the huge splenomegaly may be confused with other medical conditions. The bone marrow fibrosis results in massive splenomegaly, hepatomegaly, and extramedullary hematopoiesis as a compensatory mechanism. In India, patients with lower hemoglobin levels than standard criteria may be recognized; the other molecular tests and bone marrow evaluation are useful to identify them so that they can receive appropriate therapy. MPN patients particularly PV may show iron deficiency, this may be due to many reasons, but one important factor is disorder of iron metabolism, with the inflammation caused by PV counteracting Hepcidin suppression.[11] Iron therapy is controversial as the HU used in cytoreductive therapy in high-risk PV patients is more effective in iron-deficient than in iron-replete patients.

The diagnosis of MPNs is made in a symptomatic patient and requires a combination of parameters and tests.[12,13]

Diagnostic Criteria

The diagnosis of MPNs is made in a symptomatic patient and requires a combination of parameters and tests. The usual criteria followed are the WHO 2016 diagnostic criteria.

The diagnosis of MPN should be based on the 2016 WHO diagnostic criteria.[12] Criteria include specific findings from the CBC, blood smear, bone marrow analysis, correlated with clinical history, as well as the presence of certain molecular markers and the exclusion of other disorders.

Laboratory Tests

All patients should have a CBC, differential count test; this should be repeated to ensure no fallacy. Tests to fulfill diagnostic criteria of WHO criteria[12] should be done. In PV serum erythropoietin levels and evaluation to exclude causes of secondary polycythemia are required. In all patients, a detailed peripheral smear with evaluation for blasts, base line tests for RFT, LFT, evaluation for comorbidity, history of smoking, medications, etc., should be performed. Cardiovascular risk assessment is essential.

TABLE 3 Clinical features of JAK2 positive myeloproliferative diseases

MPN	*Clinical presentation*	*Features*
PV	• Median age 60 years, rare before 40 years. Male to female ratio 1.2:1. Median survival 14 years • Facial plethora, headaches • Heaviness of head, fatigue, weight loss, congestion of eyes, blurring vision or diplopia, and burning (erythromelalgia) sensation or itching in hands and feet, often worse after water (aquagenic pruritus). Increased risk of thrombosis—venous and arterial	• High number of RBCs (high hemoglobin, high hematocrit, red cell mass), bone marrow fibrosis, risk of thrombosis • Risk of post-PV myelofibrosis (MF) ET with poor outcome
ET	• Median age 65 years, but can be seen at any age. Female to male ratio 2:1 • Median survival 20 years • Headache, dizziness, fainting, chest pain, temporary vision changes • Numbness and tingling of hands and feet • Redness, throbbing, and burning pain in hands and feet (erythromelalgia) • Increased risk of thrombosis	• High platelet number, and risk of thrombosis. Bone marrow shows increased numbers of large, atypical megakaryocytes • Post ET myelofibrosis is rare, need to rule out if previous diagnosis of ET was actually early-phase of PMF
PMF	• Mean age 60 years. Male to female ration 1.5:1. Median survival 6 years. Increased constitutional symptoms in comparison to the blood count abnormality. Fatigue, weakness, shortness of breath, pain or fullness of abdomen (due to massive splenomegaly, hepatomegaly), early satiety, unintentional weightloss. • Fever, excessive sweating, fever, easy bruising, itching, bleeding, or bone pain	• De novo/primary MF (PMF) (rather than from the transformation of PV to MF) • Leukoerythroblastic blood smear with dacryocytes if marrow is fibrotic • Bone marrow fibrosis might be absent or minimal in early-stage/prefibrotic PMF • Reticulin or collagen fibrosis is considerable in overt PMF
CNL	Fatigue, weight loss, night sweats, bone pain, easy bruising, pruritus, or symptoms of gout	• Sustained neutrophilia in peripheral blood (cells are not immature), hepatosplenomegaly. Bone marrow is hypercellular with predominance of myeloid proliferation • CSF3R mutations may be present but not specific
CEL, NOS	Fatigue, fever, cough, muscle pain, itching, diarrhea, periorbital swelling, angioedema	• Eosinophilia due to clonal proliferation • Evidence of clonality; and abnormal bone marrow morphology
MPN-U	Same as other classic MPN	• Cases with features of an MPN but do not meet diagnostic criteria, either because features are not fully fulfill subtype or if not clear due to advanced stage or another diseases

MF, myelofibrosis; MPN-U, myeloproliferative neoplasm unclassifiable; NOS, not otherwise specified.

Diagnostic Molecular Testing

Testing for BCR-ABL1 mutation is required as by definition these conditions are BCR-ABL negative. Then evaluation for other MPN mutations should be performed. Molecular testing is used to assess clonality and to detect MPN-specific mutations. First testing for JAK2 V617F mutation should be performed in all MPN suspected patients; it is the most common mutation and occurs more than 95% patients with PV.

If the JAK2 V617F mutation is not detected, testing for CALR and then MPL mutations should follow for patients with ET or PMF.[12,13] If PV is still suspected in those with negative JAK2 V617F mutation results, testing should be performed for JAK2 exon 12 mutations. In those with ET or PMF but without JAK2, MPL, or CALR mutations (triple-negative MPNs), testing for mutations in ASXL1, CBL, CSF3R, DNM3TA, EZH2, IDH1, IDH2, LINK/SH2B3, SF3B1, SRSF2, TET2, TP53, and U2AF1 genes should then be considered. A comprehensive next generation sequencing (NGS) myeloid panel can be useful for this, instead of single-gene tests and provides details of additional prognostic genes.[13]

Bone Marrow

Bone marrow examination is very important and a bone marrow aspiration and biopsy is necessary confirm a diagnosis of MPN, and for prognosis by assessment of blast percentage and evidence of fibrosis.[12,13]

Cytogenetics

Cytogenetic analysis is important in distinguishing MPN subtypes. The chromosome analysis also serves to provide evidence of clonality and clonal evolution, it may be repeated if concerns of progression exist.

Prognosis

The overall survival of patients with MPNs is variable depending on the subtype. Several scoring systems and prognostic models have been developed for the risk stratification of patients with MPN. The dynamic international prognostic scoring system (DIPSS) is commonly used for its ease and ability to stratify patients into risk groups.[14] Treatment decisions are made per the risk stratification of the patient, higher risk patients are more likely to develop progression from their baseline MPN this can mean transformation to acute myeloid leukemia or post-fibrotic myelofibrosis. These secondary cases are more difficult to treat and have poorer prognosis.

Therapy

These patients must get a hematology consultation periodically due to their risk of thrombosis, progression, and symptom load. Shared care with primary care physicians is possible and desirable for low-risk patients. Therapy of MPN depends on the diagnosis, age, risk classification, and whether complications of thrombosis have occurred or not.[15-18]

Patients of PV and ET require low-dose aspirin to decrease the risk of thrombosis. Younger PV patients can be well managed by phlebotomy, and/or interferon alpha, but older patients or those with history of thrombosis require hydroxyurea (HU). HU is titrated to response; those who fail or are intolerant to HU can be given ruxolitinib (a JAK2 inhibitor). In ET along with low-dose aspirin, additional medications to reduce the platelet counts like hydroxyurea, anagrelide, and interferon alpha are used.[17,18]

Myelofibrosis low-risk patients may be given HU, thalidomide-prednisone or ruxolitinib. High-risk patients should be offered allo-hematopoietic stem cell transplant as a curative option. Patients with low-risk disease will have a longer life and supportive treatments like hydroxyurea and ruxolitinib are acceptable.[15,16] All of these treatments are palliative. For high-risk patients curative options of allogeneic hematopoietic stem cell transplant (bone marrow transplant, BMT) should be discussed and planned.

Glossary

- A gene is polymorphic if more than one allele occupies the gene's locus within a population. A polymorphic variant of a gene can lead to the abnormal expression or abnormal form of protein. These may cause or be associated with diseases.
- An allele is any of the possible forms in which a gene for a specific trait can occur. In humans, two alleles for each gene are inherited, one from each parent. The variant alleles arise by mutation and are found at the same place as the original gene on the chromosome.
- Wildtype gene is in its normal state, mutated gene has acquired or inherited alterations.
- Allele burden One, called the gene-dosage hypothesis, postulates a correlation between disease phenotype and the proportion of JAK2 (V617F) mutant alleles introducing the concept of allele burden, that is, the ratio between mutant and wildtype JAK2 in hematopoietic cells.
- Haplotype—A haplotype is a group of genes, which is inherited together by an organism from a single parent.

Conclusion

JAK2 associated conditions of PV, ET, and PMF may be underrecognized and underdiagnosed. The rare conditions associated with JAK2 are also often missed. High index of suspicion, appropriate tests, and timely referral can change the scenario. Correct diagnosis and treatment can prevent serous thrombotic complications and allow access to recommended treatment will help the patient.

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CHAPTER

234 Approach to a Case of Polycythemia: More Blood May Be Bad....

Tuphan Kanti Dolai, Prakash Singh Shekhawat, Malini Garg

Abstract

A 59-year-old male teacher reported with painful erythematous finger swelling and excessive itching without any rash of 3-week duration. Physical examination shows multiple excoriations, splenomegaly, and erythematous swelling of hands. Vitals were normal. Complete blood count shows Hb 17 g/dL, MCV 87 fL, TLC 14 × 10^9/L, and platelet 780 × 10^9/L. Biochemistry shows normal LFT and urea, creatinine while serum EPO was 2.4 U/L (range 7–20 U/L). He had JAK2V617F mutation and was started on regular phlebotomy and Tab Aspirin 75 mg PO OD. His hand swelling and pruritus improved.

Introduction

Polycythemia means an abnormal increase in hemoglobin or hematocrit. It is categorized as absolute and relative. Absolute polycythemia has an increased red blood cell mass (RCM), the classical example being polycythemia vera (PV). There is a mild rise in hematocrit without raised RCM in cases of relative polycythemia like severe dengue fever, severe diarrhea, or other conditions with a moderate increase of hematocrit secondary to reduced plasma volume. Absolute polycythemia is categorized into primary and secondary.[1,2] PV is the standard example for primary absolute polycythemia. Secondary absolute polycythemia has hypoxia, because of chronic lung disease, carboxyhemoglobinemia due to smoking and renal cell carcinoma producing erythropoietin. PV is a clonal malignant disorder arising from a mutation in multipotent hematopoietic stem cells with an increase in blood cell production independent of cytokine. It is the commonest myeloproliferative neoplasm (MPN) in the United States and has a male preponderance with median age of diagnosis in the seventh decade.[3] Annual incidence ranges from 1–2.5 per 100,000 persons in different countries.

Etiology and Pathogenesis

Primary polycythemia is caused by dysregulation in erythropoietin sensing mechanism and is mainly associated with low erythropoietin levels. Primary familial and congenital polycythemia has an EPOR gene mutation, which disrupts down regulation of JAK2 pathways. PV is due to an acquired, somatic mutation of multipotent hematopoietic stem cell triggering clonal proliferation plus suppression of normal polyclonal hematopoiesis. Most common mutation is JAK2V617F found in 95–98% of cases.[4] It causes persistent activation of EPO receptor signaling. In vitro development of erythroid colonies in absence of EPO is characteristic of PV.[3] PV can occur at any age because JAK2V617F expression is age-independent.[5]

Secondary polycythemia has increased erythropoietin production because of hypoxia. Secondary familial and congenital polycythemia may have mutations that exist in genes encoding hypoxia inducible factor (HIF), von Hippel-Lindau (VHL) proteins, or prolyl-hydroxylase domain (PHD) enzymes, which regulate renal oxygen sensing and EPO production. Secondary acquired causes have increased EPO levels either secondary to tissue hypoxia (pulmonary illness, CO poisoning, high

altitude, high-affinity binding hemoglobinopathy) or due to overproduction (stenosis of renal artery, kidney cyst, tumors with ectopic EPO production). Smoking history or occupational exposure to hydrocarbon may lead to increased carboxyhemoglobin and increased EPO levels.[4] Separation of primary and secondary polycythemia is important as primary polycythemia has risk of leukemic/fibrotic transformation. Phlebotomy is rarely needed in secondary polycythemia unlike primary polycythemia.[3]

Diagnosis

Polycythemic patients are often diagnosed incidentally having elevated hemoglobin or hematocrit found in CBC during baseline evaluation of other complaints. History of smoking, high altitude stay, congenital heart disease, alcohol, and drug abuse along with clinical examination becomes very important to distinguish secondary from primary causes.

Clinical spectrum varies from no symptoms to life threatening thrombosis. Genesis of these symptoms could be related to increased RCM or the underlying disease process. Increased RCM may cause hyperviscosity resulting in symptoms like vertigo, tinnitus, headache, visual disturbance, and hypertension. Both usual and unusual types of arterial and venous thrombosis can be seen. Thrombotic symptoms depend upon the site and the extent of thrombus. Polycythemic patients may have characteristic ruddy complexion.

Although aquagenic pruritus and peptic ulcer disease are common associates of polycythemia, commonly they may have signs and symptoms of the underlying disease like chronic obstructive airway disease (COAD) or cyanotic heart disease. Apart from the signs of the underlying disease patient may have splenomegaly, which is rarely seen in early phase of the disease.[4]

Pretreatment correct diagnosis is essential. Overt PV is easily revealed by clinical findings.[6] Splenomegaly is seen in 75% of the cases and is rare in other varieties.[6] Around 30% cases have hepatomegaly. Pruritus occurs in 40% of PV cases and is rare in other varieties of polycythemia. Associated thrombocytosis, leucocytosis, or basophilia indicates the diagnosis of polycythemia vera. Panmyelosis is seen in bone marrow.[6] Diagnostic marrow studies commonly show reticulin fibrosis and absent iron stores. Bone marrow cytogenetics shows clonal markers in 13–31% of untreated patients.[6] In patients lacking definite evidence of PV the differential diagnosis includes early or mild polycythemia vera, primary pure erythrocytosis or secondary erythrocytosis.[6] The history and physical examination may give clues to the presence of a cause for secondary erythrocytosis. Additional laboratory testing is often helpful. An oxygen saturation < 92% indicates hypoxemia as the cause for polycythemia.[6] HPLC and oxygen dissociation curve can pick high oxygen affinity hemoglobins which usually has a family history. Renal ultrasound, intravenous pyelography, or computed tomography is essential to rule out suspected renal lesion. In selected patients hepatic lesion is diagnosed by ultrasound, CT scan, or radionuclide scan. Similarly, for cerebellar hemangioblastoma a CT brain with stress on the posterior fossa is helpful and can determine the source of ectopic EPO production. Commercially available serum erythropoietin radioimmunoassay is helpful in differential diagnosis. Overall, increased erythropoietin suggests secondary erythrocytosis, whereas a normal value is uncertain as occasionally erythropoietin may be increased in secondary erythrocytosis. Erythropoietin assay may be most useful in those lacking obvious clinical sign of PV and no apparent cause for secondary erythrocytosis.[6] In PV patients endogenous colony formation occurs without added erythropoietin, whereas for other causes of polycythemia exogenous erythropoietin should be added.[6] **Flowchart 1** shows the approach to polycythemia.

WHO defines polycythemia vera as a myeloproliferative neoplasm with hemoglobin level >165 g/L (16.5 g/dL) for males and >160 g/L (16 g/dL) for females or hematocrit levels >49% in men or >48% in women or increased red cell mass (RCM) >25% from baseline **(Table 1)**.

Treatment of Polycythemia Vera

Age, sex, initial presenting symptoms along with blood picture must be considered for individualized therapy. Goal of therapy is to decrease symptoms, reduce likelihood of thrombus, and prevent/delay transformation.

Phlebotomy: Initially phlebotomy is needed in all patients to keep hematocrit <45% to reduce the risk of thrombotic and cardiovascular complications.[8,9] In young fit, a 450 mL phlebotomy is safely done on alternate days till this goal is reached. In older, unfit patients smaller phlebotomies approximately 200–300 mL twice weekly can be considered.[6] A standard unit of phlebotomy

Flowchart 1: The approach to polycythemia

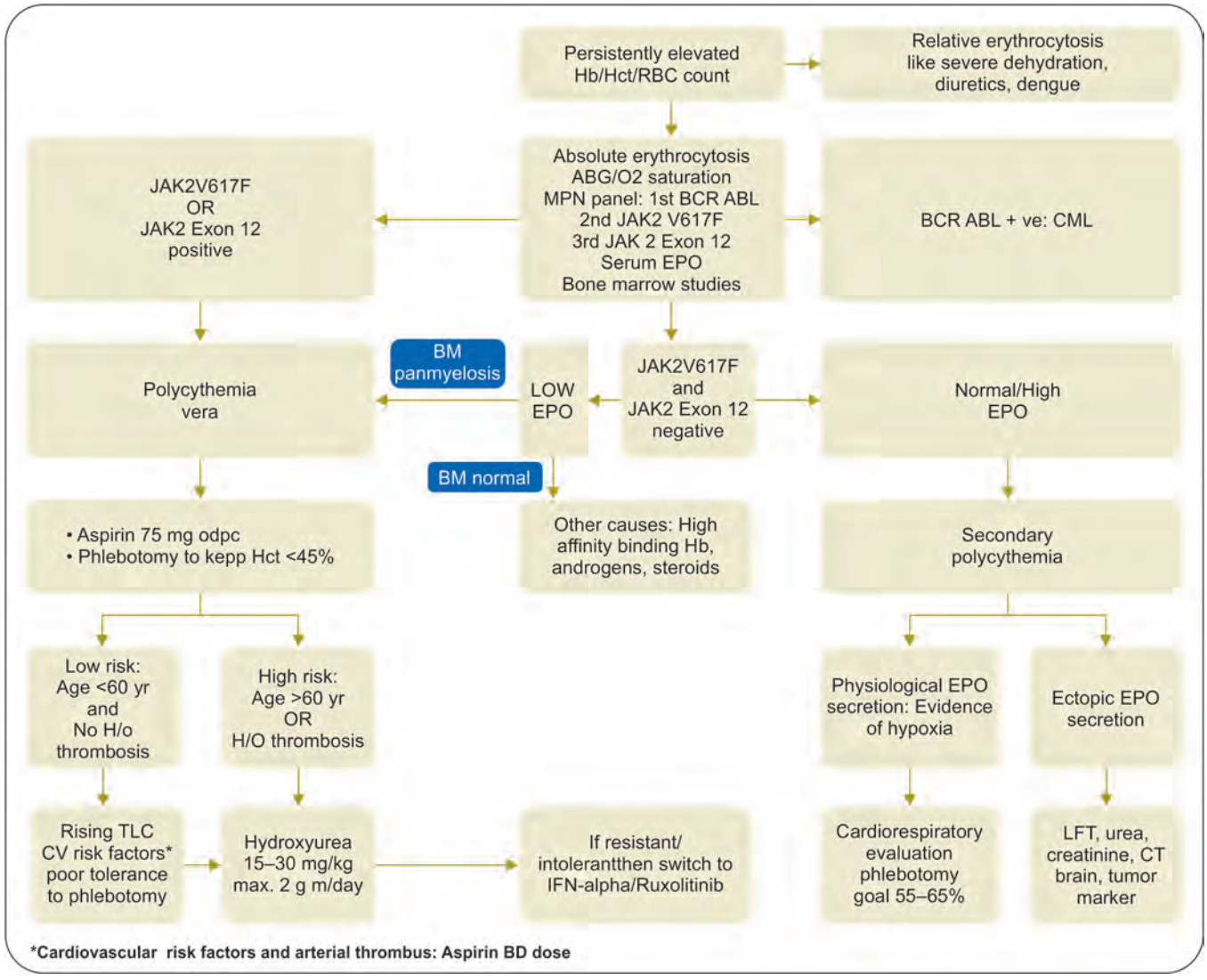

TABLE 1 WHO 2016 PV diagnostic criteria[7]

Major criteria	• Hb >16.5 g/dL in men (or Hct > 49%), Hb >16 g/dL in fematles (or Hct >48%), or >25% increase in red cell mass • Bone marrow biopsy showing characteristic panmyelosis and pleomorphic megakaryocytes • Mutation in JAK2V617F or JAK2 exon
Minor criteria	Serum EPO level below the normal reference range
Diagnosis	• All three major criteria or • First two major criteria and the minor criterion

TABLE 2 Polycythemia vera risk stratification[7]

PV risk stratification	*Age ≤60 years*	*Age >60 years*
No history of thrombosis	Low risk	High risk
History of thrombosis	High risk	High risk

decreases Hct by 3%. Polycythemia Vera Study Group (PVSG) recommends use of myelosuppressive treatment. Cytoreduction is usually not needed in low risk group whereas it is used in high risk group **(Table 2)**.

Hydroxyurea (HU): HU, a ribonucleotide reductase inhibitor, is effective and first-line recommendation for cytoreduction in high risk group. Need of cytoreduction or other therapy should be individualized, and this reminds us of Dameshek. "There is a tendency in medical practice—by no means limited to hematologists—to treat almost any condition as vigorously as possible. In hematology, this consists in attempting to change an abnormal number—whether this number is the hematocrit, white cell count, or platelet count to get normal values, whether the patient needs it or not!"[10] Overall hydroxyurea is the commonest cytoreductive drug used for ET and PV cases, based on the results of the PT-1 randomized controlled trial in 809 high-risk patients with ET, in which HU proved superiority to anagrelide in the rates of serious hemorrhage, arterial thrombosis, and myelofibrosis progression[11,12]

Interferons: Interferon-α is an important drug if HU is no longer suitable for a patient. Newer longer acting pegylated-α-2a is available and can allow less frequent administration. IFN-α has anti-clonal activity and also helps in histological improvement.[13,14]

Although it does not have leukemogenic effect and is safe for long-term use but flu-like symptoms and mood changes often limit its use.

Ruxolitinib: The JAK1/2 inhibitor ruxolitinib is approved therapy for PV cases where HU is intolerant or refractory, based on RESPONSE and RESPONSE-2 studies in patients with or without splenomegaly, respectively.[15-17] It is given in 15–20 mg BD doses for symptom control.

Treatment of Secondary Polycythemia

Cause and underlying mechanism will help in deciding treatment for polycythemia, especially secondary causes. Aggravating factors like smoking and dehydration must be rectified. Smokers must be encouraged to refrain from tobacco usage. Diuretics can reduce plasma volume, increase hyperviscosity, and thus are avoided where possible. Drugs like Androgens must be carefully discontinued or lower doses used if feasible. Smoking cessation helps in reversal of polycythemia related to carboxyhemoglobinemia and it can improve chronic obstructive pulmonary disease associated polycythemia.[6] Continuous low flow oxygen therapy may reduce hematocrit and it improves status of hypoxemic patients due to sleep apnea and chronic obstructive pulmonary disease.[18] Reducing weight may be helpful in obesity-hypoventilation syndrome. Surgical removal of EPO producing lesions usually causes improvement and resolution of the polycythemia. Likewise, polycythemia reversal may be seen after correcting underlying benign renal lesion. Some secondary polycythemics require phlebotomy. Preoperative elective phlebotomy should be considered in these cases.[6] The ideal hematocrit level in these patients is a tough call, to maximize the oxygen carrying capacity, and minimize the deleterious side effects of hyperviscosity.[6] The ideal hematocrit differs with the main disorder and usually differ amongst patients with the same illness. Usually hematocrit >60% is expected to be harmful and they must undergo phlebotomy, especially when sign/symptoms of poor oxygenation are seen.[6] There is decreased arteriovenous oxygen difference, improvement in pulmonary artery resistance, better right ventricular function along with improved hemodynamics and exercise tolerance.[6] Maintaining hematocrit between 50–55% is likely to help hypoxic lung patients. Acute hemodynamic effects of phlebotomy can be managed by isovolumic phlebotomy. Myelosuppressive treatment is best avoided in cases of secondary erythrocytosis.

Treatment of Relative Polycythemia

Numerous factors are responsible for the relatively increased hematocrit. Abstaining from alcohol intake and smoking may be helpful. Strict hypertension management is essential. Hydration status should be well supported. Phlebotomy is not recommended in cases of relative polycythemia.

Conclusion

Polycythemia included variety of causes from smoking, high altitude, dehydration, congenital heart disease to the clonal polycythemia vera, which has a risk of leukemic progression. They have an increased likelihood of vascular manifestation and risk of thrombosis. Goal is to keep Hct <45% and a cardiovascular risk factor modification. Phlebotomy and aspirin forms important part of treatment along with hydroxyurea or interferons in selected cases. Ruxolitinib is approved for HU resistant or intolerant cases.

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Section 20

Section Editor: **SV Kulkarni**

Technology and Medicine

CHAPTER

235 Artificial Intelligence: The Space-X of Diabetology!

Hem Shanker Sharma

Abstract

The age of pestilence and famine was muddled with malnutrition and infectious diseases. Metaphorically we are already sitting on the top of a volcano, the number of diabetics have already affected almost half a billion people. The artificial intelligence (AI) has revolutionized all spheres of life. The discussions on the application of AI in health-care system is omnipresent, this underlies the huge hidden potential of this unique technology in dethroning the enormous burden of several chronic medical conditions. This is an era of Industry 4.0, which is a refabricated concept of smart production and application, that is identified with the 4th industrial revolution and the emergence of cyber-physical systems and this shall govern the future of medicine. The most flabbergasting advances in the application of AI techniques come from data-driven methodologies that learn from large datasets. With AI at hand the diabetes management is headed for an elegant, personalized, custom-made management of therapies, at the level of most minuscule stratum of medical care!

Introduction (from Pestilence to Diabetes)

The age of *pestilence and famine* was flooded with malnutrition and infectious diseases. The high-fertility rates seeking to explode the living population were dismantled by an equated killing competence of these infirmities. This gradually paved way for the mechanized world with cozy couches and watches devoid of time to engage in any sort of physical activity. This again led to malnutrition, but this time featuring the other end of the spectrum. The resulting epidemic of obesity, hypertension, and diabetes signaled the new age of indolence and metabolic syndrome. Metaphorically we are already sitting on the top of a volcano, the number of diabetics have already affected almost half a billion people.

Cracking Ominous Octet with Artificial Intelligence

The complex interaction of the ominous octet for the causation and feasible interjections, which has to be intervened to diagnose and treat the diabetes has to be envisaged with something equally intelligent. The smart machines that are being made to *think and behave* in humane manner are transforming the way we manage these complexities. Way back in the 1950s, the fathers of the field Minsky and McCarthy, described artificial intelligence (AI) as any task performed by a program or a machine, which uses human intelligence to accomplish it. The AI has revolutionized all spheres of life. The discussions on the application of AI in health-care system is omnipresent, this underlies the huge potential of this unique technology in deforesting the enormous burden of several chronic medical conditions. At present diabetes appears to be the brand ambassador for its application in health care for a number of reasons.[1] This is an era of Industry 4.0, which is a restructured concept of smart production and application, that is identified with the fourth industrial revolution and the emergence of cyber-physical systems and this shall govern the future of medicine. Intelligent algorithms are utilized extensively in

the data driven methods to sustain sophisticated analysis and provide specific medical aid. This is being harnessed by a number of healthcare-related companies.[2]

Information: The Key to Intelligence

Acquirement of information is the key input required for exhibition of intelligent behavior. Because learning is an effectual way to instigate such knowledge, most AI applies such learning techniques. The chief aim of learning from knowledge is to let computers become skilled robotically without human interference or aid. The unearthing of knowledge revolves around the investigation and conception of algorithms for retrieving potential information from databases; this is commonly known as knowledge discovery in databases. Its prime purpose is to identify valid, potentially useful, and comprehensible information. The AI has already begun to revitalize the strategies to control blood glucose, the timely and correct prediction of blood glucose level, the detection of severe glycemic events, the life style support, the meal detection, and calculation of the confusing insulin boluses.

The Long Held Dream of an Artificial Pancreas

Creation of an artificial pancreas has been frantically attempted over the past decade. It consists of a mechanized system that has been made to mimics the physiology of islet cells, which include a sensor for glucose, a closed-loop management algorithm, and an infusion device for introduction of insulin. The eventual objective of this system is to perk up overall diabetes management and to trim down the frequency of life-threatening events associated with insulin dependent diabetes. The algorithms used by the artificial pancreas to compute the dosage of insulin have been thoroughly investigated, either by means of data from patients or processor created *virtual patients*. The foremost candidate algorithms are obtained from conventional control engineering theory; however, AI has become more time-honored over the past few years and could, in due course, provide better candidates to congregate the challenges of an artificial pancreas.[3,4] In a recently concluded trial which involved the evaluation of the remote patient monitoring of the fuzzy logic controller, the artificial pancreas was tested on 75 patients with insulin dependent diabetes for four successive nights. The results verified safe and competent glycemic control.[5] The fuzzy logic uses a method of reasoning that mimics human intelligence.

Conducive Insulin-Glucose Dynamics!

Harmonizing with the advances in control algorithms, efforts are being applied to progress with the models that can crack the insulin-glucose dynamics. Focus in applying neural networks for identification and control of nonlinear systems has garnered great attention. Zarkogianni et al, developed a neural network skilled with a synchronized learning algorithm that models the blood glucose kinetics of diabetic patients and foretells the glucose levels using information obtained from meal, glucose measurements, and the amount of insulin infused.[6-8] The aptitude to predict the blood glucose fluctuations would be a blessing, because it shall provide the early warnings concerning futile or poor treatments being given to the patient. Although the real-time anticipation of the glucose levels is quite challenging, pertaining to the number of physiological factors involving in the tug of war to maintain it, such as delays allied with assimilation of food and insulin, the wider variations in food intake and inadvertent stress situations which can dismantle the hemostat, but AI can take many of these variables into account to cut down the possible fallacies associated with the measurements.[9] As with blood glucose anticipation, AI has been put to use for real-time prediction of adverse glycemic episode and this involves a set of tools that deal with the convolutions of effective glucose control. These paraphernalia facilitate to spot the incidence of adverse glycemic events and give ample time to respond swiftly to their effects. This analysis takes into account the continuous glucose monitoring, self reported glucose monitoring, the EEG using the neural-fuzzy interference system to interpret and analyze the data.[10-12]

The Tedious Task for Glycemic Harmony

The most widespread insulin therapies for diabetics, the dosing computation for subcutaneous insulin and multiple daily insulin injections run based on similar doctrine.[13] The estimation of desirable insulin doses and the evaluation of the amount of calories gulped in a diet is a regular hurdle in the life of many patients dependent on insulin for their sugar management. Bolus dose advisors base their calculations on

- Insulin doses being already used
- Measurement of blood glucose level
- Premeditated carbohydrate estimates
- Insulin-to-carbohydrate ratio
- Insulin sensitivity

Manual calculation of bolus doses and counting calories can be multifarious and exigent because individuals must mull over multiple parameters to attain pleasing glucose control, and blunder of these values, if any, might very well turn the tide against harmony. To bear caloric assessment and determination of insulin doses, tools for providing bolus recommendations and carbohydrate estimates are being adopted progressively. These tools seek to boost the precision of insulin doses. Researchers at the Imperial College of London carried out an all-embracing study of an insulin doses calculation by means of case-based reasoning methodology.[14-18] The approach that they applied, which takes into account an assortment of enthusiastically optimized diabetes scenarios, was verified to be a secure decision-making algorithm. At the University of Bern, The Center for Biomedical Engineering Research carried out more than a few imperative and all-embracing studies[15-19] to explore the GoCARB system, which puts forth dietetic counsel to diabetic patients based on mechanical carbohydrate counting. Pilot studies identify it to be a brilliant assistive tool.

One Touch Personalized Care

Treatment of diabetes is influenced by bundle of inexorable factors, incorporating high intra- and interpatient inconsistencies that can spectacularly impact quality of life and undercut the medication adherence even when patients follow their treatment regime austerely. Such unpredictability sternly confines the use of universal models, which cannot incarcerate the specific physiologies. Thus, an imperative step en route for better risk recognition and intrusion is personalization of the system. Over the past decade, foremost investigative efforts have been loyal to developing administrative tools capable of stratifying patients in different segments of the population. Algorithms proficient in early uncovering of grave events affecting glycemic control, such as an infusion set failure, are critical for systematic automation. Physical activities offer multitude of benefits for diabetic patients, but these can also set hurdles in the management of diabetes. Systems and tools focused on programmed detection of exercise could develop the precision of treatments. Jacobs et al. anticipated a regression model to mechanically detect exercise in patients who carry an accelerometer and a heart rate sensor.[24] Turksoy et al. have worked on the development of a meal recognition structure based on scrutiny of continuous glucose monitoring signals using a fuzzy system to approximate the calorie content,[20-24] it revealed a sensitivity of 91.3% and an error of 23.1% in carbohydrate inference. Recently, Everett et al. offered a data system using a machine learning to endorse submission to physical activity and weight reduction. Insulin pump malfunction may upshot a protracted hyperglycemia or diabetic ketoacidosis. Detection in the early hours of failure could curtail the connected risk. Cescon et al. projected the exploitation of autoregressive model to develop a patient vigilance system. Miller et al. used a machine learning modus operandi to haul out information from drug prescriptions from electronic health record data and categorize factors tied with patient care flaws. Moreover, tools have been developed to scrutinize clinical schedules, prescriptions, and therapy adherence.

Conclusion

Transition from intelligent caretaker to intelligent care!
Beginning with the time of diagnosis, patients are obligated to optimize their lives to deal with complications and other comorbid state of affairs, with the overall goal of enhancing their own care. Time tested technologies and data warehouses bring-in-hand the solutions that replicate the data system and make eminent decisions based upon them. The most awe-inspiring advances in the application of AI techniques come from data-driven methodologies that learn from large datasets. With AI at hand the diabetes management is headed for an elegant, personalized, custom-made management of therapies, at the level of most minuscule stratum of patients or even individuals.

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CHAPTER

236 Utilities of Smartphone Applications in Medical Practice

Ashish Gautam, Prabhat Agrawal, Nikhil Pursnani,
Ajeet Singh Chahar, Vijay Singhal, Jitendra Doneria

Abstract

Smartphones have gained the position of personal assistant and full time companions for us. They are featured with numerous properties that can be used in various ways in our personal and professional life. Smartphone applications have several utility features that can be used to manage patients at clinics, hospital, and even from home. Applications can also be used for patient appointments, tracking medical records, diagnosing disease, planning treatment, follow-up care, real time treatment monitoring, risk calculation, and training and education. Using applications not only saves time at clinic but also accuracy of treatment plan improves significantly. Treatment and management methods are changing rapidly in the modern world, due to which a clinician must be aware of these technologies. A judicious use of these applications can effectively change the way of our clinical practice.

Introduction

Smartphone is greatest invention of this decade which has transformed our life both in good and bad ways. Their judicious use not only gives a better way of living but also have favorable effects on our physical and mental health. Utility applications in smartphones are the key of their success and worldwide acceptance in every professional field. In different ways, these applications have changed the tradition of clinical practice both at basic and advance level. But actually, these applications are not used in their full strength and their awareness among medical fraternity is minimal. Ignorance, lack of confidence for their use, and firm belief over traditional methods of practice are the main reasons for their under use. These applications can assist health care professionals (HCPs) for clinical judgment making, maintaining severity score, and follow-up on records, medical education and research, e-consultations and e-clinics, ready references and drug dose calculations, and legal consultations. Smartphone can never be a replacement of clinician. They are just clinicians assistant which help them to deliver better health care.

What are "Apps"?

Smartphone Applications are simple software programs designed to run on them to accomplish a specific and targeted task. Smartphone applications are of three types:

Native mobile apps: These apps are developed for one platform and are "native" to smartphone. They are preinstalled in your phone when purchased.

Hybrid mobile apps: They are downloaded from application marked and after installation they work like native apps, but they need internet and run on web browsers.

Web apps: New technology in app developed makes website to change its shape size and design according to screen size. These responsive websites thus can be accessed from different devices with extreme ease to use. Similarly, latest self adaptive web applications scale themselves to fit the different screen sizes of smartphone and similar devices.

Utility of Smartphone Devices for Health-Care System and Professionals

Features of Smartphones

Smartphone devices are featured with both different modes of communication and are useful for computing also. Because of handy size and ease of use they can be used as point of care (POC) anywhere and anytime. Besides voice calling and texting new generation devices are also having several hi-tech functions, such as browsing, GPS, ultra high quality/megapixel cameras with high definition modes, and voice/sound recorders.

Need for all Purpose Use of Smartphone Applications at POC

Broad categories of uses of smartphone applications at a POC under which we can utilize them are listed below:

- *Communication:* Voice calling, text messages & social media chatting/video calling applications, video conferencing, e-mail.
- *Hospital information system (HIS):* E-medical record (EMR), clinical decision support system (CDSS), picture archiving & communication system (PA&CS), laboratory information system (LIS), and e-health record (EHR).[1]
- *Informational resources:* e-journals, textbooks, guidelines, medical literature, drug references.
- *Clinical software applications:* Disease diagnosis aids, medical calculators, risk assessment calculators, drug dose calculators, etc.[2]

Apps for Data Management and Education

HCPs use smartphone apps for several purposes. A few of popular applications are mentioned in **Table 1**.

Recording and Sharing Data and Daily Schedules

Applications are often used for gathering and recording information, time management, and planning daily schedule. *Evernote, Notability,* and *Gboard*, assists user to dictate and/or write text and prepare notes, audio files recording, store and store photographs, and systematize different files into category contained by a searchable e-database.[3] Few apps develop modify the text from literature in such a way that it looks like a book. Most preferred E-book reader apps are *GoodReader, iAnnotate,* and *Kindle*. They make possible users to underline and highlight text as we do in books. Text and pictures can be enlarged also. Cloud enabled storage and file-sharing services such as *Dropbox,* and *Google Drive*, are used to store, update, and share documents or photographs with others without physically exchanging a flash drive or compact discs.[4]

Communication and Consulting

While working in existing health-care systems HCPs often have to visit different places in a day like clinics, wards, emergency department, operation theaters, laboratories, ICU, etc. Our health-care system is very diverse and without moving to these places giving adequate care is not possible. So, HCPs not only need to be keep themselves mobile but also need to be able to communicate and collaborate with people in these different locations.[5] Social networking apps like *whatsapp, telegram,* etc. are utility tools for enabling consultations while they are on move.

Medical Search Engines

PubMed/MEDLINE apps are equipped with powerful search engines facilitate searches of medical literature databases to identify published medical information. Smartphone medical literature search apps useful for HCPs are: *PubSearch, Medscape,* and *MEDLINE Database on Tap.*[5] Articles on *NEJM*, *The Lancet*, and *BMJ* apps can be viewed on smartphone devices.

Drug References

These groups of applications are used to get drug information like drug name, indication, dosage, side effect and interactions, contraindications, cost, and dose calculators. The most frequently used smartphone drug reference apps include: *Epocrates, Micromedex,* and *RxDrugs.*

News and Updates

MedPage Today provides breaking medical news with facility to organize news by significance, and obtaining CME credit hours.[6]

Apps Dedicated for Patient Management

Clinical Decision-Making

Smartphone are easy way to access the diagnostic clues for any disease and also let you know the differential

TABLE 1 Popular applications and their utilities

Basic purpose of application	*Examples*	*Utility*
Data collection, Data storage, and sharing	Evernote	Taking notes, vocal typing, and organization
	Notability	
	iAnnotate	PDF editing and viewer, highlighting and making notes and annotation on PDF
	GoodReader	
	dropBox	Storage in Cloud space and sharing different file formats. Limited space, which can be expanded on purchase
	box	
	Google Drive	
Communication and Consulting	Clinked	Social communication/networking site for HCPs
	Idloom-wall	
Ready reference and Information seeking	Epocrate	Medical reference and drug detailing
	Dynamed	
	Skyscape/Omnio	
	Micromedex	Drug and pharmaceutical reference
	Medscape	Clinical reference
	Dynamed	
	Medpage-Today	News and updates in medical research and practice
Tracking patient care and management and Monitoring health	Diagnosaurus	Diagnostic clues and differential diagnosis
	Pocket Lab	Laboratory reference values
	Archimedes	Biomedical Stat and clinical calculators
	Med-Calc	
	Mediquation	
	Calculate	
	AHRQ ePSS	Screening for disease and prevention by regular health parameter monitoring
Training and Education	MedPage Today	CME
	QuantiaMD	

diagnose. All the details available about a particular disease are updated and are evidenced based. Printed medical references previously used for disease diagnosis are now available at smartphone device apps that provide information on diagnosis, treatment, differential diagnosis, risk calculators, severity assessment, evidence development, and guiding flowcharts. Such apps include: *Dynamed, 5-Minute Clinical Consult (5MCC),* and *UpToDate.*[3] On the spot accurate decision to order disease specific tests and procedures reducing cost of care. Pathology and biochemistry laboratory test apps are used for reference values and interpretation. Few advance apps provide causes for abnormal values also, for example, *Pocket Lab Values* and *LabProValues.* Few apps are useful for visual acuity or color blindness, as well as blood pressure or glucose level determination.[4] *iSeismometer* gives analysis of electromyogram produced by measured tremor frequency by this app. *iMurmur* is a collection of 20 types of heart murmurs sounds, to learn and compare the physician's observations. *Perfect OB Wheel* app determines pregnancy due dates very accurately by using an ultrasonographic observations and date of last period. In our day-to-day practice there are several indices need to be calculated for treatment decisions and follow-up purposes. This requires several data to be put into complex formulas which actually is very tedious job and takes toll of time.[5] Medical calculators facilitate HCPs to determine easy calculation of various and indices. BMI, BSA, e-GFR, maddrey's discriminate function, MELD and PELD scores, and several other such applications are available at app

market which can be downloaded free of charges. Thus, HCPs only need to enter the parameters in applications to quickly produce a reliable result. Popular medical calculators are *MedCalc, Mediquations,* and *Calculate.*

Patient Tracking and Monitoring

Smartphone apps play a wonderful role to monitor vital stats, general health, and location of patients with chronic diseases or conditions even from remote places. *iWander* monitors and tracks patients with Alzheimer's disease who are prone to lost the way to or fro from home using the smartphone device GPS. Highly sensitive microphone of smartphone is used as sensor to record and analyze cardiac sounds by app *iStethoscope.* Few app in smartphone devices have also been used to track heart rate and rhythm by precision.

Medical Education and Training

Technology enabled medical studies is a real need of future. Development of mammoth sized data from various researches and studies is not possible to carry in books and hard copies of journals. Also quick ease of availability of any small information from sea of literature can be easily accessed using simple applications. Thus, smartphone devices are used by medical students to log their experiences, to access information about drugs and diseases, to perform calculations, and to make basic notes. Several smartphone apps for medical students can be used for knowledge assessment, such as case study quizzes.

Benefits Provided by Smartphone Devices and Apps for Health-care Professionals

Advanced smartphone gadgets and applications have given numerous advantages to HCPs, permitting them to settle on more fast choices with a lower mistake rate, expanding the nature of information the executives and availability, and improving practice proficiency and information. These and different advantages advanced smartphone gadgets are.

Convenience

Medical care experts get various comforts with utilizing a smartphone and PDA gadget in clinical practice, for example, transportability, and fast admittance to data and sight and sound assets, adaptable correspondences. Despite the fact that there will never be an option in contrast to conventional books; however, now clinical understudies no longer need to convey thick reference books.[1]

Better Clinical Decision-Making

Numerous clinical applications make advanced mobile phone gadgets priceless instruments that help clinical dynamic at the purpose of care. This quality is significant when rehearsing proof based medication, since clinicians may not generally look for answers to every clinical inquiry while doing assessment a case.

Improved Accuracy

More precise diagnostic coding, more successive documentation of symptoms, and expanded prescription wellbeing through diminished clinical blunders is conceivable with advanced mobile phone applications. Convenient correspondence inside emergency clinics has additionally been resolved to lessen clinical mistakes, particularly in basic consideration conditions.

Increased Efficiency

The utilization of smartphones has been appeared to give HCPs various upgraded efficiencies, including: expanded nature of patient documentation through less mistakes and more complete records, more fast admittance to new data, and improved work process designs. Physicians have reported that the use of a smartphone device for retrieving information from a drug database led to more efficient decision-making and patient care.[2]

Enhanced Productivity

Work process speed is likewise a significant part of treatment while thinking about the colossal populace in line for treatment. This requires expansion of efficiency with more exactness of medical care framework. For example, advanced mobile phone applications help increment pharmacist profitability by permitting significant medication data like contraindications and interactions, to be checked rapidly, bringing about fast handling of prescriptions.[6]

Future Trends for Smartphone Devices and Apps in Health Care

As it is happening in various different fields identified with way of life, routine works, and diversion, advanced

smartphone applications are assuming a significant function in medical care framework too. Positive and game changing patterns with respect to the utilization of advanced smartphone gadgets and applications in medical services have been anticipated for what's to come. As better physical and emotional wellness upkeep become the possible objective of the medical services framework, applications will be expected to satisfy that reason. The prevention and management of chronic health conditions, such as diabetes, obesity, and heart disease, is biggest challenge for HCPs and health-care governance system. Patient care management and compliance are other difficult challenges, especially in Indian scenario where doctor-patient ratio is far below the target. Smartphone/PDA and its applications, which can illuminate a few comparative purposes and effectively address these issues are required and anxiously anticipated. Accessibility of monetary and moderate advanced mobile phones builds its possession in each financial class of licenses, which is beyond the realm of imagination with PC Future applications will likewise have capacity to synchronize with medical clinic information base so HCPs can get to any patient record. These applications will likewise assist HCPs with observing the indoor patients continuously. Such measures will enable HCPs to use smartphone apps in a more meaningful way that hopefully leads to improved patient care. Medical services instruction as on when required is additionally a significant field to advance in future. As the utilization of clinical gadgets and applications grows, more instructive medical care programs are required to incorporate them into clinical educational plan. With the rapidly changing world, a need of full time companion who can assist in clinical practice is a need of future. Smartphone and mobile applications could serve this purpose of HCPs and effectively and easily. Some HCPs are still turn down to adopt their use in clinical practice probably due to fear of errors and lack of confidence. Medical devices and apps inarguably provide the HCP with many advantages still they are used without a methodical understanding of their associated risks. Among the worries raised with respect to advanced smartphone gadgets are: their trustworthiness for settling on clinical choices; quiet information security and protection; sway on the specialist persistent relationship; and appropriate mix into the work environment. HCPs, unexposed or uninterested in new advancements, might be off guard if the utilization of PDA gadgets turns into a necessity inside the medical care fields. Guidelines for best-practice techniques for clinical application engineers and clients additionally should be set up to keep up culture ethnical practice. Barely any applications are accessible from just about 10 years yet due to under use they are not creating information. Make sure to have a compelling and touchy application we need vigorous information, which can be utilized to create calculations and create and update them. As more information becomes accessible, this will prompt a more valuable determination of approved PDA clinical applications for HCPs. Consequently increasingly more application uses will grow better applications in future.

Conclusion

With the quickly evolving world, a need of full time buddy who can aid clinical practice is a need of future. PDA and portable applications could fill this need of HCPs and successfully and without any problem. Some HCPs are still go down to receive their utilization in clinical practice likely because of dread of blunders and absence of certainty. Clinical gadgets and applications inarguably give the HCP numerous points of interest still they are utilized without a deliberate comprehension of their related dangers. For all legitimate purposes broad assessment, confirmation, and the improvement of best-practice guidelines for clinical applications are compulsory to guarantee a degree of value and security when these apparatuses are utilized. These measures will satisfy the motivation behind improvement of these applications to give noteworthy, exact, and reasonable data and direction to the HCPs to serve the sacred expectation of accomplishing persistent results.

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CHAPTER 237

Basic Computer and Smartphone—Technology for Practicing Physicians in COVID-19 Era

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Abstract

Technology has made a great impact on the health-care outcomes in the recent years. Starting with simple apps or peripherals which can be attached to a smartphone or basic clinical evaluation equipment. The research process has advanced due to faster access to the literature and resech papers. Many new concepts like augmented, virtual, mixed, and immersive reality will be changing the spectrum of health care. Same applies for augmented artificial intelligence, big data, cloud computing, data mining, and retrieval. Telemedicine, Electronic health records, and virtual visits have made a sea change in patient management in the COVID-19 era. Many unexplored vistas of the new modality need to explored and utilized.

Introduction

The influenza pandemic a century ago was in a very different era but caused a catastrophic loss. With the onset of the COVID pandemic, the world has faced its greatest health crisis in the 21st century. There could not be a more opportune time for us to realize the value and implications of technology and there is a golden moment to radically transform health care via the use of basic smartphones and computers.

This working group has been advocating the same since the last 10 years. The basics of technology including hardware/software, world of apps, including challenges and issues not covered as quoted in our earlier publications.[1]

Specific approaches to smartphone applications include:[2]

- *For Doctors:* Developer, Content, Accessibility, Purpose, Cost
- *For Patients:* Integration, Electronic presence, Patient-doctor relationship, Outcome, Cost

Non-communicable diseases like diabetes have always been a focus of most developers and care of these patients has now been adapted and integrated via interventions at community level and social media. Besides blood glucose monitoring, data recording, control and tracking, futuristic parameters like electronic fall detectors and remote vitals monitoring are now in our reach. Exercise and fitness promotion with specific apps targeted for diabetic patients are now being absorbed for good holistic patient management.[3,4]

Medical calculators, bundled apps like *Medscape* and *UpToDate*, and specialty-specific apps are the essentials to have on a physician's smartphone. As we embrace technology especially for electronic health records, data safety, and privacy too are real concerns but must be addressed thoroughly with a simple approach of audit trails, password protection and data encryption.[5]

Artificial Intelligence (AI) is not science fiction anymore and evidence-based medicine is now taking evolutionary steps with fundamentals rooted in pattern recognition, deep learning, cloud computing, and big data. From the

decade old story of IBM's Watson, now Internet of the Things (IoT) is actually here.[6]

The future of medicine will be founded on 'The Big Five':[7]

- Artificial Intelligence
- Big Data
- Cloud Computing
- Data Mining, Retrieval, and Analysis
- Electronic Medical Records

Technology and the Primary Physician

While emphasizing that the physician's touch and clinical acumen can never be replaced, technology when used aptly can transform one's practice significantly... and, it is here to stay; and evolve, at the same pace as medicine itself!

Teleconsultations/Virtual Visits

The west was rapidly able to evolve quickly due its past adaptation to modern technology but the COVID-19 pandemic has proven and given a boost to Tele-Health in India too.[8] Inculcating it in our regular practice will become the new normal, with guidelines and regulations made for its practice and use. International response was swift to promote telesolutions.[9] MoHFW, India, already released guidelines for the practice of Telemedicine on March 25, 2020.[10]

Clinic software management companies have quickly adapted to it to include it as one of the *essential features* in their software besides

- Ease of access
- Lesser wastage of time
- Cost-effectiveness

The goal is for the patients despite being far away still get the best out of the physician.[11] Additional principles must be adapted to avoid repeated flaws we face.

- Distinguishing between need of virtual and physical visit
- Good documentation
- Observing guidelines (laid down by that country's legislation/rules)
- Well-communicated session

Clinic Management Software

Challenges:

- Difficulty for a traditional physician to shift to technology-assisted practice
- More than 50 software options available online **(Table 1)**
- Confusion, viz. cost vs. features vs. "the latest one"

Essential features and how to choose"

- Cloud-based system for easy accessibility
- Better data security and storage
- Appointment management, billing, and invoice generation
- Multiple online payment options
- Printed prescription
- Easy EHR (Electronic Health Record) management system

All these also provide smartphone-based app extension for their software which helps manage things "on the go." The physician has to choose according to individual needs. There are also specialty-specific software solutions available, which are further fine-tuned according to the specific specialty requirements (e.g., *Crystal pm*, *Ehnote*, *NETRA clinics* for Ophthalmology).

TABLE 1 Comparison of three common EHR platform providers

Examples	*Practo*	*Docon*	*Doxper*
Strengths	• Digital presence • Good appointment management • Patient feedback rating linked	• Easy & fast prescription system • Quick turnover time • Helpful for 'not-so-tech-savvy' physicians	• Good old 'pen & paper technique', digitized EHR of what is written on notes • Good prescriptions, option of additional customized audio/video advice
Challenges	• Complicated billing • Weak prescription system • Risk of commercialization?	• Minimal online presence	• Limited presence

But is that enough? We actually need a SINGLE clinic management software, which integrates and accepts readings from various clinic equipment like a Bluetooth stethoscope, a Bluetooth pulse oximeter, an ECG machine, a Bluetooth weighing machine, a BP monitor, wirelessly transmitting the patient's data to this desktop software; and the physician can use this not only for better patient management but also for extrapolating, analyzing and doing research from this data in the long run. An IDEAL software will be the one having all the features mentioned above; yet simple enough to finish the physician's work with a minimal "click count."

What's the future? The future is newer software with voice recognition and recording system, having predictive investigation and treatment algorithms, and much more beyond it. And all this is already happening today (e.g., *Augmedix*) and the same is an inevitable future, and the faster a physician adapts to it and uses it, the better.

Teleconferencing Solutions

Telehealth, teleconsultation, and telemedicine are also deeply connected with the original simple communication platforms, which have now made remote networking very easy. Besides its role in essential conferencing, these tools are now being increasingly adapted for tele-education, teleconferencing, and continues professional development.[12-14]

Various platforms are available:
Big players/professional ones:

- *Zoom*, Microsoft *Teams*, Google *Meet*, *Skype*, CISCO *Webex*
- *UberConference*, *TrueConf Online*, *FreeConference*, *Appear*.in, *Slack Video Calls*, *Facebook Live*, *YouTube Live*

Zoom, originally created for businesses is the world leader today with >200 million daily users, the best current product in the market as it was designed as a dedicated conferencing product through easy adoption with WebRTC technology.

Features which must be considered are—All device access (phone/PC, etc.), it is encrypted at both ends & secure, must have an easy to operate screen share feature, accessible via audio/(HD) video calls, flexible number from 10-1,000 participants via video can join, legal permissions for users role-based, easy to remember quick Google/Outlook calendar integration, recording/transcripts is very simple & at multiple locations Cloud or Local disk options (important for medico-legal purposes), Team chat is a boon, extra features as per our demands are available with paid versions which are not that costly. However, few lacunae like inability to display the live captions on screen as in Google meet, or tracking by word as in Ted talks, with an underline to it.

The Fourth Dimension of Evaluation in Clinical Medicine

Future of clinical medicine is going to be exponentially explored by these four technologies:

- Virtual Reality (VR)
- Augmented Reality (AR)
- Immersive Reality (IR)
- Mixed Reality (MR)

VR is the computer-generated simulation-re-organization of a three-dimensional image or environment that can be interacted with in a seemingly real or physical way by a person using special electronic equipment, called as Head Mount Unit (HMD) like a helmet with a screen inside or gloves fitted with sensors or other accessories VR head-mounted displays (HMDs), costly as HTC Vive or Oculus Rift, experience a high degree of immersion.

On low end HMDs for mobile devices, such as Samsung Gear VR and Google Cardboard, enable everyone to experience immersive virtual environments. The HMD market is expected to be valued at USD 25 billion by 2022.

It has applications exist in order to offer a higher quality of care and efficiency to patients and medical professionals alike.

VR is used in surgical preparation—check lists to patient illness, education, and therapy.

Examples:

- Embodied labs using VR simulations for attendants of Alzheimer's disease to understand the disease better, even the consequences visualized softly to understand the need of care
- *Floreo* technique—virtual reality to teach multifactorial social and communication skills to patients of autism, contexts include games and activities that explore social connections, situational training preparedness and calming-pacifying or even awarding techniques, meditation training for pain relief, writers cramps and

cognitive behavioral therapy for perimenopausal hot flashes & many varied symptoms difficult to manage.

- *SyncThink* has VR goggles with eye-tracking abilities to test for optic deficiencies and *Eye-Sync platform* (a breakthrough device designation awarded by FDA) helps test for concussions soon after a person sustains a bad blow to the head. Useful in unrecognized head injuries like hypoglycemia, alcoholism, mass gatherings, or high intensity sports.

  AR technology that superimposes a computer-generated image on a user's view component, the real world around him, thus providing a composite-interactive view in medical teaching training.
- *Augmedix* (*AR-BASED MEDICAL RECORDS)* uses *Google Glass* allows access to a patient's electronic health records. EMR relays information, like previous personal or video visits and current medications. An addition of Google Glass also acts as a scribe that records, vital information, eases in to a more natural doctor-patient interaction, saving time, money, and displays no errors on the side of past medical records, procedures, or drug history.

The new powerful, next generation, interactive headsets & AI based software AR-VR will be the new normal of clinical evaluation. Accepted by health-care professionals to provide them with hands-free working environment, greater flexibility with overlaying information, and data processed by the camera. ID Tech Ex, an investment consultant organization predicts this market to be over $20 billion.

MR is the future of real and virtual worlds to have a unique new environments and visualizations, here physical and digital objects coexist simultaneously interact in real time.

Many educative, training, & operative possibilities exist here. This happens not in either the physical or virtual world, but is a hybrid of reality and virtual reality, encompassing both augmented reality and augmented virtuality via immersive technology. A technology concept that is difficult to imagine right now.

We users experience a virtual three-dimensional representation of real objects embedded into the physical surroundings. *Microsoft HoloLens* and *Google Glass* are examples of MR devices with different technologies that demonstrate the most prominent emerging technologies.[15] India will soon have Jio Glasses as their competitors.

Around INR 14,000, Snap Spectacles 3 was launched in India at a price point of around INR 30,000. Microsoft HoloLens retails at a sky-high price of INR 2,63,000.

As the number of consumers grows, the cost will be still more affordable.

All this will make a sea change in medical education systems and learning right from our formative years in anatomy without the smell of formalin in the dissection halls.[16]

It has been proved even in training of paramedics and volunteers for life saving procedures hands on training like pediatric cardiopulmonary resuscitation.[17]

Utility of the same in psychiatry is recently been evaluated in this meta-analysis with immense practical positive outcomes.[18]

In the present dreadful COVID era, it has been very usefully in protection of HCW, in minimizing exposure to nosocomial infection, optimizing the use of PPE, and enhancing aspects of care. Deploying such *holo-lens augmented technologies* at pace requires context-specific information security, infection control, user experience, and workflow integration led by clinical end-users setting up an entirely new field for exploration.[19]

Immersivevirtualreality(*IVR*)hasendlesspermutations combinations, which exist for application in health care. We can now immerse their patients in environments to achieve exposure to a specific clinical situation like Hypoglycemia, Bowel movement irregularities as in IBS, whether constipation type,diorrhea type or mixed pattern & patients correlation with feeling of bloating, blocked or urge as his experience. After the evoked targeted physical & emotional responses, in therapy we can inspire, acclimatize, or distract from an experience occurring in reality. Best example being a patient of Agoraphobia or Claustrophobia gives instructions or commands from HMD special goggles-lenses.

IVR is a future in health care, research, practice, education, and profitable components with many studies exploring its feasibility for acute treatment of health conditions; however, evidence of its effectiveness needs further research.[20]

AI in Health Care—The Rising Horizons

AI makes medicine more *pre-emptive, predictive, & personalized.*

Today, AI and related technologies in health care are rather much more advanced and developing rapidly with the help of Big Data. These technologies have the potential to transform many aspects of patient care, administrative processes within the provider, health-care insurance and pharmaceutical organizations.[21]

The most tried AI tools in health care so far are AI-driven diagnostic tools that are helping physicians in clinical decision-making and helping with disease diagnostics. The spectrum of AI solutions like natural language processing (NLP), image analysis, and predictive analytics based on machine learning-neural networks and deep learning are widely used for diagnostics in clinical medicine.

AI-led telemedicine services are disrupting the entire value chain practice and patient care. AI is empowering telemedicine making a better diagnosis, assisting eldercare, and remote patient monitoring. As health care becomes more technology-driven, IoT and Telemedicine could offer quality service options at a reasonable cost, just by increasing the number and frequency of consumers components of IoT or IoMT has several component sensor conducted bio signals, Gyrocsope mediated motion linked data as in fall detectors or exercise Apps, contextual data components like locations, supermarket visits humidity or temperatures.

Ethical, legal, and social implications will need to be considered for use of AI in health care. The use of smart machines to make or assist health-care decisions raises issues of privacy, permission, transparency, and accountability.[21] Also, ensuring the use of capable and useful AI technologies in the health-care domain in daily clinical practices remains a challenge.

Undoubtedly, AI has a great future in health care. With the help of smart devices and health-care apps, they can act as a personal health assistant for common people. Apart from early diagnosis, fast and accurate clinical decision-making, cost reduction in health care, AI techniques like machine learning have the capability behind the development of precision medicine.

Technology and India during COVID-19

We as Indians are less jubilant as far as use of technology is concerned compared, to either eastern or western users. But there was tremendous surge in uses of smartphones and its applications during this initial COVID-19 pandemic time. Some sources report to have increased by 120% within initial couple of months of lockdown. Some sources which have collected data, line Cybermedia Reserch Surveys that more emphasis was on different content creation which was spread out by users to others. Also there was significant increase usage of video calling applications.

Gradually as the lockdown curbs were eased and online sales platform started activities for non-essential goods. People had obviously picked up the activities on these applications for ease and to maintain restrictions. Most people had upgraded their devices like smartphones and laptops. People tried different applications and processes that were supported by faster internet connections and such devices. But the usage of such processes although was very significant was limited to knowledge of government schemes and other information like epidemic progression and whether forecasting. Although usage of Aarogya Setu app was increased overall usage for health-care benefit was not that significant.[22]

There is a resolute demonstration by the people of India to accept technology. The health-care sector must embrace this opportunity to radically adapt technology.

Simple starting steps would be use of the basic apps, which would assist greatly with health care during the pandemic:

- Web-tools for symptoms like *https://www.mayoclinic.org/covid-19-self-assessment-tool* and *diy.health/help-yourself*
- Apps like *Calculate by QxMD* for risk-stratification and management, which can be used for COVID including CURB-65, qSOFA, NEWS, ROX-index.
- Specific infectious diseases apps like *John Hopkins Guide, Sanford Guide, Micromedex, Sepsis Guide,* and *Infectious Disease Compendium*.
- Apps for infusion management of vasopressors and glycemic control like *IV Infusion calc* and *InsPro* are extremely helpful in these manpower-resource-limited times
- Drug-drug interactions especially when COVID-cocktail therapy is being practiced can be evaluated by simple apps like *Epocrates*
- Peripheral smartphones add-ons like pulse-oximeters and digi-stethoscopes are already commercially available now
- *Medscape* and *UpToDate* still remain the best bundled apps with continuous rolling updates about the pandemic from verified sources.

Conclusion

The pandemic has brought the world to its knees but given all of us a chance to rise up to this once-in-generation challenge. The government too has set off a pace of reforms for enhancing the use of technology in medicine with significant resolve in areas of telemedicine and concept of Unique-health-ID with a promise of complete horizontal and vertical cross-integration. The future has arrived for technology in health care.

While understanding its tremendous power and scope for exponential promises in thrust areas of AI and the four realities (AR/MR/VR/IR); the physician needs to start with the simple steps of using telemedicine and basic apps in their practice for a simple reason… The best interest of the patient!

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