POCKET NOTEBOOK

# POCKET PRIMARY CARE

**Meghan M. Kiefer**

**Curtis R. Chong**


A Massachusetts General Hospital Handbook

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NOTE BOOK

# *Pocket* PRIMARY CARE

*Edited by*
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*A Massachusetts General Hospital Handbook*


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# FOREWORD

The last decades have witnessed tremendous advances in scientific knowledge and medical technology. At the same time that these advances have transformed our ability to diagnose and treat disease, this new world has also served to remind us of the critical importance of the doctor–patient relationship. The longitudinal relationship between a patient and their doctor is at the heart of what makes medicine work and of what brought so many of us to the field. In many ways, the field of primary care embodies our commitment to that relationship. Thus, perhaps it should not be surprising that, even as technology grows around us, there is a widespread and growing reaffirmation of the importance of primary care to the field of medicine, to our health care system, and, ultimately, to the health of our nation.

Primary care is a rewarding but challenging field. It is hard to overestimate the impact of caring for a patient across his or her adult life, but such care also requires managing a range of problems that can make one's head spin. Many of the most challenging and important communication opportunities reside in primary care as primary care providers try to change health-related behaviors, support informed decision making, and navigate the end of life. It is clear that new tools are needed to support education and practice in primary care.

Pocket Primary Care is just such a new tool. Representing the effort of a dedicated team of housestaff and attending physicians at the Massachusetts General Hospital, it brings together evidence and experience to guide physicians through the many domains of primary care, providing concise and useful information for topics from chronic pain to incontinence. Building upon the tradition of the Pocket Medicine handbook, Pocket Primary Care understands that information is most effective if it is accessed and understood when the question arises. I have no doubt that Pocket Primary Care will become a stand-by of medical training and make a major contribution to the "health" of the field of primary care itself. This outstanding team has my deepest gratitude for what they have created.

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# PREFACE

*To Will, Liam, and Rowan—MMK*
*To my family, Dina Reiss, and my teachers*
*(Melvin Welinsky, DSA, ARF, DJS, JOL, RFS, JLC, RCZ, DBH, LA, MMP, BAO, JAC, DMJ, PAJ, BEJ, BAC, DM, RJM, CAH, EPR)—CRC*

More than a century ago, the great physician Sir William Osler wrote, "It is much more important to know what sort of patient has a disease than what sort of disease a patient has." While the pace of patient care and increasing administrative burdens of modern medicine are challenging, the relationship forged between patient and physician can be an incredible source of satisfaction and renewal. We believe physicians who take primary ownership for patient care have what has been described as the "best job in medicine" (*NEJM* 2006;355:864).

*Pocket Primary Care* is intended to support providers and trainees who take such ownership for their patients. Its aim is to concisely present the most current evidence-based approaches to delivering quality care in the outpatient setting. Given the breadth of modern medicine, this text is meant as a starting point for further exploration, and hundreds of references are provided. While we attempt to present summaries on disease diagnosis and management as accurately as possible, sound clinical judgement must be applied to every patient.

We would like to acknowledge the many people who were instrumental to this project's success. This text is the cumulative effort of over one hundred members of the Massachusetts General Hospital community; the MGH's faculty, trainees, and graduates authored these chapters, edited these sections, and reviewed this content to ensure it reflects the hospital's dedication to conscientious, superb care for each and every patient. This project would not have been possible without the support of the Department of Medicine under the superb leadership of Dennis Ausiello and Katrina Armstrong. Valerie Stone's early support, vision, and longitudinal mentorship were invaluable to this work's development. We also thank Hasan Bazari for his encouragement of this project and for his dedication to his residents and his patients, and we thank Marc Sabatine for his generosity and advice. Finally, we are grateful to our patients, who have been our greatest teachers.

# ROUTINE VISIT

## Background (*JAMA* 1997;277:350; 2011;305:1802)

- **Frequency of visits:** General recommendation every 2 y for healthy adults <40 y, annually for >40 y; general health checks (preventive screening/counseling) not assoc w/ all-cause, cancer, or CV mortality benefit (*JAMA* 2013;309:2489,2496; *JAMA Intern Med* 2013;173:371)
- **Preparation:** Review medical records, health maintenance to create tentative agenda
- **Mindfulness:** Self-awareness of personal biases, limitations in knowledge, & how provider mood, stress, expectations, & past experiences influence pt care (*JAMA* 1997;278:502; 1999;282:833; 304:2532; *NEJM* 2013;368:2445)
- **Establishing a provider–patient partnership:** Warmly greet pt by preferred name (default should be w/ title, e.g., Mr. Smith); introduce self & role; elicit identity of others present in nonjudgmental fashion (e.g., "How do you know the pt"), ask if pt is comfortable w/ their presence; apologize for any delay; beginning & ending visit w/ small talk, i.e. "How was Thanksgiving?" helpful in establishing rapport
- **Agenda-setting:** Should be shared decision: "I was thinking we could talk about … What would you like to talk about today?"; verbalize plan to set specific items aside for future visit (*NEJM* 2012;366:1653)

## Comprehensive History

- **HPI:** Description of sx: **OPQRST AAAA: O**nset, **P**rovocative/**P**alliative factors, **Q**uality, **R**adiation/location, **S**everity, **T**iming/duration; **A**ssoc/**A**lleviating/**A**ggravating factors, pt **A**ttribution; "Has this happened before?" "What do you think is going on?"
- **Medications:** Include OTC & supplements, pt adherence & s/e
- **Allergies:** Ask about details of reaction "What happened (when you took penicillin)?" distinguish btw true hypersensitivity & medication s/e
- **Past medical, surgical, obstetrical/gynecologic, psychiatric history**
- **Social history:** Occupation, education, home situation, hobbies,

religion

**Tobacco:** Cigarette smoking expressed in pack-y; Other tobacco use (pipe, chew)

**EtOH:** CAGE screen for alcoholism (see *"Alcohol Use Disorders"*)

**Illegal drugs:** Amount of money spent useful in quantifying use

**Domestic violence:** "Do you feel safe at home?" (see *"Domestic Violence"*)

- **Family history:** Age, health status, cause of death; FHx is dynamic, aids risk stratification/screening & should be updated q5–10y in pts 30–50 y (*JAMA* 2011;306:172,208)
- **Sexual history:** Reassure pt: "We ask all patients these questions"; sexual orientation, practices, # of partners, hx STIs, contraception, sexual dysfunction, hx abuse
- **Health maintenance:** Exercise, diet, safety (smoke detectors, seat belts, firearms), age-appropriate disease screening (see "*Disease Screening*")
- **Advanced directives:** Resuscitation preferences, health proxy (*see "End-of-life and Advance Care Planning"*)

**Review of systems**

| |
|---|
| **Constitutional:** Fever, chills, night sweats, fatigue, wt changes |
| **Neuro:** HA, dizziness, hearing loss, weakness, seizures, tremor, numbness, tingling |
| **ENT:** Δ vision, Δ hearing/tinnitus, nasal/sinus problems, hoarseness, dry mouth |
| **CV:** CP, palpitations, orthopnea, PND, edema, claudication, ↓ exercise tolerance |
| **Pulm:** Dyspnea, cough, wheezing, snoring, sputum, hemoptysis, TB exposure |
| **GI:** N/V, diarrhea, constipation, abd pain, rectal bleeding, dysphagia, odynophagia |
| **Skin:** Rashes, itching, bruises, dryness, changes in moles, changes in hair |
| **GU:** Dysuria, nocturia, hesitancy, incontinence, hematuria |
| **Heme:** Easy bruising/bleeding, LAD |
| **Endo:** Heat/cold intolerance, polyuria/polydipsia, appetite changes |
| **Gyn:** LMP, AUB, dysmenorrhea, vaginal odor/discharge, sexual function |
| **Musculoskeletal:** Muscle/joint pain, myalgias, back pain |
| **Psychiatric:** Anxiety, depression, suicidal/homicidal ideation |

## Physical Exam

- Routine exam should be tailored to individual pt (age, gender) & guided by hx + ROS; often best to step out prior after hx to have pt change into gown for full exam

- **Vital signs:** Temp, BP, HR, RR, oxygen saturation ($SaO_2$), ht, wt, BMI, pain level
- **General:** Distress/pain/anxiety, body habitus, alertness, grooming

## Concluding Visit

- **Summarize visit** (medicines started/changed, advice given) verbally and/or in writing; establish anticipated time frame & mechanism for pts to receive results of any studies ordered; set plan for time frame & agenda of f/u ("I'll see you in 3 months to talk about…")
- **Documentation:** *Problem list:* create/update to organize issues for future visits; *results:* inform pts in writing or via documented phone calls
- **Follow-up:** Encourage pt to contact w/ any questions or concerns; "If you haven't heard from me about your blood work by next week, please call"; "If your rash doesn't get better by the end of the week, let me know"
- **Patient information:** ahrq.gov/questions; jointcommission.org/speakup.aspx

# DISEASE SCREENING

## Background

- **Definition:** Disease screening is intended to identify disease in asx individuals when **early detection** is feasible & early tx **improves outcomes**
- **Assessing benefits of screening:** Can be difficult to compare direct outcomes between screened & unscreened groups; often established using:
  1. Proportion of tested population who test positive
  2. Ability of test result to detect disease while still asx
  3. Treatment effectiveness in test-positive people
- **Harms of screening:** False ⊕ can→overdiagnosis & overtreatment, which can have individual & public health costs; screening may identify disease early w/o being able to modify outcome; risks/harms vary based on test & disease; best to discuss w/ pt

**Characteristics of ideal screening test**

| | |
|---|---|
| **Disease** | High disease prevalence (↑ PPV of ⊕ test)<br>Tx of early disease is effective: can improve outcomes/avoid complications<br>Disease has known asx/early stage which can be identified |
| **Test** | Can detect disease while it is still asymptomatic<br>Is not overly time-consuming, cumbersome, or financially prohibitive<br>Is sensitive (unlikely to give false ⊖); ideally, should also be very specific (unlikely to give false ⊕), but this is more important for confirmatory testing |

- **Screening recommendations:** Several government agencies (including US Preventive Services Task Force, or USPSTF; CDC, NCI) periodically undertake systematic reviews of available data to make recommendations; professional societies (ACOG, AUA, ACP, AAFP) & advocacy organizations (ADA, ACS) also offer independent screening recommendations; may refer to www.guidelines.gov to compare recommendations
- **Applying recommendations:** All recommendations are *population-based* & based on principle of long-term/future benefit; they may not apply to certain individuals, particularly those w/ limited life expectancy
- Patients w/ active sx concerning for disease→ *testing*, not screening (diagnostics may be different: e.g., hx/PE concerning for cervical CA→referral for colposcopy, not Pap)

## Evaluation

- During routine visits, consider which screenings are indicated; guidelines typically by age & gender; can be helpful to organize screening by category (below)
- Potential risks & benefits of screening tests should be discussed w/ pt; goal is shared decision-making (*NEJM* 2012;366:780)

**USPSTF Screening Recommendations**

| Disease | Population, preferred test & interval (if given), & notes |
|---|---|
| | **Cancer** |
| **Colon Cancer** | **50–75 y:** FOBT (q1y), sigmoidoscopy (q3y), or colonoscopy (q10y)<br>Se: colo > sig ≥ FOBT, Sp: colo = sig > FOBT |
| **Breast Cancer** | **40–49 y** ♀: Consider mammography q2y after discussion w/ pt<br>**50–74 y** ♀: Mammography q2y<br>Excludes those at ↑ risk (known genetic mutation, hx chest XRT)<br>ACOG, ACS, ACR recommend more screening (annual mammogram + CBE ± SBE starting at age 40); other groups (AAFP) recommend individual shared decision-making re: screening for ♀ 40–49 y; consider local practice patterns in light of medicolegal risk (*JAMA* 2013;309:2555) |
| **Cervical cancer** | **21–29 y** ♀: Pap q3y<br>**30–64 y** ♀: Pap q3y **or** (Pap + HPV q5y)<br>See *"Cervical Cancer Screening"* |
| **Prostate cancer** | See *"Prostate cancer"*; most groups recommend pt discussion |
| **Lung cancer** (prelim guidelines) | 55–79 y w/ 30 pack-y tobacco hx **and** smoked w/in past 15 y:<br>Annual low-dose CT; guideline notes quitting much more effective |
| | **Cardiovascular** |
| **HTN** | **All adults:** q1y if last SBP 120–139 or last DBP 80–89; q2y if <120/<80 |
| **AAA** | **65–75 yo ♂ ever-smokers:** Abd U/S, 1-time screening |
| | **Endocrine** |
| **Diabetes** | **Adults w/ BP >135/80:** HbA1c, FPG, glucose tolerance test all ok<br>ADA recommends screening all adults >45 & overwt adults <45 w/ 1 add'l risk factor (e.g., ⊕ FHx or PCOS); see *"Diabetes"* |
| **Hyperlipidemia** | **All adults at ↑ risk; all ♂ >35:** Total chol, HDL, LDL q5y<br>May ↓ testing interval if borderline; ↑ interval if repeatedly nl |
| **Osteoporosis** | **All ♀ >65; ♀ <65 at ↑ risk:** DXA of hip & lumbar spine<br>**For ♀ <65, calculate FRAX score:** If 10 y fx risk >9.3%, considered ↑ risk; see *"Osteoporosis"* |
| | **Infectious Disease** |
| **HCV** | **Hx IVDU, blood transfusion, all adults born btw 1945–1965:** Once<br>**Pts at ongoing risk (IVDU):** More frequent testing |
| **HIV** | **All adults:** Once<br>**↑ Risk (MSM, IVDU):** More frequently (see *"HIV"*) |
| **Chlamydia** | **Sexually active & (<25 y or ↑ risk):** Screen (see *"Sexually Transmitted Infection"*) |
| **Gonorrhea** | Adults at ↑ risk (see *"Sexually Transmitted Infection"*) |
| **Syphilis** | Adults at ↑ risk (see *"Sexually Transmitted Infection"*) |
| | **Social, Ψ, & Substance Use** |
| **Depression** | **All adults:** Brief screening, e.g., PHQ-2, if clinic has care support (SW, mental health counselor to assist in depression care) |
| **EtOH abuse** | **All adults:** Brief screening, e.g., AUDIT-C, single question (see *"Alcohol Use Disorders"*) |
| **Tobacco use** | **All adults (see *"Tobacco"*):** If screen ⊕, offer counseling |
| **Intimate partner violence** | **All ♀ of childbearing age:** Brief screen; see *"Domestic Violence"*; if screen ⊕, provide or refer to intervention services |

(USPSTF *uspstf.org*, *Diabetes Care* 2013;36:S11)

## Provider Tools

- USPSTF recommendations available as application for mobile devices at http://epss.ahrq.gov/PDA/index.jsp; enter basic pt info (age, gender) to see list of screening & other recommendations
- National Guidelines Clearinghouse at http://www.guidelines.gov lists recommendations from major government/nongovernment groups, organized by topic

# HEALTH LITERACY

## Background (*Institute of Med* 2004; *NEJM* 2010;363:2283)

- **Definitions: Health literacy:** Set of skills/abilities needed to gain access to, understand, & use health-related info; an interaction between individual skills & health system demands
  **Numeracy:** Math skills needed for timing, scheduling, dosing medications & understanding math concepts (arithmetic, percentages, probability) in order to understand provider recommendations
- **Epidemiology:** 33% of US adults read at <5th grade level; 55% have difficulty w/ basic calculations; when directly assessed, **36% have basic or below-basic health literacy** (e.g., unable to calculate healthy BMI on chart for a given ht, unable to correctly interpret Rx label re: timing of medication in relation to food)
- **Risk factors:**↑Prevalence among elderly,↓education,↓income, ethnic/racial minorities, ESL (http://nces.ed.gov/pubs2006/2006483.pdf)
- Inadequate health literacy is strongly assoc w/ poor health (↓ med adherence, ↓f/u,↓DM control,↑costs,↑morbidity,↑mortality) even when controlling for other factors; may potentially mediate some health care disparities
- However, pts w/↓health literacy may benefit most from education targeted at their level of understanding, esp for chronic disease mgmt (*JAMA* 2004;292:1711; *JGIM* 2011;27:190)

## Evaluation

- Brief, validated screening tools exist to identify inadequate health

literacy; any one of the following questions appropriate (*Fam Med* 2004;36:588):
"How confident are you filling out medical forms by yourself?"
"How often do you have someone help you read hospital materials?"
"How often do you have problems learning about your medical condition because of difficulty understanding written information?"

- However, many recommend "universal precautions" w/ all pts rather than screening; okay to↑complexity/speed/terminology of explanation as indicated by pt response

## Management (ahrq.gov)

**Health Literacy Universal Precautions**

| | |
|---|---|
| • Slow down<br>• Use plain language; avoid confusing terms (e.g., "positive test")<br>• Show/draw pictures | • Limit info provided to priorities<br>• Use "teach-back" method (below)<br>• Encourage questions (below) |

- **Teach-back:** Having pt explain in own words; not asking, "Do you understand?" but instead, "Show me how you're going to take this…" or "What are you going to tell your wife about this?"
- **Encourage questions:** Pts who don't have questions often have not fully understood the conversation; ask "*What* questions do you have?" rather than "*Do* you have any questions?"
- **Medication review:** Consider having pts bring in their meds to appt; can help w/ clarifying pt understanding & med adherence
- **Discussing risk** (*BMJ* 2003;327:745)
  Freq is easier to understand than percentages i.e., "2 in 10 people will have a side-effect" is better understood than "a twenty percent chance of side-effect"
  Framing influences pts, i.e., "If 100 pts are treated with drug A, 99 will experience no side effects" vs. "One patient in 100 using drug A will experience hair loss"
  Present absolute **and** relative risk: "5 out of 100 people will die of disease X in 10 y; If all 100 people are screened annually, 2 of them will be saved from dying of X"

Visual aids (e.g., bar graphs) & comparisons to common risks (e.g., driving) are helpful

# COUNSELING PATIENTS

## BEHAVIORAL COUNSELING

### Background

- **Definition:** A form of therapy that seeks to change behavior(s); general approach includes discussion of pt's awareness of behavior pattern & its effects, soliciting pt's perspective on behavior & reasons for change
- **Strategy:** Different techniques available; important to find a strategy that is a good fit for the topic, the provider, & the individual; avoid arguments & confrontation, which can↑pt defensiveness & resistance to change; changing most of these behaviors are long-term goals & benefit from a therapeutic relationship; nonjudgmental listening key
- **Efficacy:** Most counseling shows a "dose–response" relationship;↑success at changing behavior w/ recurrent discussions; providers can effect change despite their time limitations, but should also consider referral to others trained in this approach as local resources & situation allow (e.g., social workers, chemical dependency specialists, therapists)

### Selected Approaches (*AFP 2009;79:277*)

- **Motivational interviewing:** Pt-centered technique proven helpful in↓substance, EtOH abuse; can help develop therapeutic relationship & set individual goals (*Cochrane Data System Rev* 2011;5:CD008063)
  **Agenda:** "Can we talk about exercise today?"
  **Exploration:** "Are you interested in exercising?" (desire); "Can you walk for 30 mins daily?" (ability); "How would exercising help you?" (pt's need)
  **Educating:** "Exercise prevents so many diseases & will make you feel better"
  **Listening:** "What do you think about that?"

**Strategizing:** "What would work best for you? Walking w/ friend? Joining a gym?"

- **FRAMES** (*Prim Care* 2007;34:551): Provides framework for provider to discuss impact of behavior & offer recommendations for change
  **Feedback:** "Our labs show EtOH consumption is damaging your liver."
  **Responsibility:** "Only you can decide it's time to stop drinking."
  **Advice:** "I strongly recommend you stop drinking."
  **Menu:** "There are many strategies to help people stop drinking, such as …"
  **Empathy:** "Staying sober can be a real challenge, but I am here to help."
  **Self-efficacy:** "You seem determined to make this important change in your life."
- **Transtheoretical:** Behavioral changes occur in stages; model allows provider to assess pt readiness for change
  **Precontemplation:** Advise pt of health consequences & ask what he/she thinks; "Being overweight is linked to heart disease & diabetes. I think it might be helpful for your health to lose wt. What do you think? Have you tried to lose weight before? What would signal to you that it's time to lose weight?"
  **Contemplation:** "What are the pros/cons of weight loss?"
  **Preparation:** "Do you think you could start making those changes next week?"
  **Action:** Praise/support pt efforts
- **5 As:** See *"Tobacco Use"*
- **5 Rs:** Designed for smoking cessation, but may be useful in other circumstances
  **Relevance:** Why changing behavior is personally relevant (e.g., children's health)
  **Risks:** Negative consequences of behavior (e.g., shortness of breath, cancer)
  **Rewards:** Potential benefits of changing behavior (e.g., improved health, saving money)
  **Roadblocks:** Barriers to changing behavior (e.g., fear of wt gain, withdrawal sx)
  **Repetition:** Approach these issues on a regular basis

## BREAKING BAD NEWS

- Providers often have responsibility for sharing potentially upsetting news; wide ranges in nature of pt–provider relationship & in emotional impact for pt (& provider)
- When delivering upsetting findings, providers can often have significant positive impact on encounter by preparing & supporting the pt appropriately

**SPIKES protocol** (Adapted from *Oncologist* 2000;5:302)

**S: SETTING:** Private setting, tissues ready, pager/phone set to silent; let pt decide who is present; *sit down* w/ pt, establish rapport (eye contact, touching pt on arm/shoulder); advise pt of time constraints & potential interruptions

**P: PERCEPTION:** Assess pt knowledge/expectations; "What is your understanding of your medical situation?" or "What is your understanding of what we're going to talk about?"

**I: INVITATION:** Ask pt what info they wish to know; "What info would you like to know about your situation?"

**K: KNOWLEDGE:** Warn about bad news, provide info/knowledge in lay terms, & pause periodically to allow pt to digest/process info; "I'm sorry to tell you that the cancer has spread" – PAUSE – "There are new lesions in the liver" – PAUSE – "This is likely why your skin has turned yellow & itchy"

**E: EMPATHY:** Recognize & respond to pt emotion, goals, & hopes; sometimes it is helpful to name the emotion pt is expressing, i.e., "You seem upset"

*Respond to their cues;* try moving closer to pt & offering an empathic gesture (e.g., offering tissue) while being silent until pt speaks

*Align provider goals w/ pt* ("I wish…") while acknowledging situation ("…but"), e.g., "I wish you didn't need insulin, but the pills we prescribed aren't enough anymore"

*Offer empathy & honesty* for pts w/ unrealistic expectations: "I wish Alzheimer's disease was curable, but I've never seen it happen. I'll always be honest with you about your health."

*Invite pt response:* "I imagine this is very upsetting" or "Could you tell me what you are worried about?"; assess pt safety if indicated (See *"Suicide Risk Assessment"*)

**S: STRATEGY & SUMMARY:** Discuss tx options; offer reasonable hopes for situation; invite questions & arrange f/u; consider specialist/social work/counselor referral

## PSYCHOSOCIAL COUNSELING (*AFP* 2009;79:277)

- **Epidemiology:** >50% of mental health visits are to PCPs; supportive counseling may be therapeutic for pt mood & physical sx (*Prim Care Clin Office Pract* 2007;34:551)
- **Challenges:** Providing supportive counseling in a busy primary care practice is challenging, esp if pts p/w numerous other medical problems; The BATHE technique may provide therapeutic counseling

in a time-efficient manner (1–5 mins)

**BATHE protocol** (*Stewart MR, Lieberman JA. The 15-Minute Hour*, 2008)

**B: BACKGROUND:** Elicit stressors, "You seem upset; what's going on in your life (or how is life treating you)?"
**A: AFFECT:** "How do you feel about it?"
**T: TROUBLES:** Identification of a specific part of a problem makes it manageable & provides something the provider may assist with, "What *troubles* you the most about losing your job?"
**H: HANDLING:** Assess coping mechanisms; "How are you *handling* the divorce?"
**E: EMPATHY:** Validate pt emotions; "That sounds very difficult for you"; attempt to address main issue, e.g., "Would you like to talk to our social worker about housing resources?"

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## GRIEF (*JAMA* 2013;310:416)

- **Definition:** Grief is bereavement, often after the death of a loved one, typically lasting 6–12 mos; *Complicated grief:* Yearning/preoccupation for deceased, preoccupation w/ circumstances at death, intense sorrow/anger/self-blame, and/or denial/avoidance that impairs function, causes significant distress, & does not improve w/ time
- **Risk factors:** ♀, pre-existing psych d/o (anxiety, depression), childhood trauma, nature of death, death of spouse, social support/resources available, EtOH/illicit use
- **Epidemiology:** ~7% of pts experience complicated grief
- **Diagnosis:** Clinical; Inventory of Complicate Grief scoring system available (*Psychiatry Res* 1995;59:65); Ddx includes depression, anxiety, PTSD, all of which may be comorbid
- **Treatment:** Bereavement support groups, mgmt of comorbid d/o, targeted psychotherapy
- **Patient information:** *JAMA* 2005;293:2686

# EVIDENCE-BASED MEDICINE

## Definitions (*Gordis, Epidemiology*, 4th ed.)

- **Incidence:** (*New* cases of a disease)/(pop at risk) in a given period of time
- **Prevalence:** (Cases of disease)/(pop), can be at single timepoint

("point prevalence") or over a period of time ("period prevalence")

- **Sensitivity (True-positive rate):** *Among pts w/ disease*, probability the disease will be detected by ⊕ test (desirable for screening); **A/(A + C)**
- **Specificity (True-negative rate):** *Among pts w/o disease*, probability the disease will be excluded by ⊖ test (desirable for confirming dx); **D/(B + D)**

| | | Disease | |
|---|---|---|---|
| | | + | − |
| Test or exposure | + | A | B |
| | − | C | D |

- **Positive predictive value:** *Among pts w/ ⊕ test*, probability of a ⊕ result being due to disease; PPV depends on disease prevalence in pop (↑ prevalence→↑ PPV); **A/(A + B)**
- **Negative predictive value:** *Among pts w/ ⊖ test*, probability of a ⊖ result being due to lack of disease; NPV depends on disease prevalence (↑ prevalence→↓ NPV); **D/(C + D)**
- **Odds ratio:** (Odds of exposure in disease group)/(odds of exposure in control group) = A/C divided by B/D = **AD/BC**
- **Risk difference:** (Disease risk in exposed group) − (disease risk in unexposed group), e.g., 15% risk of CA in exposed vs. 5% risk in unexposed→risk difference of 10% or 0.1
- **Relative risk:** (Disease risk in exposed group)/(disease risk in unexposed group), e.g., 15% risk of CA in exposed vs. 5% risk in unexposed→3 × ↑RR in exposed group; RR of 1 suggests no assoc between exposure & outcome
- **Number needed to treat/harm:** # of pts that must be treated to prevent/cause 1 pt to have the measured outcome; 1/(risk difference), e.g., 1/(0.1)→NNT of 10

## Types of Studies (Weiss, *Clinical Epidemiology*, 3rd ed.)

- **Case-control:** Observational study to identify differences in *risk factors/exposures* between groups characterized by *outcome*; e.g., pts w/ lung cancer are compared to those w/o disease to determine if smoking exposure is different between groups; assoc measured w/ odds ratio (*not* RR)

- **Cohort:** Observational study to identify differences in *outcome* between groups characterized by *exposure/risk factor*; e.g., pts who smoke & those who don't are followed over time to determine if lung cancer incidence is different between groups
- **Cross-sectional:** Assess simultaneously for outcome & exposure at single point in time (e.g., how many people in telephone survey are smokers? How many have lung cancer?); may use RR or OR
- **Randomized control trial:** Enrolled group randomly allocated to groups assigned to intervention (e.g., diet vs. exercise for wt loss) & then followed over time to identify differences in outcome; allows for inferred causality (exposure→outcome) rather than just association (exposure & outcome are somehow linked)
- **Meta-analysis:** Analysis which pools data from several studies to↑statistical power; can be limited by weaknesses in individual studies or by combining disparate groups (e.g., combining studies for tx for acute LBP & chronic LBP)

## Considerations in Study Review

- **Applicability:** How closely do study subjects in a study resemble my pt? Are they healthier? Sicker? Older? Younger? Different gender?
- **Confounding:** Minimized by randomization in RCT, but major limitation of observational studies; when the assoc between 2 factors is at least partially explained by another, unmeasured factor; can lead to misattribution (e.g., HRT assoc w/↓CAD risk in cohort study, but only because healthier women more likely to take HRT & less likely to have CAD; all other things being equal, HRT can actually↑CAD risk)
- **Bias/study design:** Depending on nature of bias, can minimize **or** exaggerate true association

  *Selection bias:* (Primarily an effect of how study was designed) Other than the *known* way they differ (exposed/unexposed in cohort, disease/healthy in case control), how comparable are the two groups? Are they from the same time period, geographic location, SES, occupational group? Was one group more likely to be "lost to follow-up?"

  *Information bias:* (Primarily an effect of how data were collected) Pts

w/ known diseases may be prone to differential recall of exposure(s), providers may have different testing patterns for pts w/ risk factors or elicit different hx based on presence/absence of disease; nature of measurement may differ across groups (minimized by blinding)

# CHRONIC PAIN

## Background ( *J Pain* 2008;9:883; *cdc.gov/nchs* 2010 *Nat'l Health Statistics; Pain* 2011;152:1219)

- **Definitions: Chronic pain:** Pain which persists **beyond timeframe of healing** or pain due to ongoing/recurrent insult; variously defined, but >**6 mos** generally accepted
- **Classification:** *Neuropathic pain:* Due to damage to nerves themselves (diabetic neuropathy, postherpetic neuralgia, cancer (e.g., plexal involvement); see *"Peripheral Neuropathy"; Nociceptive pain:* Nl processing of persistent noxious/potentially noxious stimuli; may be somatic (arthritis, burns) or visceral (IBD, obstruction)
- **Pathophysiology:** Can be due to mechanisms at many levels of peripheral & central nervous systems including aberrant nerve growth (nl stimuli processed along pain pathway→perceived as painful); biochemical imbalance (5HT + NE both shown to↓peripheral pain signals); severity of pain does not correlate w/ degree of tissue damage
- **Epidemiology:** Often not assessed separately from other conditions, but affects 26–43% of US population: LBP, arthritis, and HA all common causes; many people have pain at multiple sites; chronic pain is more prevalent among pts w/↓SES, ↓education, or↑social stressors, older age, ♀, poor physical health
- **Risk factors/comorbidities** (*Gen Hosp Psych* 2009;31:206)
  **Depression:** Strongly assoc w/ chronic pain (>25% of pts w/ MDD have chronic pain; 25% of pts w/ chronic pain have MDD); MDD often underdiagnosed when presenting as chronic pain (*Arch Intern Med* 2003;163:2433); comorbid depression↑ ▮ disability,↓coping,↓favorable response to & pt satisfaction w/ tx
  **Anxiety:** People w/ multisite pain 3.6× more likely to have anxiety

d/o than those w/o pain

**PTSD:** Higher rates of chronic pain (up to 80% in study of Vietnam combat veterans) ( *J Psychosom Res* 1997;43:379)

**SUD:** In primary care setting, estimates of SUD in pts w/ chronic noncancer pain range from 3–34%; may be higher in pts on chronic opiates (*Ann Intern Med* 2007;146:116; *Pain* 2011;152:488)

**Injury:** 15% of those w/ mod–severe traumatic injury→chronic pain 1 y later; ↑ risk if: Severe injury, severe pain at presentation, belief at presentation in future need for pain meds, or hopelessness re: ability to relieve pain (*Pain Med* 2010;11:1599)

## Evaluation

- **General approach:** A thorough initial history-taking can be part of treatment; helps assure pt & provider that, if etiology unknown, search for cause has been appropriately undertaken
- **Pain history:** In addition to evaluating/identifying any medical condition responsible for the pain, focus on *impact* of pain rather than its intensity

  **Impact:** What has been the effect on pt QoL, activity level, occupation, social life?

  **Assoc sx:** Depression, anxiety, stress

  **Beliefs:** Pt's understanding of including diagnostic studies & responses to specific therapeutics, including Rx & OTC medications, (noting dosage, duration), CAM, & nonpharmacologic approaches
- **Past medical history:** Assess for comorbidities or diseases which may impact tx plan: *Psychological:* Mood or SUD; *physical:* OA, mobility restrictions, advanced CHF, COPD
- **Social history:** What is current & prior level of functioning? Assess recreational & fitness activities, occupational hx; ask about social supports, hx of abuse
- **Exam:** Complete PE recommended, w/ particular focus on MSK & neuro exam; additionally, observe for pain behaviors
- **Diagnostics:** As per clinical scenario

## Treatment

- **General approach:** Goal is to identify & definitively treat underlying

cause whenever possible; if pain persists, redirect toward adaptation, creating, an individualized, multifaceted approach to sx mgmt **which focuses on function**

*If cause is unknown after complete eval:* Provide reassurance (see below); periodic reassessment of current diagnostics & consideration of further eval as indicated

*If cause known:* Treatment of cause & exacerbating factors as able; review of available treatment options & periodic reassessment of tx course appropriate

- **Counseling: First,** validate experience ("I hear that this has really been affecting your life")

  **Expectations:** Chronic pain is a complicated problem; currently available therapies rarely result in complete resolution of sx (often "not a curable disease")

  **Reassurance** (when appropriate): Some pain is more bothersome when thought to be a sign of significant pathology; pts w/ chronic pain often have↑level of health anxiety ( *J Psychosom Res* 2006;60:155)

  **Education:** Pain can affect sleep, mood, fitness, family life, & employment; by working on improving other aspects of QoL, we can reduce the impact of pain

  **Goal setting:** "How will we define improvement?"—should be **SMART (S**pecific, **M**easurable, **A**chievable, **R**elevant, & **T**ime-bound) (*Pain Med* 2009;10:S101)

  **Follow-up:** Needs assessment over time: Ask "What is your pain avg? How does it interfere w/ enjoyment of life/general activity?" at each visit (*JGIM* 2009;24:733)

- Management of known causes & comorbid conditions as applicable (see *"Peripheral Neuropathy," "Fibromyalgia," "Inflammatory Bowel Disease," "Herpes Zoster," "Pelvic pain," "Headache," "Jaw & Dental Pain," "Musculoskeletal,"* section *"Depression," "Anxiety"*)
- **Exercise:** Strength & aerobic exercise beneficial in fibromyalgia (*BMJ* 2002;325:185); pts w/ chronic widespread pain randomized to exercise were 3 × more likely to report feeling "much better" at 6 mos than pts w/ usual care (*Arch Intern Med* 2012;172:48); evidence for efficacy in chronic low back pain as well (*Ann Intern Med* 2008;148:247); may consider low-impact exercise such as swimming,

tai chi, for pts w/ knee or hip OA (*Arthritis Care Res* 2012;64:465), gentle yoga

- **Sleep:** Poor sleep assoc w/↑incidence of pain &↓pain threshold in healthy subjects & fibromyalgia pts; 50% of pts w/ LBP c/o insomnia; at any given pain intensity,↑emotional response to pain (e.g., pain is "tiring" or "terrifying" assoc w/ insomnia) (*Eur J Pain* 2012;16:522; *Pain* 1996;68:363; *J Sleep Research* 2007;16:185); studies lacking re: sleep interventions, but reasonable to discuss sleep habits & encourage sleep hygiene
- **Relaxation techniques:** Mindfulness, biofeedback, diaphragmatic breathing may be helpful & no/low risk of harm
- **Psychotherapy:** *Cognitive Behavioral Therapy (CBT)*: Shown to↓disability & improve mood in chronic pain pts, although not shown to ↓ pain itself; can↓pain-related distress in elderly;↓pain for chronic low back pain (*Ann Intern Med* 2008;148:247; *Cochrane Data Syst Rev* 2012;11:CD007407; *Pain* 2013;154:824)
  *Acceptance and Commitment Therapy (ACT):* Goal of awareness/acceptance of experiences assoc w/ chronic pain & continued movement toward personal goals; can↓pain interference in activity &↓pain-related anxiety (*Pain* 2011;152:2098)
- **Nonpharmacologic therapies:** *Acupuncture:* Some evidence can improve pain/stiffness in fibromyalgia, some evidence in LBP (*Cochrane Database Syst Rev* 2013;5:CD007070)
  *Massage:* Evidence for benefit in LBP, shoulder pain, & possible benefit in fibromyalgia/neck pain (*Lancet* 2011;377:2226)
  *Heat:* Evidence in OA, MSK pain; limit to 20 mins at a time, avoid using over lidocaine patch
  *Transcutaneous electric nerve stimulation (TENS):* RCT data limited, but helpful for some pts

## Pharmacotherapy (*ICSI* 2011 Chronic Pain guidelines, icsi.org)

- **General approach:** Many classes available; studies of efficacy often restricted to certain causes, prescribing choices based on type(s)/source(s) of pain & s/e profile
- For short-acting agents, consider prescribing PRN specific scenario (before a walk, before making dinner) rather than simply time-based

(e.g., "q4h PRN") to emphasize function

- **Antidepressants:** Frequently first-line, particularly in pts w/ comorbid mood or anxiety d/o; studies suggested that antidepressants↓pain & MDD sx simultaneously (*Arch Int Med* 2003;163:2433); however, can also help pts w/o depression; explain to pts that these are neurologic agents which may alter how brain interprets painful stimuli

## Pharmacotherapy for Chronic Pain by Pain Type

| Pain Type | Treatment |
|---|---|
| Neuropathic pain | *1st-line:* TCAs, gabapentin (see *"Neuropathy"*) |
| Fibromyalgia | *1st-line:* SNRIs, TCAs<br>*2nd-line:* Non-BZD muscle relaxants, gabapentin (see *"Fibromyalgia"*) |
| Knee or hip OA (*Arthritis Care Res* 2012;64:465) | *1st-line:* APAP<br>*2nd-line:* NSAIDs<br>*3rd-line:* Tramadol, opiates, intra-articular corticosteroids |
| Chronic low back pain (*Spine J* 2008;8:173; *AFP* 2009;79:1067) | *1st-line:* APAP, NSAIDs<br>*2nd-line:* TCAs, SSRIs<br>(see *"Low Back Pain"*) |
| Hand OA (*Arthritis Care Res* 2012;64:465) | *1st-line:* Topical capsaicin, topical NSAIDs<br>*2nd-line:* Oral NSAIDs, tramadol |
| Localized MSK pain | Topical agents (lidocaine, capsaicin, topical NSAIDs), heat |
| Irritable bowel | TCAs or SSRIs, antispasmodics (see *"Irritable Bowel Syndrome"*) |
| Complex regional pain syndrome | May benefit from topical/local agents; tx similar to neuropathic pain (above) |
| Myofascial pain | Tx similar to fibromyalgia |

**Pharmacotherapy for Chronic Pain by Medication Type**

| Medication | Condition Recommended | Notes |
|---|---|---|
| TCAs | Neuropathic pain, fibromyalgia, low-back pain, HA, & IBS | ↑ Risk CV events, ↑ QT |
| SNRIs | Fibromyalgia, consider for knee/hip OA (2nd-line), neuropathy | *S/e:* Nausea, ↑ BP; caution if liver disease, HTN |
| Gabapentin, pregabalin | Fibromyalgia, neuropathic pain | *S/e:* Sedation, dizziness, edema, wt gain; renally cleared, caution if ↓ GFR |
| NSAIDs | OA, RA, low back pain; topical NSAIDs for shoulder, back pain | No evidence for fibromyalgia or neuropathic pain, risk gastritis, AKI/ESRD, hepatitis; s/e may be ↓ w/ topical NSAIDs |

| | | |
|---|---|---|
| APAP | OA (1st-line) | Should be continued as NSAID or opiate-sparing adjunct in severe pain; preferred over NSAIDS in pts w/ CAD; S/e: ↑ LFTs, drug rash |
| Tramadol | ↓ Pain substantially in OA, fibromyalgia, & neuropathic pain | SNRI + opioid agonist; ↑ risk of 5HT syndrome if used w/ SSRI, cyclobenzaprine |
| Capsaicin | Must be applied BID, max efficacy not reached until ~2 wks due to ↓ substance P over time | For neuropathic & MSK pain (incl OA) when limited to focal area |
| Lidocaine patch | Postherpetic neuralgia | 12 h on, 12 h off; may have local or (rare) systemic s/e |
| Muscle relaxant (cyclobenzaprine) | Fibromyalgia; no evidence for chronic MSK pain | Sedating; avoid carisoprodol 2/2 risk of dependency |
| α2-agonist (tizanidine) | Antispasticity agent, used for tension HA, low back pain | HoTN, sedation, dizziness |
| Heat | OA, MSK pain | Limit to 20 mins at a time; avoid using over analgesic patch |
| Opiates | Not routinely recommended | See *"Chronic Opioid Use"* |

(Adapted from: *Arthritis Care Res* 2012;64:465; *JAMA* 2004;292:2388; *Lancet* 2011;377:2226)

## When to Refer

- Referral threshold dependent on local resources; multiple disciplines may be helpful
- **Pain specialist:** Consideration of interventional therapies, such as injectables (e.g., nerve block), implantable device (e.g., spinal cord stimulation, controversial); pain specialists may also be able to suggest tx plans which can be administered by PCP
- **Other specialist:** Severe/refractory pain which is potentially correctable w/ intervention should be referred to appropriate discipline (e.g., knee OA→orthopedics)
- **Cancer-related pain:** Generally managed by (or w/ assistance of) palliative care or pain specialist
- **Therapist:** Can assist w/ pain-related distress-coping techniques, mgmt of mood or SUD
- **Palliative care:** Co-management of pain & psychological suffering

# CHRONIC OPIOID USE

## Background (*MMWR* 2011;60:1487; *JAMA* 2013;309:657)

- **Definition: Opioids** are pharmacologic agents which bind to opioid receptors, found in CNS, PNS, & GI tract; **opiates** are opioids derived from poppy (e.g., morphine, opium)
- **Efficacy:** For chronic, nonmalignant pain, opioids no better than other analgesics in↓pain, & somewhat worse at↑functioning; however, in some individuals can safely→long-term pain relief (*Cochrane Database Syst Rev* 2010;1:CD006605)
- **Side effects:** Nausea, constipation, somnolence,↑fall risk in elderly, hyperalgesia (paradoxical↓in pain tolerance), hypogonadism, medication misuse, addiction (*Ann Intern Med* 2007;146:116; *AFP* 2012;85:49)
- **Misuse:** 5% of US adults have used opioid Rx either for nonmedical reasons, in excessive dose, or via unauthorized routes; pts who misuse opiates more likely to have panic d/o or social phobia, report fair/poor health (*Drug Alcohol Depend* 2008;94:38); *Risk factors:* Personal or FHx substance use, younger, men, Ψ hx
- **Overdose:** Prescription opioids most common cause of drug O/D, involved in 75% of fatal O/Ds; most O/Ds unintentional; highest rates in middle-aged men
- **Treatment disparities:** Evidence that nonwhite pts may receive↓analgesics,↓pain specialist referrals, & have↓PCP trust even when similar rates of opioid misuse/illicit drug use (*Pain* 2013;154:36; *JGIM* 2011;26:846)

## Evaluation

- **Should a trial of chronic opiates be initiated?**
  1. What is risk of misuse? (See *"Risk Assessment"*, below)
  2. Have other agents w/ more favorable s/e profiles been tried?
  3. What are potential benefits & tx goals?
- **Risk Assessment:** Multiple screening tools exist; intended to provide framework for clinical judgment
  *Opioid Risk Tool:* 5-question survey; low vs. high risk, 5% vs. 90% risk of→aberrant behavior (early refills, unauthorized dose escalation, O/D, abnl utox, soliciting opioid Rx from other providers); available at opioidrisk.com/node/887 (*Pain Med* 2005;6:432)

*DIRE score:* Diagnosis, Intractability, Risk, Efficacy→helps predict opiate efficacy (↓ pain &↑function) & risk of aberrant behavior requiring d/c of Rx; available at opioidrisk.com/node/517, mobile app at opioidrisk.com/node/2404 ( *J Pain* 2006;7:671)

## Treatment

- **Deciding not to prescribe opiates:** "Based on my medical opinion, I would not recommend using opiates for this pain;" acknowledge pt frustration if present; discuss other tx, offer reassurance; consider referral to pain specialist for tx suggestions
- **High-risk patients:** Use↑monitoring; consider involvement of pain specialist for recommendations; untreated pain may also be a risk factor for SUD relapse (*AFP* 2003;68:1971)
- **Initiation of opioid therapy** should be considered part of an overall comprehensive treatment plan (see *"Chronic Pain"*)
  1. Start as a trial (e.g., 30 d); establish mutually accepted, specific, measurable outcomes in advance (see "Goal setting" in *"Chronic Pain"*): "How will we know if this is working? Not working?"
  2. Create opioid tx agreement for all pts; frame as informed consent & chance to be explicit about expectations, rather than a "contract" (prescribing bound by provider's best judgment of benefit & safety, rather than by written document)
  3. Follow-up: Review the 4 As (*Adv Ther* 2000;17:70; *Pain Med* 2005;6:107):
     *Analgesia:* Effectiveness of medications at↓pain
     *ADLs:* Has this tx↑functioning?
     *Adverse events:* Any s/e or toxicities of the medication
     *Aberrant behavior:* Any signs of abuse of the medication?
- **Efficacy:** If some progression toward goals, consider↑Rx; if lack of benefit, significant s/e→taper to off; express shared frustration at lack of efficacy (*JAMA* 2013;309:919)

**Recommended Components of Opioid Treatment Agreement**

| Component | Sample Details |
|---|---|
| Indications | Type/location of pain targeted, other tx which have been tried |
| Time frame | E.g., initial trial of 30 d |
| Goals of Rx | Agreed upon w/ pt; see "Goal Setting" above |
| Potential risks | S/e, med interactions (other sedating Rxs, EtOH), activity restrictions/hazards (driving, other activities that put self/ others at risk), risk of physical dependence, risk of addiction |
| Comprehensive tx plan | E.g., other activities for pain mgmt (exercise, PT) tx for hx substance use or mood d/o |
| Provider expectations | Obtaining opioids from one (named) provider, one (named) pharmacy, no unauthorized escalation in dose, limits on early refills or replacing lost/stolen medications, rules & timing of requesting refills (e.g., not at night/weekend) |
| Monitoring to reduce risk of harm | Urine drug testing, pill counts, assessment of efficacy, & s/e |
| Indications for changing or stopping opioids | When risks/harms may outweigh benefits (not meeting tx goals, s/e, aberrant behavior, safety concerns, lack of efficacy) |

(American Academy of Pain Medicine clinical guidelines, *J Pain* 2009;10:113; US Substance Abuse & Mental Health Services Administration, Treatment Improvement Protocol 54 www.samhsa.gov)

- **Sample agreement:** www.aapainmanage.org/literature/Articles/OpioidAgreements.pdf
- **Monitoring:** Avoid paradigm of "catching" pt; explain that many Rx require monitoring due to safety risks (e.g., isotretinoin "i-pledge", AEDs, ACEI); combined chemical + behavioral monitoring↑effective at detecting misuse (*Pain Med* 2009;10: Suppl 2:S101); explain that provider cannot provide risky medications w/o the pt's participation in↓risk
  *Chemical:* Planned & random urine testing, freq determine by provider (↑ risk generally↓interval)
  *Behavioral:* Aberrant behavior assessment, Rx monitoring program (available in many states), pill counts, corroborative reports of others
- **Approach to aberrant behavior** ( *J Pain* 2009;10:131; *Pain Med* 2009; 10 Suppl 2:S101)
  1. Confirm findings
  2. State findings to pt in nonjudgmental way "I notice that your last urine toxicology test was positive for cocaine. Can you tell me what happened?"
  3. Listen to pt
  4. Consider potential causes of aberrant behavior & treat the causes as

able

5. Express concerns that such behavior, regardless of underlying reason, is problematic
6. ↑ therapeutic structure, (incl spot urine drug testing *at time of aberrant behavior* when feasible) remind pt that aberrant behavior signals increased risk & suggests opiates may not be a good choice
7. If behavior continues, taper to alternative meds; if addiction likely, require eval/tx (see *"Substance Use Disorders"*)

**Aberrant Behaviors which Predict Addiction or Opioid Use Disorder**

| |
|---|
| Selling meds or falsifying Rx<br>Obtaining medications from nonmedical sources<br>Resistance to changing medications despite ↓ in function or significant s/e<br>Lack of control over EtOH use, use of illegal drugs/unprescribed controlled substances<br>*Recurrent episodes of:* Rx loss or theft, obtaining opioids from other providers, unauthorized dose escalation, early refill requests |
| **Behaviors Which Arouse Suspicion for Addiction, But are Less Predictive of Abuse** |
| Asking for more or specific medication<br>Stockpiling medications during times when pain is less severe<br>Use of the pain medications to treat other sx<br>Reluctance to ↓ opioid dosing once stable<br>*In earlier stages of tx:* Unauthorized dose escalation, obtaining opioids from other providers, sharing or borrowing similar meds from friends/family |

| Differential Diagnosis of Behaviors Suggestive of Addiction | |
|---|---|
| **Inadequate pain management** | Stable condition but inadequate pain control<br>Progressive condition/pathology, tolerance to opioids |
| **Inability to comply w/ treatment** | Cognitive impairment, Ψ conditions, self-medication of Ψ or sleep d/o, diversion by pt/others |

(Minimizing Misuse of Rx Opioids in Chronic Nonmalignant Pain. 2010; *drugabuse.gov; Clin J Pain* 2002;18:S28)

- **Discontinuing opiates:** Present the evidence for lack of efficacy &/or↑riskiness or harm of the drug, citing objective evidence & pt's own reports; plan taper & discuss alternative tx; consider specialist referral for add'l recommendations; it is the medication, not the pt, that has failed

# IMMUNIZATIONS

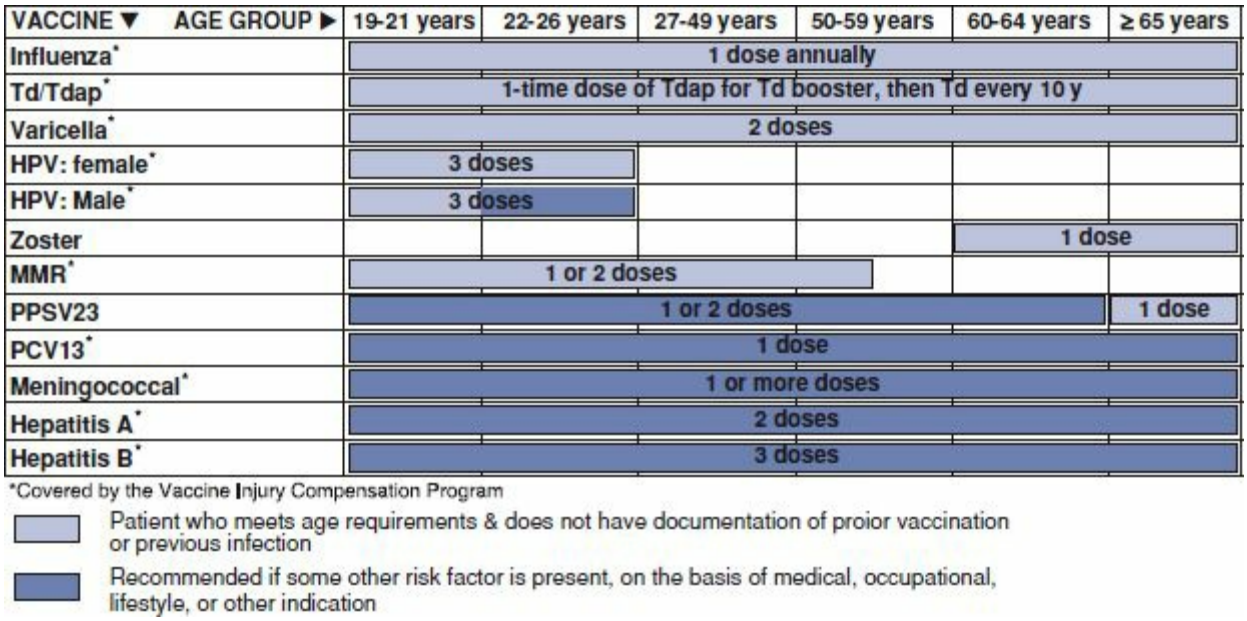
## Background (*Healthy People 2020, cdc.gov*)

- Current US guidelines recommend adults be immunized against 12 pathogens (14 for adults >65 or w/ certain comorbid conditions) w/

the goal of↓infectious disease incidence & complications in susceptible pts

- **Immunization goals: Protect individuals** from infection/↓ complications **Reduce transmission** to at-risk population (infants, elderly, poor health) **Reduce population disease burden:** Smallpox eradicated, polio & diphtheria becoming rare
  **Confer herd immunity:** Immunization of a significant proportion of a population can↓the number of susceptible members of that pop; this↓probability of transmission of infection overall
- Improving rates of completion of all vaccines, but at risk (≥65 or diabetics/asthmatics) still inadequately covered; 64% elderly had pneumococcal vaccine, 70% get annual flu shot
- CDC estimates that↑immunization→elimination of diphtheria, measles, mumps, rubella in US; 75% reduction in hepatitis A & B incidence

## CDC Adult Vaccine Schedule (*MMWR* 2013;62:S9)

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## SPECIFIC VACCINES

### Pneumococcal: PPSV23 (*ACIP* guidelines *MMWR* 2012;61:613)

- **Goal:** Prevention of invasive disease (e.g., bacteremia, meningitis); conflicting data re: its efficacy for the prevention of PNA
- **Target:** All adults ≥65 y, or 19–64 y w/ chronic disease (CHF, COPD,

asthma, ESLD, DM); functional/anatomic asplenia; immunocompromised pts (incl HIV, leukemia, lymphoma, solid organ transplant, CKD); smokers; pts w/ EtOH abuse, SNF residents)

- **Dosing:** Vary based on immune status & age (see table)
  *Recent admin of PCV13:* Wait 1 y for PPSV23 admin
- **Efficacy:** Highly variable in current studies; 50–80% in most observational studies of healthy elders or 18–64 y olds w/ chronic conditions; up to 74% effective in meta-analysis of 15 RCTs (*MMWR* 2010;59:1102)
- **Vaccine-specific side-effects:** ~50% have injection site pain, redness; <1% w/ fever, muscle aches, severe local reactions; more serious reactions can occur but rare

## Pneumococcal: PCV13 (*Ann Intern Med* 2013;158:191; *MMWR* 2012;61:81)

- **Background:** Protects against additional 13 strains of *S. pneumoniae;* as of 2012, recommended for immunocompromised adults (who have ↑ risk of invasive disease & ↓ response to PPSV23)
- **Target population:** Recommended for adults >19 y w/ immunocompromising conditions (same as for PPSV, above), functional/anatomic asplenia, or CSF leaks or cochlear implants; unlike PPSV23, not recommended for pts w /chronic disease
- **Dosing: Single lifetime dose;** timing in relation to PPSV23 intended to maximize immune response to each vaccine
  *Recent admin of PPSV23:* Wait 8 wks for PCV13

### Pneumococcal Vaccine Dosing Schedule

| Clinical Scenario | Age <65 | Age >65 |
|---|---|---|
| **Immunocompetent;** eligible for PPSV23 | PPSV23 now, PPSV23 again at age 65 (or after 5 y, whichever is longer) | PPSV23 now |
| **Immunocompetent;** eligible for PPSV23 & PCV13 | PCV13 now, PPSV23 8 wks later, PPSV23 again at age 65 (or after 5 y, whichever is longer) | PCV13 now, PPSV 8 wks later |
| **Immunocompromised;** no prior pneumococcal vaccination | PCV13 now, PPSV23 8 wks later, PPSV23 repeat in 5 y, then again at 65 (if not >65 at time of 2nd dose) | PCV13 now, PPSV 8 wks later |
| **Immunocompromised;** already received 1st dose PPSV23 | PCV13 >1 y after initial PPSV23, PPSV23 5 y after initial PPSV23, then again at 65 (if not >65 at time of 2nd dose) | PCV 13 now, PPSV 8 wks later |

## Influenza (*MMWR* 2010;59:1102)

- **Goal:** Prevention of individual infection & spread of influenza virus
- **Target population:** All persons aged ≥6 mos; esp. pts w/ asthma, DM, chronic lung disease, pregnant ♀, people >65
- **When to administer:** Annually; ASAP once available, optimally before onset of flu to the community; should be offered throughout flu season (Oct–Mar in US); recommended even in pts who already had influenza-like illness this season
- **Strain variability:** Flu strains vary by season→each year, vaccines developed to protect against 3 strains of influenza (mix of A & B)
- **Dosage forms**
  *Inactivated (IM):* Recommended for all age groups, incl pregnant, HIV ⊕; avoid admin during febrile illness; *contraindications:* GBS after prior immunizations, anaphylactic reaction to egg or vaccine components; *s/e:* Arm soreness, low-grade fevers, myalgia
  *Live attenuated vaccine (intranasal):* For use in healthy adults <50 y; *Contraindications:* Immunosuppressed or those in close contact w/ immunosuppressed, chronically ill, pregnant, hx GBS, or egg allergy; *S/e:* Rhinorrhea, HA, pharyngitis
  *High-dose inactivated* (Fluzone High Dose): Consider in pts >65 y (*MMWR* 2010;59:485)
  *Trivalent influenza vaccine (FluBlok, IM):* Approved by FDA in 2013 for healthy adults <50 y; does not use eggs to prep**Æsafe for pts w/ egg allergy;** *Contraindications:* Hx of anaphylaxis to individual components; *S/e:* Similar to other forms
- **Egg allergy: Use trivalent influenza vaccine (FluBlok);** if unavailable, pts w/ egg allergy of *hives* can receive inactivated w/ 30 mins of monitoring; pts w/ hx of *angioedema, resp distress, emesis, lightheadedness*, or *requiring epinephrine* to flu shot→allergy referral
- **Efficacy:** Variable based on pt, mode of vaccination, & strain: vaccine "fit"; 2 meta-analyses of healthy individuals, inactivated vaccine, good "fit" w/ 59–73% efficacy (*Lancet* 2012;12:36; *Vaccine* 2011;29:9159); live attenuated efficacy possible less (32–67%) effective; in pts w/ comorbidities or immunosuppression, efficacy varies (*Lancet* 2012;12:36)

**Responses to common patient objections to influenza vaccination**
(*JAMA* 2013;309:881)

| |
|---|
| **"I never get sick":** Pts may become infected w/ minimal or no sx, then infect close contacts at risk for serious complications |
| **"The vaccine does not work":** On a population-wide basis, known to ↓ flu-related illness, abx use, time lost from work, hospitalizations, & deaths |
| **"The vaccine causes the flu":** Misperception can be due to mistaking URI for influenza, acquiring influenza around time of vaccination, or ineffectiveness; nearly all providers receive influenza vaccine; use own experience to reassure; "I tested it for you" |
| **"I am allergic to eggs":** See "Egg allergy" above |
| **"I am pregnant" or "I live w/ an immunocompromised pt":** These groups may receive greatest benefit; obtaining flu shot protects immunocompromised family members |

## Human Papilloma Virus (*MMWR* 2007;56:1)

- **Goal:** Reduce current rates of genital HPV infection & transmission; currently most common STI in US (6.2 million new infection/y) (cdc.gov/std/HPV)
- **Target population:** Ideally vaccinate prior to initial sexual activity; however, sexually active individuals should still be vaccinated if ≤26 y; also ok if HPV⊕, or immunocompromised (although may↓efficacy)
- **Administration:** 3 doses; at 0, 1–2 mos, & 6 mos
- **HPV strains:** HPV 6,11 (low-risk virus strains) assoc w/ low-grade cervical cell changes, genital warts; HPV 16,18 (high-risk strains) assoc w/ cervical or anogenital CA
- **Dosage forms:** Both inactivated vaccine of virus-like particles
  HPV4 (Gardasil): Quadrivalent, provides protection against HPV 6,11,16,18
  HPV2 (Cervarix): Bivalent, protects against HPV 16,18
- **Efficacy:** Successfully reduces HPV infection; efficacy against CIN2⊕ containing HPV16/18 DNA was >90%; also reduces risk of cervical intraepithelial neoplasia grade 2, grade 3, & adenocarcinoma in situ (*Lancet* 2007;369:2161; 2007;369:1861)

## Herpes Zoster (*MMWR* 2008;57:1)

- **Goal:** To prevent zoster or prevent/reduce the severity and duration of postherpetic neuralgia (see *"Herpes Zoster"*)
- **Target population:** Pts aged ≥60 y including persons who report a previous episode of zoster who do not have contraindications

- **Contraindications:** Hx anaphylaxis to gelatin, neomycin, or previous VZV vaccine; *Immunocompromised persons:* Leukemia, lymphoma, other BM compromise, or HSCT recipients; HIV⊕ w/ CD4 ≤200 or CD4% ≤15%; high-dose corticosteroids (≥20 mg/d prednisone ≥2 wks, until ≥1 mo after discontinuation); high-dose immunosuppressives or any immune modulators; persons who received varicella vaccine; pregnancy; breastfeeding not a contraindication
- **Dosage form:** Zoster vaccine is a live, attenuated virus vaccine; safe w/ inactivated influenza, Td, Tdap, PCV13, PPSV23; give 4 wks apart from live, attenuated vaccines
- **Efficacy:**↓Zoster incidence by 51%,↓severity by 61%,↓postherpetic neuralgia by 66%

## ADVERSE REACTIONS

- **Overview:** Most pts can receive most vaccinations w/ only local s/e or minor cold sx; not giving immunization→↑ risk of individual infection & assoc morbidity w/ public health implications
- **True contraindications:** Hx anaphylaxis to a vaccine→avoid only that vaccine; anaphylaxis to egg→avoid MMR, yellow-fever, influenza as above; pregnant or immunosuppressed→avoid all live virus vaccines
- **Immunization-specific precautions** see MMWR 2011;60(RR02):1
- **Safe to admin vaccines to pts w/:** Minor URIs, otitis media, (even if febrile), diarrhea, mild–mod local reaction to a previous dose of vaccine, pts on current antimicrobial Rx, or pts in the convalescent phase of an acute illness
- **Red flags:** Pts should seek medical attention for high fever, unusual behavior, or signs of serious allergic reaction (difficulty breathing, hoarseness, wheezing, hives, paleness, weakness, a fast heart beat or dizziness)
- **Reportable reaction (all immunizations):** Anaphylaxis (up to 7 d beyond admin); encephalopathy, encephalitis, or seizures (time limits below); any sequelae of reportable events; s/e listed in package insert as contraindications to future vaccination

**Selected Immunization-specific Reportable Reactions**

| Immunization | Adverse Reactions |
|---|---|
| Tetanus | Brachial neuritis (w/in 28 d) |
| Pertussis | Encephalopathy or encephalitis (w/in 7 d) |
| Measles, mumps, or rubella | Encephalopathy or encephalitis (w/in 15 d) |
| Rubella | Chronic arthritis (w/in 42 d) |
| Measles | TTP (7–30 d) |

- **Adverse events:** File report via Vaccine Adverse Event Reporting System (VAERS at http://www.vaers.hhs.gov or by calling 1-800-822-7967

# INFERTILITY

## Background (*Clin Ob Gyn* 2012;55:692; *Fertil Steril* 2008;90:S60; *Hum Repro* 2005;20:144)

- **Baseline fertility rates:** 50% of heterosexual couples who are not using contraception conceive w/in 3 mos, 72% w/in 6 mos, 85% w/in 1 y
- **Definition:** Infertility is characterized for a heterosexual couple as failure to conceive despite regular, unprotected intercourse; timeframe is based on the age of the woman; for couples w/ woman <35 y = failure to conceive after 1 y; for couples w/ woman ≥35 y = failure to conceive after 6 mos
- **Epidemiology:** 10.9% of US women 15–44 y have↓fertility & 6% of married women 15–44 y meet definition for infertility; >10% of women of reproductive age have undergone infertility tx (*cdc.gov*, Nat'l Survey Family Growth, 2006–2010; *NEJM* 2010;363:965)
- **Etiology:** May be caused by endocrine, genetic, structural, or infectious causes in either partner; when known, ♀ factors contribute to 50–75% of cases, ♂ factors contibute to 25–50%; approximately 25% of all cases of infertility are unexplained

## Evaluation (*Can Fam Physician* 2003;49:1465; *Clin Ob Gyn* 2012;55:692)

- **General approach:** Consider as a problem that affects couples rather individuals, ideally complete hx & exam of both partners

- **History:** *Both partners:* Age, duration of infertility, frequency of coitus, prior pregnancy/paternity, PMHx (hx XRT/chemo, systemic illness) meds, FHx (infertility, birth defects, CF, genetic mutations, mental retardation), social hx (EtOH, tobacco, stress)
  - ♀ : Assess for ovulation (regular cycle length, ⊕ PMS sx, see *"Abnormal Uterine Bleeding"*);↓estrogen (vaginal dryness, hot flashes), pregnancy hx, FHx (POI, endometriosis), PSHx (gyn or intra-abd procedures); meds, incl herbal/OTC/vitamins
  - ♂ : Assess for mechanisms of testicular injury (hx mumps, hx testicular trauma/torsion, undescended testes), PSHx (GU or inguinal surgery); meds (sulfasalazine, cimetidine, nitrofurantoin), drugs (marijuana, cocaine, tobacco), environmental exposures (lead, arsenic), external factors (biking, hot tubs/saunas)
- **Exam:** *Both partners:* BMI, general appearance, secondary sex characteristics
  - ♀ : Thyroid exam, breast exam (galactorrhea), e/o androgen excess; signs of androgen excess (acne, hirsutism, baldness, virilization), speculum exam (purulent d/c, cervical/vaginal structural abnormalities), pelvic exam (uterine size/mobility, tenderness, masses, nodularity in posterior cul-de-sac)
  - ♂ : Signs of masculinization, genital exam (testes size/consistency, varicocele, hypospadias)
- **Initial diagnostics** (*NEJM* 2010;363:965)
  - ♀ : TSH, PRL, FSH/Estradiol on day 3 of cycle; hysterosalpingogram to assess tubal patency, uterine cavity; if e/o hypoandrogenism, PCOS eval (see *"Polycystic Ovary Syndrome"*), d 21–25 progesterone level→level $>3$ ng/mL confirms ovulation
  - ♂ : Semen analysis; best performed after 72 h abstinence ($<72$ h $=\downarrow$sperm count, $>72$ h $=\downarrow$sperm motility); ♂ karyotype if oligospermia

**Selected Female Infertility Etiologies**

| Category | Diagnoses |
|---|---|
| *Ovulatory dysfunction* (32%) | Hypothalamic–pituitary dysfunction: (↑ stress, eating d/o, ↑ exercise); see *"Amenorrhea"*<br>Anovulation (PCOS; see *"Polycystic Ovary Syndrome"*)<br>Endocrinopathy (↑ PRL, thyroid)<br>Ovarian insufficiency (idiopathic, related to medications, hx XRT/chemo) |
| *Tubal pathology* (22%) | Occlusion or other abnormalities |
| *Endometriosis* (15%) | Anatomic distortion or possibly 2/2 cytokine release interference w/ ovulation, fertilization, implantation |
| *Pelvic adhesions* (12%) | 2/2 intra-abdominal surgery, infection, trauma |
| *Other* (19%) | *Structural:* Uterine fibroids, polyps, Asherman syndrome, reproductive tract anomaly, cervical stenosis from prior procedure; *Genetic:* Turner syndrome, androgen insensitivity syndrome; *Meds:* OCPs, progestins, Ψ medications, corticosteroids, chemotherapeutics |
| **Selected Male Infertility Etiologies** | |
| 2° *hypogonadism* | See *"Male Hypogonadism"*<br>*Hypothalamic–pituitary dysfunction:* GnRH, LH, FSH deficiency; exogenous steroid use, obesity (*Arch Intern Med* 2012;172:440) |
| 1° *hypogonadism* | Klinefelter, cryptorchidism, varicocele, Y chromosome deletions, androgen insensitivity syndrome, 5α reductase deficiency, infection, autoimmune disease, toxins/exposures, medications (see "History," above) |
| *Structural* | Ejaculatory dysfunction (neurologic or anatomic), epididymal dysfunction, congenital absence of vas deferens |

(*WHO Tech Report Series* 1992;820:1; *NEJM* 2010;363:965)

## Treatment (*Hum Repro* 1999;14:7; *Am J Obstet Gynecol* 2008;199:596)

- Treat underlying cause as indicated; *Lifestyle modifications as indicated:* Wt loss/gain, mod exercise, smoking cessation,↓EtOH,↓stress,↓caffeine (though data lacking/inconclusive except for maintaining nl wt); *PCOS:* Consider metformin although inconclusive data re: efficacy for fertility
- **General recommendations to increase fertility:** Intercourse every other day on d 12–18 of cycle; women should be on multivitamin w/ 400–800 μg folic acid/d; this↓risk of neural tube defects & *may*↓anovulatory cycles &↑fertility ( *J Reprod Med* 2004;49:289; *PLoS One* 2012;7:e46276)

## When to Refer

- Patients should be referred to gynecologist experienced in basic infertility eval; women >35 or w/question of POI should receive prompt referral

- **Reproductive endocrinologist:** For advanced tx, including further w/u or surgical intervention for structural factor, assisted reproductive technology for egg/ ♂ factor
- **Urology:** ♂ w/ hx STI, urogenital surgery/pathology, varicocele, or abnl genital exam

## Patient Information:

- www.reproductivefacts.org/detail.aspx?id=876, www.aafp.org/afp/2007/0315/p857.html

# OBESITY

## Background (*AFP* 2010;81:1449; *JAMA* 2012;307:491)

- **Definitions:** Obese: BMI ≥30(wt [kg]/ht [m²]); overweight: BMI >25
- **Body mass index:** Serves as proxy for amount of relative body fat; however, this is indirect, &↑BMI may reflect higher lean mass for certain pts (e.g., athletes)
- Obesity is a multifactorial, chronic disease affected by social, behavioral, cultural, metabolic, & genetic factors
- **Comorbidities:** Health risks assoc w/ obesity include prediabetes & DM2, HTN, HLD, CVD, gallstones, NAFLD, GERD, OA, CA, OSA, stroke, mood/anxiety/eating d/o, disability, significantly↑mortality (obesity itself accounts for est 5–15% US deaths/y) (*NEJM* 2009;361:2252)
- **Epidemiology:** >1/3 US adults obese, >2/3 overwt or obese; dramatic (>2 ×) ↑prevalence in past 30 y, now leveling off (*JAMA* 2012;307:491; *NCHS Data Brief* 2010;No.50)
- **Risk factors:** Assoc w/↑age; race/ethnicity: non-Hispanic black >Mexican Americans >any Hispanic race/ethnicity;↓socioeconomic status;↓education (♀ only)

## Evaluation

- **Screening:** All adults by BMI & waist circumference at periodic health visits
- **History:** *Complications* (as above), *RFs for complications* (tobacco use, ⊕ FHx CAD); *contributing factors:* (Mood d/o, thyroid disease); *meds:* Especially those with wt-related s/e (atypical antipsychotics, antidepressants, antiepileptics, diabetes medications, steroids); *social hx:* Support system, resources (time, money), motivations for wt loss, barriers to wt loss; stressful life events
- **Weight history:** Past wt loss attempts, diet (esp breakfast, fast food, sweet beverages, high-fat, dairy), physical activity, ⊕ FHx obesity
- **Physical exam:** Height, wt, waist circumference, BP; look for signs of insulin resistance (acanthosis nigricans) & hypothyroidism *Distribution* of adiposity important: Waist circumference >40″ (♂

)/ > 35″ (♀) independently↑health risks in pts w/ BMI < 35 (note↓cut-offs in people of East Asian descent: > 35″ (♂)/ > 31″ (♀) (*AHRQ* 2011;11-05159-EF-1)
- **Lab:** Chem 7 (Cr for HTN/DM-related renal disease screening), LFTs (NAFLD screening), TFTs (r/o underlying hypothyroidism), HbA1c (DM screening), fasting lipids (HLD screening); consider Vit D

## Treatment (*Cochrane Database Syst Rev* 2004;3:CD004094; *NIH* 1998;98:4083)

- **General approach: Goals** are (1) prevent further wt gain, (2) reduce body wt, (3) maintain wt loss over long term; gradual wt loss (rate = 1–2 lb/wk) w/ initial goal of 10% wt loss recommended
- **Indications for weight loss:** Recommended for obese/overwt pts **or** high-risk (waist circumference plus ≥ 2 CV RFs)
- **Benefits:** Health benefits seen w/ **any** wt loss, *even if pt remains above ideal body wt* (↓ risk DM, HTN, CVD, HLD, disability;↓HbA1c for pts w/ DM)

## Lifestyle Modification

- **Comprehensive behavioral change** = cornerstone of therapy
- **Energy balance equation:** Net body balance (weight) = Energy input (food) − Energy output (metabolism, physical activity)
- **Diet:** Low-calorie diet essential; recommend reduction of 500–1000 kcal/d (1000–1200 kcal/d ♀, 1200–1500 kcal/d ♂), individual goals set w/ nutritionist; reduction of 500 kcal/d results in wt loss of 1–2 lb/wk
- Goal ≤ 30% calories from fat; some suggestion of efficacy of low-carb diets, though evidence is conflicting (*NEJM* 2009;360:859)
- Emphasize↓soda/other sugary beverage consumption, given significant contribution to wt gain (25% of US consumes > 200 cal/d of soda) (*NEJM* 2012;367:1397; *Am J Clin Nutr* 2006;84:274; *NCHS Data Brief* 2011;71:1); reframe as "liquid candy"
- ↓ EtOH intake as appropriate (20% of men consume > 300 cal/d of EtOH ≈ 2 beers) (cdc.gov, NHANES 2010)
- **Exercise:** Exercise alone will not→significant wt loss, but important for prevention of wt gain &↓CV/DM risk independent of wt loss; goal ≥ 30 min/d ≥ 5 d/wk, US Dept of Health & Human Services

recommends 150 mins of moderately vigorous activity/wk

- **Other:** Behavior therapy (food/exercise journal, stress mgmt, stimulus control, contingency planning, social supports, etc.), nutritionist referral, group program (e.g., Weight Watchers) (*JGIM* 2013;28:12)

## Pharmacotherapy

- **Indications:** Obese or BMI ≥27 w/ CV RFs who have failed lifestyle modifications alone
- **General considerations:** Always prescribe in combination w/ ongoing lifestyle modification counseling (*AHRQ* 2011;11–05159-EF-1); titrate↑from lowest dose; wt loss effect often lost after medication d/c
- **Phentermine, diethylpropion** (*Tenuate*): FDA-approved for ≤3 mos
  *Mechanism:* Inhibits NE/5HT reuptake→early satiety,↓food intake
  *S/e:* Tachycardia, HTN→monitor BP/HR
  *Contraindications:* CAD, uncontrolled HTN, hyperthyroidism, MAOI use, caution in pts w/ renal disease (1° excretion = renal for both), anxiety
  *Notes:* Phentermine more effective in combination w/ topiramate (*Qsymia*) (CONQUER, *Lancet* 2011;377:1341)
- **Orlistat** (*Xenical, Alli*): FDA-approved for ≤1 y
  *Mechanism:* Inhibits pancreatic lipase→↓ fat digestion/absorption; prescribe w/ vitamins A, D, E, & K; *S/e:* Bloating, flatulence, oily stools; some concern for severe liver disease (rare)
  *Notes:* Often not covered by insurance, $^{1}/^{2}$ strength OTC formulation available; no long-term safety data yet
- **Lorcaserin** (*Belviq*): FDA-approved for chronic wt mgmt
  *Mechanism:* Activates 5HT 2C receptor→early satiety,↓food intake
  *S/e:* HA, nausea, fatigue, constipation, dry mouth
  *Contraindications:* Concurrent MAOI use, caution in CHF, DM (→ hypoglycemia)
  *Notes:* No long-term safety data; no effect on 2B receptor (which in fenfluramine →valvular disease)

## Bariatric Surgery (*Cochrane Database Syst Rev* 2009;2:CD003641; *Ann Int Med* 2005;142:547)

- **Indications:** Pts w/ BMI ≥40 **or** BMI ≥35 w/ related comorbidities

(severe OSA/DM) who have failed conventional Rx

- **Efficacy:** Surgery more effective at↓wt &↓comorbidities (DM, HLD, HTN, OSA) than medical Rx for pts w/ BMI >30
- When referring, document wt loss hx (including prior wt loss attempts), medical necessity, pt comprehension & accountability, & acceptable level of risk; always refer to experienced ctr→↓ surgical risk (*Can Fam Physician* 2010;56:873)
- **Laparoscopic Roux-en-Y gastric bypass:** Most common procedure; excess wt loss > gastric banding; 30 d mortality rate = 0.3–1%; complications include wound infection/dehiscence, stomal stenosis, hernias, gallstones, vitamin deficiencies, dumping syndrome
- **Laparoscopic adjustable gastric band:** 2nd most common; approved for pts w/ BMI ≥30 & <40; min mortality risk (0.02–0.4% at 30 d); complications include band slippage/erosion, pouch dilatation
- **Other procedures:** Under investigation/development include lap sleeve gastrectomy (no long-term effectiveness data), intragastric balloon, duodenojejunal bypass sleeve, transoral gastroplasty, & transoral endoscopic restrictive implant

# TOBACCO USE

## Background

- Tobacco use **is the leading preventable cause of death in the US;** 50% of smokers will die due to their tobacco use, losing 10 y of life expectancy (*BMJ* 2004;328:1519; *JAMA* 2004;291:1238)
- Smoking is considered a chronic disease requiring longitudinal, coordinated care w/ behavioral & medical tx
- **Epidemiology:** 19% of US adults currently use tobacco (*MMWR* 2012;61:889); ♂ >♀, Native American >Caucasian, African-American >Hispanic, Asian;↑prevalence in pts w/ mental illness & SUD; tobacco contributes to health disparities w/↑use & exposure among people w/↓incomes & education (cdc.gov/tobacco; *JAMA* 2000;284:2606)
- **Quit attempts:** 69% of US smokers want to quit, 52% attempt, only 6% succeed (*MMWR* 2011;60:1513); only 32% of pts who attempt to

quit use any medications to help them do so

*Good prognosis:* Highly motivated, ready to quit, good self-efficacy, social support

*Poor prognosis:* High nicotine dependence (≥ 20 cig/d, 1st cig <30 mins after waking), Ψ comorbidity, substance use, high stress, living w/ other smokers

- **Benefits of quitting:** Exist for pts of all ages/comorbidities (*Public Health Service* 2008)

  *Age <35:* Quitting now→survival comparable to nonsmokers

  *Age <65:* Quitting now→avg of 4 y of life gained

  *Prior MI:* Quitting→36%↓relative mortality, comparable to other 2° prevention

  *Head & neck CA:* Quitting→40%↓relative mortality (*NEJM* 1993;328:159)

  1 y after quitting→50%↓in risk of CAD; 5 y after quitting→stroke risk normalized to risk of nonsmokers; 10 y after quitting→lung cancer risk normalized to nonsmoker

## Evaluation

- 70% of smokers see a provider each year; only 51% of these recall being advised to quit despite evidence that medical advice to quit↑chances of success (*Prev Chronic Dis* 2012;9:E130; *Addiction* 2012;107:1066)
- Brief interventions can be delivered by provider in 3 mins, based on 5As model

### 5As Model for Treating Tobacco Use and Dependence

| | |
|---|---|
| **A**sk | Identify & document use of tobacco *(e.g., cigarettes, cigarillos, chewing tobacco, loose tobacco, pipe tobacco, hookah)* routinely for every pt |
| **A**dvise | Strongly advise every user to quit; individualize using pt's current health concerns, costs, or impact on their household & children<br>"As your provider, I strongly recommend that you quit smoking"<br>"Quitting smoking is the most important thing you can do to protect your health now & in the future" |
| **A**ssess | "Are you ready to quit smoking in the next 30 d? I can help with this" |
| **A**ssist | For those ready to quit, offer medication & counseling<br>For those not ready to quit, provide a motivational intervention |
| **A**rrange | F/u w/in 1 wk after quit attempt & at each visit for active smokers |

*(US Public Health Service, AHRQ, ahrq.gov)*

- For those not ready to quit: **Motivational interviewing**, a specialized counseling technique that↑future quit attempts (see *"Counseling Patients"*)

## Treatment (*Am J Prev Med* 2008;35:158; *Public Health Service* 2008; *JAMA* 2012;308:1573)

- **General approach:** For pts ready to quit, **combination of counseling & meds most effective** tx (2.1 × more likely than brief intervention; 1.7 × more likely than counseling alone, 1.3 × more likely than meds alone (*Cochrane Database Syst Rev* 2012;5:CD001837)
- **Counseling:** Range of options; generally↑intensity, time, or number of sessions →↑ likelihood of quitting; odds of quitting 2.3 × ↑if counseling >10 mins (*Public Health Service* 2008); group, individual, & telephone counseling all effective, some evidence effective via text message (*JAMA* 2012;308:1573; *Lancet* 2011;378:49; *Addiction* 2009;103:478); **quitlines** (smoker offered a series of scheduled telephone calls by trained counselor to guide through quitting process) available nationwide
- **Behavioral:** Smoking "bans" in home & car assoc w/↑quit attempts & abstinence, as well as↓2nd-hand smoke exposure (*Nicotine Tob Res* 2009;11:1131)
- **Pharmacotherapy:** All smokers trying to quit should be offered medication, except when contraindicated (n.b. evidence insufficient in light smokers, smokeless tobacco users, pregnant smokers)
- **Nicotine replacement therapy (NRT):** Multiple forms available (below); contraindications include caution in immediate post-MI period (<2 wks), pts w/ serious arrhythmia or UA; however, NRT is safe in pts w/ stable CAD

**Nicotine Replacement Therapy** (*JAMA* 2012;308:1573)

| Form | Sample Rx | Notes |
|---|---|---|
| **Patch** | *Dosing:* 21 mg/24 h × 4 wks, then 14 mg/24 h × 2 wks, then 7 mg/24 h × 2–6 wks<br>*Duration:* 8–12 wks | Slow onset, steady levels for 16 or 24 h<br>Available OTC<br>*S/e:* Skin irritation, insomnia, vivid dreams<br>*Efficacy:* RR vs. placebo: 1.66 |
| **Gum** | *Dosing:* ≥25 cig/d → 4 mg/piece; <25 cig/d = 2 mg/piece, use q1–2h x 6 wk, max 24 pieces/d<br>*Duration:* 12 wks | Rapid onset: 20–30 mins<br>Available OTC<br>*S/e:* Mouth soreness, dyspepsia, hiccups, jaw ache<br>*Efficacy:* RR vs. placebo: 1.43 |
| **Inhaler** | *Dosing:* 6–16 cartridges (4 mg ea)/d<br>*Duration:* Up to 6 mos | Rapid onset: 20–30 mins<br>*S/e:* Local irritation in mouth, throat<br>*Efficacy:* RR vs. placebo: 1.90 |
| **Lozenge** | *Dosing:* 1st cig after waking:<br><30 min → 4 mg/piece<br>>30 min → 2 mg/piece<br>9–20 pieces/d<br>*Duration:* 12 wks | Rapid onset: 20–30 min<br>Available OTC<br>*S/e:* Nausea, hiccups, heartburn, HA, coughing<br>*Efficacy:* RR vs. placebo: 2.00 |
| **Nasal Spray** | *Dosing:* 1–2 sprays (0.5 mg) ea; nostril/h, min 8 doses/d, max 40 doses/d<br>*Duration:* 3–6 mos | Most rapid onset: 5–10 mins<br>*S/e:* Nasal irritation, congestion, highest dependence potential of NRT<br>*Efficacy:* RR vs. placebo: 2.02 |

- **Bupropion SR:** works by↑DA levels; independent of antidepressant effect; delays wt gain assoc w/ quitting; 1.69 RR of quitting success vs. placebo
  *Dosing:* Start 1–2 wks before quit date; 150 mg QAM × 3 d, then 150 mg BID
  *Duration:* 7 wk–6 mos; *S/e:* Insomnia, dry mouth,↓seizure threshold (0.1% sz risk); avoid in pts w/ epilepsy, eating d/o, using another bupropion form or recent (<2 wks) MAOI use; monitor pts w/ psych hx for exacerbations or↑SI
- **Varenicline:** Selective partial α4β2 nicotinic receptor agonist, relieves withdrawal & blocks smoking reinforcement
  *Dosing:* Start 1 wk before quit date; 0.5 mg QD × 3 d, then 0.5 mg BID × 4 d, then 1 mg BID
  *Duration:* 3–6 mos
  *S/e:* Nausea (take w/ food), insomnia, vivid dreams, depressed mood, agitation; use w/ caution in pts w/ >stage 3 CKD; monitor pts w/ psych hx for exacerbations or↑SI; some concern for↑CAD risk but not seen in other studies (*BMJ* 2012;354:e7176; *BMJ* 2012;344:e2856)
- **Combined pharmacotherapy:**↑effective than monotherapy; approved combos:

1. Nicotine patch **&** PRN (gum, nasal spray, or inhaler); RR vs. patch alone 1.3–1.9
2. Patch + bupropion SR (RR vs. patch alone: 1.3)

- **Second-line agents:** (not FDA-approved for smoking cessation); *Nortriptyline:* 75–100 mg QD, start 10–28 d before quit, 6 wks–6 mos, RR vs. placebo 2.03; S/e: Dry mouth, sedation, lightheadedness; avoid if hx arrhythmia, MAOI use; *Clonidine:* Initial 0.10 mg PO BID or 0.10 mg/d patch, start 1–2 d before or on quit date; S/e: Dry mouth, sedation, HoTN
- **Electronic cigarettes** (e-cigarettes): Not enough evidence to assess safety/efficacy
- **Complications of quitting**
  *Wt gain:* Most smokers experience modest ($\leq$10 lb) wt↑after quitting; bupropion & NRT may delay wt gain; counsel re: diet/exercise (*Fiore et al. Public Health Service* 2008)
  *Drug interaction:* Tobacco smoke (but not NRT) induces cytochrome P450, quitting can→supratherapeutic drug levels (e.g., theophylline, fluvoxamine, olanzapine, or clozapine)
- **Relapse counseling:** For those recently quit: relapse is common; best strategy is encouraging use of evidence-based tx w/ each quit attempt
- **Patient resources:** Smokefree.gov, 1-800-QUIT-NOW

# CORONARY ARTERY DISEASE

## Background

- **Definitions:** Coronary artery disease (CAD) refers to atherosclerotic deposition in the coronary vasculature and its complications
- **Varying presentations:** May manifest as angina, acute coronary syndromes, sudden cardiac death, or heart failure
  **Silent MI/ischemia:** Asx disruption in coronary circulation detectable by ambulatory ECG or stress testing (ECG, TTE, or nuclear imaging); new Q-wave on ECG (*Ann Intern Med* 2001;135:801); risk of silent ischemia ↑ in DM & hypothyroid pts
  **Ischemic cardiomyopathy (CMP):** EF ≤40% due to CAD
  **Cardiac syndrome X/Microvascular angina:** Angina + ST depression on ETT w/ nl angio (*NEJM* 2007;356:830); due to microvascular CAD or hypersensitivity to cardiac pain (*Circulation* 2004;109:568); treated w/ βB, CCB, nitrates, reassurance
  **Variant/Prinzmetal angina:** Angina + ST elevations 2/2 to coronary vasospasm w/o significant coronary artery stenosis; typically, attacks occur at rest in younger pts
- **Pathophysiology:** Endothelial + intimal dysfunction, cholesterol deposition, Mφ foam cell accumulation → fatty streak; + inflammation → atheroma → fibrous cap formation & remodeling → calcification & plaque formation → stenosis (angina) or plaque rupture + thrombosis (MI ± HF or SCD) (*Nature* 2011;473:317; *NEJM* 2013;368:2004)
- **Epidemiology:** 1 in 2 ♂ & 1 in 3 ♀ will develop CAD (*Lancet* 1999;353:89); CAD is the leading cause of death in US, responsible for 1 in 6 deaths (*Circulation* 2010;121:948)
- **Women and CAD:** Less likely than ♂ to have typical angina, & typically present at a later age than ♂ (*Am Heart J* 2006;151:813; *Eur Heart J* 2008;29:707)
- **Risk factors: ≠ risk:** Smoking (2.9 OR), HLD, HTN (1.9 OR), DM (2.4 OR), obesity (1.1 OR), ↑ age, rheumatoid arthritis (RA) (3.1 ↑ RR), SLE, FHx of CAD, ♂ gender, HIV, XRT exposure, metabolic syndrome; **Ø risk:** Daily fruits & vegetables (0.7 OR), regular EtOH consumption (0.91 OR), ASA, regular exercise (0.86 OR) (*Circulation* 2003;107:103;

*Lancet* 2004;364:937; *NEJM* 2012;366:321)

**Genetics:** Inheritance of CAD is complex & assoc w/ multiple genetic loci (*Nat Genet* 2012;45:25)

**CAD risk equivalents:** Carotid artery disease, PAD, AAA, DM, CKD

**Definition of ⊕ FHx:** MI or CAD death in 1° relative <50 y for ♂, <60 y for ♀

**CKD:** ↓ GFR & ↑ proteinuria assoc w/ ↑ risk of CV events (*Circulation* 2003;108:2154; *Lancet* 2010;375:2073)

**Estrogen supplementation in ♀:** USPSTF recommends against use of HRT to prevent CAD in postmenopausal ♀ or s/p hysterectomy (AFP 2005;72:311)

## Evaluation

- **History:** Assess for presence/quality of chest discomfort (see *"Chest Pain"*), presence of risk factors (above), activity level, DOE, diet, exercise, tob/EtOH use, FHx, depression & ED (often comorbid w/ CAD) (*Circulation* 2008;118:1768)
- **Risk estimation: Framingham risk model** most commonly used in US; version for non-DM pts at http://hp2010.nhlbihin.net/atpIII/calculator.asp (*Circulation* 2008;117:743)
- **Workup:** Waist circumference, BMI, lipids, & DM2 screening (see *"Screening"*); Framingham risk should be calculated at least q5y; ambulatory ECG monitoring useful in dx of silent ischemia, variant angina; may consider use of CRP & LpA for further risk stratification (*Circulation* 2003;107:363;499; *Arch Intern Med* 1997;157:1170)

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## PREVENTION

| | Primary (1°) Prevention | Secondary (2°) Prevention |
|---|---|---|
| **Goal** | **Prevent Disease** | **Prevent Harm From Disease** |
| Exercise, healthy diet | X | X |
| Quit tob, mod EtOH | X | X |
| BMI 18.5–24.9, waist <40″ ♂, 35″ ♀ | X | X |
| Lipids at goal | X | X |
| DM well controlled | X | X |
| BP at goal (<140/90) | X | X |
| ASA | See below | X (unless contraindicated) |
| ACEI/ARBs | | DM2, HTN, MI, EF <40%, CKD |
| βB | | Hx MI or CHF |

(*AFP* 2010;82:289; 2011;83:819; *Circulation* 2002;106:388; *JACC* 2006;47:2130)

- **Diet:** Rich in fruits, vegetables, fiber; low in red meat, trans fatty acid, saturated fats, high-fructose corn syrup; stepwise implementation of 1–2 dietary improvements q3–6mos may ↑ compliance (*AFP* 2009;79:571)
  **Mediterranean diet:** ↓ CV events by ~30% in pts at high CV risk (*NEJM* 2013;368:1279); rich in vegetables, locally sourced, minimal consumption of processed foods, low in red meat, <4 eggs/wk, moderate intake dairy products, olive oil as main source of fat, moderate red wine, fresh fruit for dessert (*AFP* 2009;79:571)
  **Vitamin supplementation:** RCT do not demonstrate benefit of β-carotene, Vit C, or Vit E (*Arch Intern Med* 1998;158:668; *JAMA* 2005;294:56; 2008;300:2123; *Lancet* 2001;357:89; *NEJM* 1996;334:1145;1150); USPSTF does not recommend vitamin supplementation in prevention (*Ann Intern Med* 2003;139:51)
- **Aspirin:** Established role in 2° prevention (*NEJM* 2005;353:2373; 2013;368:204); role in 1° prevention depends on pt risk for CV events (*JAMA* 2012;307:2318); *Dose recommendations:* 75–325 mg QD (FDA), 75–162 mg QD (ACC, AHA), 75–100 mg QD (ACCP) (*Chest* 2012;141:e637s; *JACC* 2006;47:2130); in pts anticoagulated w/ warfarin, addition of ASA does not significantly ↓ risk of CV death, MI, & stroke (*JACC* 2003;41:62S)
  **1° prevention:** In meta-analysis of pts w/o hx CAD, ASA ↓ risk of nonfatal MI (NNT = 162) w/o mortality benefit & w/ significant ↑ in bleeding (NNH = 73) (*Arch Intern Med* 2012;172:209); benefit of ASA must be weighed against risk of bleeding & incorporate pt preference (*Ann Intern Med* 2009;150:396; 405); risk of bleeding

likely to outweigh benefits in pts w/ Framingham 10 y risk score < 10%; consider in pts w/ DM2 who have a 10 y CVD risk > 5%, & in pts w/ CKD (*Diabetes Care* 2010;33:1395)

**USPSTF recommendations:** In ♂ 45–79 y ASA encouraged when CV benefit (MIs avoided) > risk of GIB; in ♀ 55–79 y ASA encouraged when CV benefit (stroke prevented) > risk of GIB; ASA for MI prevention not recommended in ♂ <45 y & not recommended for stroke prevention in ♀ <55 y (*AFP* 2011;83:1464)

**2° prevention:** In pts w/ hx vascular disease (i.e., MI, stroke, PAD), ASA ↓ risk of MI/stroke/vascular death by ~20% w/o difference btw 75–325 mg QD dose (*BMJ* 2002;324:71)

**Bleeding risk:** While ASA for CV protection assoc w/ ↑ risk of major GI (2.1 RR) & intracranial (1.7 RR) bleeds, absolute risk of bleeding is low (add'l 1.3 bleeds/1000 ASA treated pts compared to placebo) (*Am J Med* 2006;119:624); No difference btw 75–325 mg/d in bleeding risk; in pts w/ hx GIB who must be on ASA, *H. pylori* eradication + a PPI ↓ risk of rebleed (*NEJM* 2002;346:2033); ASA + esomeprazole superior to clopidogrel at ↓ risk of rebleed (*NEJM* 2005;352:238)

**Enteric-coated ASA:** Variable absorption may ↓ effectiveness (*Circulation* 2013;127:377)

- **Patient information:** *AFP* 2010;82:275 (MI risk); *JAMA* 2013;309:1645 (ASA use)

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## TREATMENT

### Medical Management

**All pts:** 1° & 2° prevention (see above); screening for depression
**Cardiac rehab:** Exercise-based tx programs ↓ risk of reinfarction, cardiac, & all cause mortality (*Am Heart J* 2011;162:571); recommended by Medicare for pts w/ stable angina or who are s/p MI or CABG

**After CABG:** (*NEJM* 2003;348:1456)
**ACEI:** Quinapril & ramipril evaluated in pts s/p CABG
**βB:** Atenolol or metoprolol validated

**After STEMI:** (*Circulation* 2013;127:529)
**ACEI:** For pts w/ anterior STEMI, CHF, EF < 40%; consider for all STEMI survivors; use ARB in pts intolerant of ACEI
**Aldosterone antagonist:** For pts already on an ACEI + βB & w/ EF < 40%, sx CHF, or DM
**βB:** Continue for at least 3 y & consider indefinitely (*Circulation* 2011;124:2458)

**After NSTEMI:** (*JACC* 2011;57:e215)
**ACEI:** For pts w/ DM2, CHF, EF < 40%; use ARB in pts intolerant of ACEI
**Aldosterone antagonist:** Same as after STEMI (above)
**βB:** Metoprolol or atenolol; continue for 3 y & consider indefinitely
**CCB:** Useful if βB contraindicated or ischemia/pain persists despite βB and/or nitrates
**NTG:** Pts should be instructed on PRN use & when to seek medical attention

## Antiplatelet Therapy (*Chest* 2012;141:e637S; *Circulation* 2011;124:2574)

**ACS w/o PCI:** ASA (75–100 mg QD) indefinitely + clopidogrel (75 mg QD) for 1 y

**After CABG:** ASA (75–100 mg QD) indefinitely + clopidogrel (75 mg QD) or ASA (325 mg QD) for 9–12 mos depending on surgeon preference

**Balloon angioplasty w/o stenting:** ASA indefinitely (75–100 mg QD) + clopidogrel (75 mg QD) for 1 mo (*Chest* 2012;141:e637S)

**BMS (elective PCI):** ASA (75–100 mg QD) indefinitely + clopidogrel (75 mg QD) for a minimum of 1 mo & preferably for 12 mos*; Ticagrelor or prasurgrel may be substituted for clopidogrel if PCI was assoc w/ ACS

**DES (elective PCI):** ASA indefinitely (75–100 mg QD) + clopidogrel (75 mg QD) for a minimum of 3 mos (-limus stents) to 6 mos (-taxel stents) & preferably for 12 mos; Ticagrelor or prasurgrel may be substituted for clopidogrel if PCI was assoc w/ ACS

***Indefinite clopidogrel:** Consider shared decision-making for indefinite clopidogrel in pts w/o bleeding risk factors w/ complex PCI or who are at risk for catastrophic consequences for stent thrombosis (i.e., left main or proximal LAD stent); cardiology consultation advised

**Warfarin + dual antiplatelet Rx (i.e., ASA + clopidogrel):** If warfarin is needed for AF, mechanical valves, hx DVT, etc., aim for INR on the low side of target range (i.e., 2–2.5 if the goal is 2–3), & use ASA 81 mg QD (*JACC* 2008;51:172); for stented pts, consider discontinuation of clopidogrel after the minimum duration of dual antiplatelet Rx to minimize bleeding risk; use a PPI as below

**Mgmt of bleeding risk for dual antiplatelet Rx:**
*Pts w/ hx GI bleeding:* Use PPI; *Pts at risk for GIB:* Consider PPI in elderly, pts on warfarin, steroids, NSAIDs, or *H. pylori* infection

- **Percutaneous coronary intervention (PCI):** Includes stenting & balloon angioplasty (w/o stenting); Morbidity/mortality 2/2 stent restenosis/thrombosis (*AFP* 2009;80:1245)

**BMS:** ↑ restenosis compared to DES; requires a *minimum* of 2–4 wks of dual antiplatelet Rx compared to 3–6 mos for DES, ∴ BMS preferable in pts at ↑ risk for bleeding, noncompliance, or antiplatelet interruptions for procedures, or who are on warfarin (*NEJM* 2007;356:984)

**DES:** Drug impregnated in stent is slowly released, ↓ neointimal growth & restenosis → less susceptible to restenosis in 1st y compared to BMS, but requires compliance w/ 1 y of dual antiplatelet Rx due to ↑ risk of stent thrombosis 2/2 to delayed endothelialization compared to BMS (*NEJM* 2013;368:254)

- **Platelet receptor blockers:** Clopidogrel & ticlopidine evaluated in stable CAD (i.e., elective PCI); ticlopidine rarely used (↑ risk of TTP & neutropenia) (*JAMA* 1999;281:806)

  **Clopidogrel–PPI interaction:** Observational studies suggested PPIs ↓ the efficacy of clopidogrel (*JAMA* 2009;301:937), however a RCT of clopidogrel + omeprazole showed the combination ↓ the rate of GI events (i.e., bleeds) (2.9% vs. 1.1%) compared to placebo with **no difference in CV events** (COGENT, *NEJM* 2010;363:1909)

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## ANGINA (*NEJM* 2005;352:2524; 2007;357:1762)

- **Pathophysiology:** Myocardial oxygen demand >> supply → chest discomfort
- **Definition:** Chest discomfort reproduced by exertion/stress, relieved by rest/NTG
- **Diagnosis:** Clinical; typical angina + CV risk factors
- **History:** Squeezing, heaviness, pressure, burning, tightness in chest that radiates to shoulder/neck/jaw/arm; ♀ may report breast pain, palpitations, sharp/stabbing pain
- **Workup:** ECG, stress test for risk stratification, assessment of LV function

  **Angiography:** Indicated for sx that interfere w/ pt's life, even w/ optimal medical Rx, abnl stress test, or for dx of recurrent atypical chest discomfort

### Treatment (*Circulation* 2012;126:3097)

- **Medical management:**
  **βB:** First-line Rx, titrate to resting HR of 55–60 bpm as BP allows; metoprolol & atenolol most commonly used; meta-analysis shows βB have similar rates of MI & cardiac death compared to CCB, but fewer s/e & an improvement in the number of weekly anginal episodes (*JAMA* 1999;281:1927); improved survival in CHF (see *"Heart Failure"*) & after MI; survival benefit in pts w/ angina less clear

  **Pathophysiology:** βB compete w/ catecholamines for binding to β receptors; ↓ $O_2$ demand by ↓ HR & ↓ contractility, resulting in ↑ exercise tolerance, ↓ sx

  **Toxicity:** HoTN, bronchoconstriction, fatigue, ED, nightmares, insomnia, worsening depression/PAD/Raynaud's (less so w/ β1-selective agents); taper rather than abrupt d/c due to w/d effects; antacids ↓ bioavailability of atenolol

**CCB:** Vasodilate & reduce contractility (*NEJM* 1982;307:1618); diltiazem, verapamil, & amlodipine typically used; may be used alone if βB contraindicated (e.g., in pts w/ resting bradycardia) or in combination w/ βB if sx poorly controlled by βB alone (combination of amlodipine & βB preferred due to ↓ s/e)

**Toxicity:** Edema; verapamil & diltiazem may worsen CHF & should be used cautiously in pts w/ sinus or AV node dysfunction; verapamil s/e incl constipation

**Nitrates:** Long-acting used as 2°-line Rx in combo w/ βB if sx poorly controlled on βB alone; may be used as monotherapy if βB contraindicated; ↑ arterial & venous dilatation, ↓ preload, ↓ myocardial $O_2$ demand (*NEJM* 1998;338:520)

**Rapid-acting (SL tablet or spray):** Rx acute anginal sx & in Ppx (i.e., before activities that trigger attacks); pts should be instructed on when to seek medical attention (i.e., call 911 if pain does not improve after 1 SL NTG)

**Long-acting:** 12–14 h nitrate-free interval (usually at night when there is less activity) & eccentric dosing (e.g., q8AM, q1PM, q6PM for isosorbide dinitrate, or q8am, q4pm for isosorbide mononitrate) may ↓ tolerance; isosorbide dinitrate lasts 3–6 h; isosorbide mononitrate available in BID or extended release (QD) dosing;

NTG patches may ↓ tolerance if used 12 h on, 12 h off

**Toxicity:** Flushing, HoTN, HA, syncope, nausea; tolerance; contraindicated in pts on sildenafil or w/ HOCM

**Ranolazine:** ↓ angina in pts w/ continued sx on βB, CCB, or nitrates; works by ↓ Ca overload in ischemic myocytes; ↑ QTc (*Circulation* 2006;113:2462)

**ASA:** 75–150 mg QD or 325 mg QOD ↓ CV morbidity & mortality by 20–25% (*NEJM* 2005;352:2524); clopidogrel may be substituted in pts intolerant of ASA

**ACEI:** Pts w/ angina & CHF, DM2, CKD, HTN; meta-analysis of ACEI or ARB in pts w/ stable angina & a nl EF shows ↓ risk of overall mortality, nonfatal MI, stroke, & revascularization compared to standard medical Rx (*AFP* 2012;86:21)

**Statin:** See *"Dyslipidemia"*

**Risk factor modification & exercise:** See secondary prevention above

## Revascularization (*Circulation* 2011;124:2610; e574)

| |
|---|
| **Indications:** (1) Sx limit activities despite optimal medical Rx; (2) Pts do not tolerate medical Rx; (3) Revascularization may ↑ survival (i.e., >50% left main disease, large area of myocardium at risk for ischemia) |
| **PCI:** Preferred for 1 or 2 vessel disease w/o left anterior involvement, or in pts who are not surgical candidates; consider for *highly select* & stable pts w/ left main disease |
| **CABG:** >50% stenosis in LM (survival benefit seen), diffuse 3 vessel disease (>70% stenosis) w/ large area of myocardium at risk or EF < 40%, proximal LAD + another major coronary artery, or pts who are not PCI candidates |

- **Ischemic cardiomyopathy:** See *"Heart Failure"* for more details; pts should avoid diltiazem, verapamil, & NSAIDs other than ASA; pts w/ hibernating myocardium or ongoing angina despite optimal medical Rx may benefit from revascularization
- **Cardiac rehabilitation:** Provides comprehensive eval of risk factors, psychosocial factors, & 2º prevention (*AFP* 2009;80:955); state index of cardiac rehab programs: www.aacvpr.org/Resources/SearchableCertifiedProgramDirectory/tab
- **Sexual activity:** Requires 4–5 METs (walking ~4 mph on flat ground); Sex ↑ HR & ↑ BP, causing pts to worry about triggering MI (*Am J Cardiol* 2000;86:27F; 51F); exercise training & medical Rx (ASA & βB) help mitigate risk; pts should wait 3–4 wks after MI & have a ⊖ ETT

before resuming sexual activity (*Am J Cardiol* 2005;96:313)

**Treatment of impotence:** Reassurance in low-risk pts; PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) *contraindicated* in pts on nitrates & αB & should be used cautiously in pts w/ active ischemia, HF, low baseline BP, or on multiple BP meds (*JACC* 1999;33:273); yohimbine may cause ↑ HR & ↑ BP (see *"Male Sexual Dysfunction"*)

- **Patient information:** *JAMA* 2012;308:1824

**Second Princeton Panel Recommendations for Risk Assessment for Sex**

| |
|---|
| **Low risk:** Sex is safe & impotence may be treated if pt is: Asx w/ < 3 CV risk factors (excluding gender), controlled HTN, mild, stable angina, has undergone successful revascularization, >6–8 wks s/p uncomplicated MI w/ ⊖ ETT, has mild valvular disease, or asx LV dysfunction |
| **Intermed risk:** Cards consult and/or ETT advised if pt has: ≥3 CV risk factors (excluding gender, including sedentary lifestyle), mod, stable angina, recent MI (<6 wks) w/o revascularization or ⊖ ETT, EF < 40%, NYHA II HF, PAD, or hx stroke/TIA |
| **High risk:** Cards consult for mgmt: UA, poorly controlled HTN, NYHA III/IV HF, MI <2 wks, HOCM, mod–severe AS, high-risk arrhythmias |

# AORTIC DISEASE

## Background (*Lancet* 2005;365:1577; *Circ* 2006;113:e463; *Circ* 2005;111:816; *AFP* 2006;73:1198)

- **Definition:** Abdominal aorta >30 mm *or* any section w/ >1.5× nl diameter
- **Location:** Abdominal (AAA), thoracic (TAA), thoracoabdominal aorta or aortic root
- **Prevalence:** AAA: 1.3–8.9% prevalence in men & 1–2.2% in women, ↑ w/ age; 15,000 deaths/y from AAA-related problems in US (13th leading cause of death)
- **Risk factors:** Age, ♂, smoking, HTN, HLD bicuspid AV, CAD or PAD, FHx

## Types (*Lancet* 2005;365:1577; *Circ* 2006;113:e463; *Circ* 2008;117:242; *JAMA* 2007;297:395)

- **Atherosclerotic:** Most common, assoc w/ typical atherosclerotic risk factors (smoking, age >65, HTN, as well as HLD, CAD/PVD, & FHx);

also assoc w/ COPD & PCKD

- **Congenital:** Marfan, Ehlers–Danlos, association of TAA w/ bicuspid AoV
- **Infectious:** Bacterial inflammation of aortic wall caused mainly by staph & salmonella
- **Inflammatory abdominal aortic aneurysm (5–10% cases):** Pts typically p/w back/abdominal pain; CT/MRI notable for periaortic inflammation & fibrosis; ESR/CRP ↑ (*JAMA* 2007;297:395)
- **Dissection:** Surgical emergency; risk factors: HTN, bicuspid AoV or AVR, coarctation, connective tissue d/o (e.g., Marfan), cocaine, trauma, recent cath (*JAMA* 2002;287:2262)

## Evaluation and Screening (*Lancet* 2005;365:1577; *Circ* 2005;111:816; *JAMA* 2009;302:2015)

- **History:** Often asx; vague, chronic abdominal/CP radiating to back/flank
- **Exam:** Often unremarkable; sensitivity of palpation for AAA 4–4.9 cm = 50%, >5 cm 76%; Limited by body habitus (*JAMA* 1999;281:77)
- **Red flags:** Suspect dissection in pts w/ risk factors (above) & abrupt onset of severe, "tearing or ripping pain," mediastinal or aortic widening on CXR, or >20 mmHg BP difference between arms; **If suspected Æ ED** (*Arch Int Med* 2000;160:2977)
- **Thoracic aortic aneurysm:** No routine screening recommendations; pts w/ known TAA should be imaged at 6 mos & then annually if stable; also screen for coexisting AAA
- **Abdominal aortic aneurysm:** U/S × 1 men 65–75 who smoked >100 lifetime cigarettes (may be covered by Welcome to Medicare Physical Exam), & men >55 or women >65 w/ an affected 1st-degree relative; consider screening women >65 who smoked >100 lifetime cigarettes based on clinical hx
- **Rupture risk:** ↑ w/ larger diameter, ↑ rate of expansion, HTN, smoking; some studies suggest for small AAA (<5.5 cm), longer surveillance intervals may be used (*JAMA* 2013;309:806)

**Abdominal Aortic Aneurysm Screening** (*Circ* 2004;110:16; *NEJM* 2003;348:1895)

| AAA Diameter | Screening Interval |
|---|---|
| >4.5 cm | q3–6mos |
| 4–4.5 cm | q6–12mos |
| <4 cm | q1–2y |
| **AAA Diameter** | **Annual Rupture Risk** |
| 4–4.9 cm | 0.5–5% |
| 5–5.9 cm | 3–15% |
| 6–6.9 cm | 10–20% |
| 7–7.9 cm | 20–40% |
| ≥8 cm | 30–50% |

## Diagnosis (*Circ* 2005;111:816; *Circ* 2006;113:e463)

- **Abdominal aortic aneurysm:** U/S preferred for screening & surveillance; CT or MRA useful for inflammatory AAA & for peri-operative eval to define anatomy
- **Thoracic aortic aneurysm:** CT/MR angiography or TTE/TEE preferred tests (CT, MRI, & TEE have similar sens/spec) (*Arch Intern Med* 2006;166:1350); MRI preferred if aortic root involvement

## Treatment (*Circ* 2006;113:e463; 2008;117:1883; 2010;121:1544; *JAMA* 2009;302:2015)

- **Medical: Smoking cessation,** mgmt of HTN, HLD; limited evidence for βBs, ACEI, abx (*PLoS ONE* 2008;3:e1895); statins may have mortality benefit (*Am J Cardiol* 2006;97:279); benefits of ASA in pts w/ aortic aneurysm likely to outweigh risk given ↑ prevalence of CAD in this population
- **Surgical (Abdominal aortic aneurysm):** Repair if diameter >5.5 cm, expansion >5 mm in 6 mos, complications (e.g., hematoma, ulcer, infection), genetic syndrome, pregnancy or if pt is symptomatic; RCTs show repairing AAA <5.5 cm does not improve long-term survival compared to surveillance (*NEJM* 2002;346:1437; *Lancet* 1998;352:1649)

  **TAA:** Repair if >5.5 cm unless bicuspid AoV or congenital abnorm

  **Contraindications:** Severe angina, CHF, CKD, COPD, limited life expectancy/quality

  **Endovascular repair:** Available for descending TAA & AAA; may be considered for pts ineligible for open repair; typically requires healthy aorta below renal arteries & adequate iliac arteries; similar all-cause mortality (*JAMA* 2009;302:1535; *NEJM* 2010;362:1863)

- **Patient handouts:** *AFP* 2006;73:1205 & *JAMA* 2009;302:2050

# ATRIAL FIBRILLATION AND FLUTTER

## Background (*Ann Intern Med* 2008;149:ITC5–2; *JAMA* 2001;285:2370; *Mayo Clin Proc* 2013;88:394)

- **Paroxysmal:** <1 wk, self-terminates; **Persistent:** >1 wk, can be terminated w/ cardioversion; **Permanent:** Lasts >1 y, cardioversion failed or not attempted
- **Valvular:** 2/2 to valve d/o (MR, MS, MVP, valve replacement/repair) vs. **nonvalvular**
- **Lone:** Age <60, structurally nl heart, no clinical cardiac disease (incl HTN)
- **Secondary causes:** Pericarditis, myocarditis, thyrotoxicosis, COPD, obesity, OSA, pheo, cardiac surgery, MI, PE, CHF, PNA, EtOH ("holiday heart"), caffeine
- **Prevalence:** ↑ w/ age, underlying heart disease, men, Caucasians; 0.1% of adults age <55, 9% of adults >80; overall US prevalence ~1% adults
- **Pathophysiology:** Atrial fibrosis & loss of atrial muscle mass → nonhomogeneous wave propagation → creates multiple wavelets & focal automaticity (often originating in the pulmonary veins) → anatomical & electrical remodeling
- **Risk factors:** ↑ *Atrial pressure:* valvular disease, CHF, MI, cor pulmonale, PFO, COPD, CMP, HTN w/ LVH; ↑ atrial size (obesity, AFL), SVT, atrial ischemia (CAD), atrial fibrosis/infiltrate (age, amyloid, atrial neoplasm), neurologic processes (SAH, stroke)

## Evaluation (*Circ* 2006;114:e257; *NEJM* 2004;351:2408)

- **Symptoms:** Asx (esp if elderly, recurrent AF), SOB, DOE, fatigue, ↑ urination, lightheadedness (syncope rare), angina, palpitations, stroke, CHF; Sx more prominent w/ paroxysmal, less evident w/ persistent & permanent
- **Exam:** Irregularly irregular pulse, tachycardia, irregular heart sounds, ± HoTN

- **Workup:** H&P (focused on classification criteria above, & signs of reversible causes), ECG (?LVH, prior MI, BBB, WPW → changes mgmt options), CXR (?cardiomegaly, pulm pathology), TTE (for new-onset AF); TSH & free T4 (?hyperthyroidism), electrolytes, renal & LFT function (to eval risk of toxicity w/ specific therapies); FOBT (prior to starting anticoag); eval for MI *not necessary* unless ischemic sx; ✓ HR at rest & w/ exertion (i.e., walking) in pts w/ sx related to exertion; 12-lead ECG, 24–48 h Holter, loop recorder (if sx)
  **ECG Ddx:** AT, sinus tach w/ premature atrial beats, MAT, AFL, SR w/ frequent PACs; AF should have *no discernible P-waves*, no pattern in ventricular response
- **Additional testing to consider:** Holter or 6 min walk test (eval rate control), TEE (if cardioversion planned), EP study (if AF due to SVT, WPW, ablation planned)
- **Indications for hospitalization:** Hemodynamic instability, elderly, assoc medical problem (i.e., 2° cause of AF), DCCV, initiation of antiarrhythmic Rx or heparin
- **Indications for cardiology referral:** Failure of rate control, complex cardiac disease, candidate for PPM, defibrillator, ablation or surgery (*AFP* 2011;83:61)

## Rate Control (*Circ* 2010;123:104; *NEJM* 2002;347:1825; 2002;347:1834; 2008;358:2667)

- **Preferred initial approach** in most pts, including those w/ CHF; no significant difference in survival or stroke w/ rate vs. rhythm control; aim is to reduce sx & hemodynamic instability, or tachycardia-mediated CMP
- **Therapeutic goal:** Lenient rate control (rest HR <110) as effective as strict rate control (rest HR <80, mod exercise HR <110) in pts w/ persistent AF, well-controlled sx & an LVEF >40% (*NEJM* 2010;362:1363)

### Pharmacologic Therapy (*Annals* 2008;149:ITC5–2; *Circ* 2006;114:e257)

| | Agent | Maintenance (PO) | Comments |
|---|---|---|---|
| βB | Metoprolol | 25–100 mg BID/TID | Preferred in CAD, CHF; caution w/ COPD, asthma; contraindicated in WPW; use cautiously in *decompensated* CHF |
| | Atenolol | 25–100 mg QD | |
| | Propranolol | 80–320 mg/d (total) | |
| CCB | Diltiazem | 120–360 mg QD divided doses | Preferred in COPD; caution in CHF w/ ↓ EF due to ⊖ inotropy; ↓ HR & BP through myocardial suppression; ↑ digoxin levels; contraindicated in WPW |
| | Verapamil | 120–360 mg QD divided doses | |
| Other | Digoxin | 0.125–0.5 mg QD | Useful in CHF/sedentary pts; controls only resting HR (no effect on adrenergic tone); adjust for CrCl; avoid in paroxysmal AF, WPW; may cause heart block, ↓ HR; levels correlate poorly w/ rate; >2 ng/mL toxic; caution in elderly |

- Beta-blockers are most effective agent for rate control; if single agent ineffective, consider switching to a different class or using a combination (*JACC* 2004;43:1201); Digoxin may be used as 2nd agent b/c of additive effect to βB or CCB on HR

## Rhythm Control (*Circ* 2010;123:104)

- Rhythm control typically managed by cardiology or provider w/experience prescribing Rx's below
- **Therapeutic goal:** Pursue rhythm control if AF sx, rate control has failed, or if there is reasonable chance for prolonged SR (structurally nl heart); rhythm control assoc w/ ↑ adverse drug effects & ↑ hospitalizations compared to rate control; hospitalization may be required for telemetry during initiation of some agents; TTE or stress test may be needed to select agent; refer to cardiology/EP for rhythm control

**Common Medications Used to Maintain sinus rhythm (cards consult advised)**

| Drug (Class) | Dose (PO) | Adverse Effects & Comments |
|---|---|---|
| Amiodarone (III) (*NEJM* 2005;352:1861; 2007;356:935; *Arch Intern Med* 2000;160:1741; *JAMA* 2008;300:1784) | 200–400 mg QD (Load: 600—800 mg in divided doses QD up to 10 g total) | Most effective at maintaining SR & least proarrhythmic but most long-term s/e: Pulm/thyroid/hepatotoxicity, neuropathy, skin photosensitivity, ↓ HR, optic neuritis, *torsades*, ↑ QTc; episodic Rx after cardioversion ↑ mortality & AF recurrence; ✓ TFTs, LFTs q6mos, baseline PFTs, CXR, & ECG q12mos; ↓ warfarin/digoxin metabolism, follow INR/digoxin level closely; preferred for CHF, CAD, HTN w/ LVH; outpt initiation in select pts; anticoagulate prior to Rx due to stroke risk w/ conversion to sinus rhythm |
| Dofetilide (III) | 0.5 mg BID | *Torsades*, ↑ QTc; dose adjustment in renal insufficiency; monitor K; preferred for CHF, CAD; initiation requires hospitalization for 72 h |
| Dronedarone (III) (*NEJM* 2007;357:987; 2008;358:2678; 2009;360:668; 2011;365:2268; *J Cardiovasc Electrophys* 2010;21:597) | 400 mg BID | ↓ HR & SBP, ↑ QTc, rare hepatotoxicity; ↑ mortality in sx or sev HF (EF <35%); ↑ stroke, MI, systemic embolism, or CV mortality in pts w/ permanent AF & hx CAD, stroke/TIA, sx CHF, PAD, EF <40%, or ≥75 y w/ HTN & DM; better tolerated than amiodarone but ↓ effective; ✓ LFTs 1st 6 mos; may be initiated outpt; ↑ digoxin levels; no warfarin interaction |
| Flecainide (IC) | 200–300 mg | VT, CHF, AFL; avoid in pts w/ CAD or structural heart disease; pretreat w/ βB or CCB to prevent AFL |
| Sotalol (III) | 80–160 mg BID | *Torsades*, CHF, ↑ QTc, bradycardia, COPD exacerbation; adjust dose in renal insufficiency; ✓ K, QTc; used in CAD; initiation requires hospitalization |

- **Counseling:** Recurrence not indicative of failure; episodes may be fewer/shorter; rhythm control assoc w/ arrhythmia → warn pts about significance of syncope/palpitations
- **Nonpharmacologic treatment:**
  **Radiofrequency ablation:** Alt in *sx* pts who have failed antiarrhythmic tx: 70% free of AF at 9 mos (*JAMA* 2010;203:333); may be considered as initial tx for sx pts; noninferior in pts <70 yo w/o other significant heart disease (*NEJM* 2012;367:1587)
  **Surgical MAZE:** If undergoing cardiac surgery, 70–95% success rate
  **Other (rare):** Atrial pacing & implantable atrial defibrillators

## Cardioversion (*Ann Intern Med* 2003;139:1018; *NEJM* 2001;344:1411)

- **When:** 1st episode or sx AF (causing CHF exacerbation, angina, HoTN); address reversible causes of AF prior to cardioversion; pts w/ new onset AF do not need maintenance antiarrhythmic therapy after

cardioversion (*Ann Intern Med* 2003;139:1009)

- **How:** Pharmacologic is less likely to be successful than DCCV
  **"Pill in Pocket":** Flecainide or propafenone safe as outpt if previously proven safe in hospital, pt w/o CAD, structural or conduction system disease, prolonged QT (*NEJM* 2004;351:2384); consider βB or CCB to prevent rapid AV conduction w/ AFL
- **Anticoagulation:** Risk of embolization identical for spontaneous, pharmacologic, or electrical cardioversion; if AF >48 h **or** duration **or** <48 h w/ MS **or** hx thromboembolism → 3–5% risk of stroke; ∴, anticoagulate all pts for DCCV
  **Anticoagulate:** >3 wks prior to cardioversion & ≥4 wks postcardioversion (due to atrial stunning); warfarin: INR target 2.5 (range 2–3); dabigatran 110 or 150 mg BID equiv to warfarin in preventing stroke in nonvalvular AF (*Circ* 2011;123:131)
  **TEE:** Consider if pt hospitalized, at risk for bleeding from prolonged anticoagulation, or unlikely to tolerate prolonged AF; if ⊖ for thrombus, DCCV may be performed w/ heparin → warfarin bridge or dabigatran (4 wk Rx)
- **Factors affecting success:** Time in AF (better if AF <1 wk), LA size, age, pretreatment w/ antiarrhythmic (class IC or III) esp if prior DCCV failed

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## ANTICOAGULATION (*Circ* 2006;114:e257; 2011;123:104; *Chest* 2008;133:546S)

- **Risk stratification:** $CHADS_2$ most validated & clinically useful score for long-term anticoagulation in paroxysmal, chronic AF, & s/p cardioversion (*JACC* 2008;51:810)
  **Other risk factors** (less validated): Age 65–74, ♀ sex, CAD
  **Risk-benefit analysis:** Benefits of anticoagulation weighed vs. pt hx (i.e., GIB, ICH, ↓ PLT, noncompliance, SUD/EtOH abuse, Ψ hx, heavy NSAID use, liver disease, pregnancy); prognostic scores for bleeding risk available (*Am J Med* 2013;126:105); generally, anticoagulation ↑ risk of ICH by ~2× to 0.3–0.8%/y compared to pts who are not anticoagulated (*Am J Med* 2013;126:105); benefit of anticoagulation >> risk of bleeding at other, extracranial sites or from falls

**$CHADS_2$ Scoring for Stroke Risk** (*JAMA* 2001;285:2864; *JACC* 2011;57:1330)

| |
|---|
| **$CHADS_2$:** **C**HF (1 point), **H**TN (1), **A**ge >75 (1), **D**M (1), hx **S**troke/TIA (2) |
| **$CHADS_2$** score **0** → Consider ASA (81–325 mg); **1** → ASA, warfarin, or dabigatran based on pt preference & shared decision-making; **≥2** → warfarin or dabigatran<br>*Pts w/ low initial $CHADS_2$ scores should be continually reassessed for anticoagulation* |
| **INR Goals** (Blood 2012;119:3016) |
| **Nonvalvular AF:** 2–3; **Valvular AF: Native valve**, goal INR 2–3; **prosthetic valve**, goal INR 2.5–3.5; newer anticoagulants not eval for valvular AF |

- **Nonvalvular atrial fibrillation:** Unless a reversible cause for AF is corrected, AF → long-term anticoagulation (even if in SR) regardless of AF classification (paroxysmal vs. persistent) or tx (rate vs. rhythm); avg stroke risk w/o anticoagulation ≈ 5%/y vs. 1.4% w/ warfarin; AF → 15% of strokes in US (*JAMA* 2002;288:2441; 2003;290:2182; 2003;290:2685)
  - **Warfarin:** Only 60% of pts at goal INR in "usual" clinical practice (*NEJM* 2011;365:952); Warfarin ↓ stroke risk by 68% vs. 21% for ASA but ↑ bleeding; most pts do not need LMWH bridge while awaiting therapeutic INR; consider LMWH bridge in pts at ↓ risk of bleeding, & hx TIA/stroke or intracardiac thrombus; warfarin is anticoagulant of choice for pts w/ CrCl ≤30 mL/min (*Blood* 2012;119:3016)
  - **Use w/ anti-PLT agents:** For pts on warfarin (e.g., AF w/ stent) ASA 81 mg QD and/or clopidogrel 75 mg QD may be used; aim for INR 2–2.5 due to ↑ bleeding
  - **Comparison w/ newer agents:** Rivaroxaban/dabigatran: fixed dose, rapid onset, ↓ drug & no food interactions, no monitoring, subtherapeutic anticoagulation with a single missed dose, & no antidote (*Am J Med* 2013;126:105)
  - **Rivaroxaban:** Oral factor Xa inhibitor, once-daily dosing (20 mg PO QD); noninferior to warfarin for preventing stroke or systemic embolism; ↓ risk of intracranial or fatal bleeding compared to warfarin (ROCKET AF, *NEJM* 2011;365:883); 15 mg PO QD used if CrCl 30–49 mL/min, contraindicated for CrCl <15 mL/min; may be reversed w/ prothrombin complex concentrate (*Circulation* 2011;124:1573), interacts w/ CYP3A4 inhibitors (ketoconazole, clarithromycin) & P-glycoprotein inducers (rifampin, carbamazepine, phenytoin) (*AFP* 2012;85:577); contraindicated in

pregnancy

**Dabigatran:** Direct thrombin inhibitor for anticoagulation in AF (150 mg BID), no INR monitoring, ↓ embolic stroke & ICH vs. warfarin w/ similar bleeding risk (*NEJM* 2009;361:1139); adjust for CrCl; not recommended for CrCl <15 mL/min; No antidote

**ASA w/ clopidogrel:** Inferior to warfarin for stroke prevention (*Lancet* 2006;367:1903); superior to ASA alone but w/ higher bleeding risk (*NEJM* 2009;360:2066); acceptable if pt/provider preference against warfarin or if pt unsuitable for warfarin

**Periprocedural:** Pts at low risk for thromboembolism (i.e., no mechanical valves, hx thromboembolism, low EF, or MS) do not need a heparin bridge during periprocedural discontinuation of anticoagulation if interruption is <7 d see *"Perioperative Evaluation"*

**Apixaban:** Oral factor Xa inhibitor, BID dosing, FDA approval pending; superior to warfarin in preventing embolic/hemorrhagic stroke or systemic embolism, w/ ↓ major bleeding (ARISTOTLE, *NEJM* 2011;365:981); no antidote

- **Nonpharmacologic therapy:** Percutaneous LAA occlusion device (noninferior to warfarin (*Lancet* 2009;374:534)), but not yet FDA approved; surgical LAA amputation
- **Patient handout:** *AFP* 2011;83:71; *JAMA* 2010;303:380

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## Atrial Flutter

### Background

- **Definition:** Reentrant atrial rhythm (typical cycle at rate of 300/minute), often → AF, presentation and RF similar to AF
- **History:** Similar to AF
- **Risk factors:** CHF, COPD, obesity, thyroid d/o, MVP, rheumatic heart disease
- **Evaluation:** ECG (typically 2:1 conduction, absent p-waves, saw-toothed flutter waves, atrial rate ~300 bpm), TTE; ✓ CBC, Chem-12, TSH; CXR or ETT if indicated

### Treatment

- **Cardioversion:** Spontaneous, electrical, pharmacologic, radiofrequency ablation, or pacemaker based; useful if pt sx or if rate poorly controlled/tolerated
- **Rhythm control:** Many of the same drugs used to maintain SR in AF used in AFL
- **Rate control:** CCB (Verapamil or diltiazem)—use w/ caution in pts w/ SSS, AV block, & CHF; βB & digoxin also useful
- **Anticoagulation:** Managed in same way as pts w/ AF, including peri-cardioversion

# CAROTID DISEASE

## Background (*JAMA* 2008;300:81; *NEJM* 2000;342:1693; *Neurology* 2003;60:1429)

- **Epidemiology:** ~700,000 stroke/y in US (85% ischemic); Internal carotid artery (ICA) disease prevalence = 0.5% by age 50, 10% by age 80 (*Stroke* 2010;41:1294); 15% strokes are caused by ICA disease; ~36% of pts who p/w TIA are found to have ICA disease
- **Pathophysiology:** Plaques form in common carotid bulb, extend to ICA → ulceration & rupture → embolization → TIA or stroke
- **Risk factors:** Smoking (RR = 2), African ancestry, HTN, DM, metabolic synd, ♂, HLD
- **Asymptomatic:** Defined as no prior hx TIA or stroke; asx pts w/ a stenosis ≤60% → 1.6%/y risk of stroke; ≥ 60% stenosis → 3.2%/y risk of stroke
- **Symptomatic:** Defined by hx TIA (transient focal neuro deficit or amaurosis fugax) or nondisabling stroke (in a vascular territory supplied by a stenosis) w/in the last 6 mos; carries ↑ risk of future vascular events so managed more aggressively

## Evaluation (*Lancet* 2006;367:1503)

- **Screening:** Routine screening of asx pts *not* recommended (USPSTF) (*Ann Intern Med* 2007;147:854); new stroke, TIA, or carotid bruit should prompt testing
- **History and exam:** Most asx cases detected due to a harsh, blowing carotid bruit on exam; assess for TIA/stroke sx (see *"Stroke"*) incl

homonymous hemianopsia, sensory loss, or motor deficits (*NEJM* 2005;352:2618); in comparison, vertebrobasilar insufficiency → cranial nerve loss, diplopia, vertigo, or dysarthria (*NEJM* 2005;352:2618)

- **Diagnosis: Duplex U/S:** Most widely used & studied; evaluates artery based on peak-flow velocity (85–92% sensitive, 77–89% specific, operator dependent, should be performed in an accredited lab) (*J Vasc Surg* 1993;17:152); **MRA:** 88–97% sensitive, 89–96% specific (*Stroke* 2008;39:2237); **CTA:** 68–84% sensitive, 91–97% specific (*Stroke* 2004;35:2306); MRA tends to overestimate & CTA tends to underestimate degree of stenosis (*J Neurol Neurosurg Psychiatry* 2002;73:21)

## Management (*Circulation*, 2011;124:e54; *NEJM* 2008;358:1617)

- **Medical management:** Manage HLD (see *"Dyslipidemia"*), HTN (see *"Hypertension"*), DM (see *"Diabetes mellitus"*), smoking (see *"Tobacco use"*); Education about s/sx of TIA, stroke, & amaurosis fugax

**Antiplatelet Agents for Stroke Prevention** (*J Vasc Surg* 2009;50:431)

| Indication | Regimen |
|---|---|
| Asymptomatic | ASA 81 mg QD or clopidogrel 75 mg QD |
| 2° prevention | ASA/dipyridimole 25/200 mg BID or ASA 81–325 mg QD or clopidogrel 75 mg QD |
| S/p carotid artery stenting | ASA 50–325 mg QD & periprocedural clopidogrel (loading dose + 75 mg QD ×4–6 wks) |
| S/p CEA (*Chest* 2008;133:630S) | ASA/Dipyridimole 25/200 mg BID or ASA 81–325 mg QD or clopidogrel 75 mg QD |

- **Revascularization:** Interventional tx w/ carotid endarterectomy (CEA) and/or carotid artery stenting (CAS) is controversial & evolving, thus a vascular medicine and/or surgery consult is reasonable for any ICA stenosis >50%
- **Asymptomatic:** Consider CEA in pts w/ ≥70% stenosis on U/S or ≥ 80% on CTA/MRA if stenosis on U/S 50–69%; CEA pts should have reasonable life expectancy & be a good surgical candidate; CEA should be done by experienced surgeons in ctr w/ <3% morbidity/mortality; NNT to prevent 1 stroke in 3 y = ~33 pts (*Cochrane Database Syst Rev* 2005;CD001923); CAS controversial

(CREST, *NEJM* 2010;363:11)

- **Symptomatic:** In good surgical candidates who have reasonable life expectancy, interventional options include (*Cochrane Database Syst Rev* 2011; *NEJM* 1991;325:445):
  **≥70% stenosis:** CEA ↓ stroke & death; NNT to prevent 1 stroke in 5 y = 6.3
  **50–69% stenosis:** CEA ↓ stroke in ♂, unclear benefit in ♀; NNT to prevent 1 stroke in 5 y = 13
  **30–49% stenosis:** No benefit for CEA
  **<30% stenosis:** CEA harmful
  **Total occlusion:** Intervention is contraindicated (Class III)
  **CEA timing:** Greatest benefit if done ≤2 wks for mild stroke/TIA (*Lancet* 2004;363:915)
  **Risk modeling:** stroke.ox.ac.uk
  **Stenting (CAS):** Useful in sx pts w/ 70–99% stenosis who are high-risk surgical candidates, have restenosis s/p CEA, or stenosis due to XRT; ↑ risk of stroke/death & ↓ risk of MI w/in 30 d of procedure as compared to CEA; long-term outcomes similar; pts ≥70 y have 2× ↑ risk periprocedural stroke or death w/ stenting vs. CEA (*Lancet* 2010;376:1062; *NEJM* 2010;363:11)
- **Patient education:** ncbi.nlm.nih.gov/pubmedhealth/PMH0004669

# CHEST PAIN AND NONINVASIVE TESTING

## Background (*AFP* 2011;83:603; *Circulation* 2003;107:149; *JAMA* 2002;288:2745)

- **Epidemiology:** 6 million pts p/w chest discomfort each year in US; for pts presenting to PCPs, Etiologies are: MSK (36%), GI (19%), CV (16%), nonspecific (16%), Ψ (8%), pulm (5%); dx of CV disease ↑↑ in pts presenting to ED (54%)
- **Pretest probability of coronary artery disease:** Stress testing indicated for pts w/ intermed pretest probability (discussed below)
  **Definite/"classic" angina:** (1) Substernal chest discomfort; (2) Provoked by exertion/emotional stress; (3) Relieved by rest/NTG
  **"Atypical"/probable angina:** Chest discomfort w/ 2 of the 3 features of definite angina
  **Nonischemic chest discomfort:** ≤1 of the 3 features of definite

angina

## Likelihood of Chest Pain being due to Angina?

| Age (y) | Sex | Typical/ Definite | Atypical | Nonanginal | Asymptomatic |
|---|---|---|---|---|---|
| 30–39 | M | Intermed | Intermed | Low | Very low |
| | F | Intermed | Very low | Very low | Very low |
| 40–49 | M | High | Intermed | Intermed | Low |
| | F | Intermed | Low | Very low | Very low |
| 50–59 | M | High | Intermed | Intermed | Low |
| | F | Intermed | Intermed | Low | Very low |
| 60–69 | M | High | Intermed | Intermed | Low |
| | F | High | Intermed | Intermed | Low |
| **Definition of probabilities:** High >90%, intermed 10–90%, low <10%, very low <5%<br>↑ **Pretest probability:** DM2, HLD, smoking, Q-waves, or ST abnormalities | | | | | |

**Ddx of Chest Discomfort** (*see specific chapters for further discussion*)

| | Dx | Clues |
|---|---|---|
| CV | Angina | Typically discomfort/pressure/burning/squeezing brought on by exertion or emotion, ↓ by rest or NTG; may radiate to jaw, neck, shoulder, arm; ± diaphoresis, nausea, paresthesias; Levine sign (fist over chest) |
| | Unstable angina | Angina that is new-onset, worsening, or occurs at rest |
| | Aortic dissection | "Ripping or tearing" pain radiating to back, >20 mmHg difference in BP btw arms, widened mediastinum on CXR; loss of pulses; may be assoc w/ new neuro deficit or syncope |
| | Pulmonary embolus | Dyspnea, tachypnea, tachycardia, hypoxemia, ± sudden pleuritic pain; hx immobility, clotting, malignancy; ECG sinus tach ± SI, QIII, TWI in III, right heart strain |
| | Pericarditis | Pleuritic discomfort worse supine, relieved by sitting forward; friction rub, diffuse ST elevation, PR ↓ |
| | Myocarditis | Recent URI or flu-like illness → CHF; younger pts |
| | Valvular heart disease | Progressive angina/dyspnea, syncope |
| | Pericardial tamponade | ↓ voltage ECG, electrical alternans, ⊕ pulsus |
| Pulm | PNA | Fever, chills, cough, sputum, pleuritic pain, consolidation on chest exam; ⊕ CXR |
| | Pneumothorax | Acute onset pleuritic pain, dyspnea; ↓ breath sounds |
| | Pleurodynia | CP from URI or coughing; precordial catch syndrome is sudden pleuritic pain relieved by deep breathing thought caused by folding of pleura on itself |
| | Pulmonary HTN | Exertional dyspnea, fatigue, peripheral edema |
| GI | GERD | Burning brought on by eating, relieved by antacids; acid taste, dyspepsia, regurgitation |
| | Esophageal spasm | May respond to NTG; provoked by swallowing |
| | Esophageal rupture | Mediastinal air on CXR, hx vomiting/instrumentation |
| | Other | Cholecystitis, pancreatitis, biliary & PUD |
| Other | Muscular pain, costochondritis, disc disease | Pain w/ palpation, hx injury, strain, repetitive use |
| | Rheumatic (fibromyalgia, rheumatoid/OA) | Pain found in other joints/tender points, hx RA, OA, fibromyalgia |
| | Shingles | Dermatomal distribution, rash |
| | Ψ/anxiety | Hx Ψ problems, anxiety, ROS often diffusely positive |
| | Rib fractures, bone mets | Hx malignancy, trauma, coughing |

## Evaluation (*AFP* 2005;72:2012; *JAMA* 2005;294:2623)

- **History: OPQRST—O**ther sx (diaphoresis, nausea, dyspnea), **P**rovocative/**P**alliative factors (exertion, rest, breathing, eating, position), **Q**uality (sharp, dull, throbbing, stabbing, pressure), **R**adiation/**R**isk factors, **S**everity (scale 1–10)/**S**ite of pain, **T**iming: Constant vs. intermittent, onset (abrupt vs. gradual); ask "What were

you doing? Has this happened before?"

**Cardiac risk factors:** Personal or FHx CAD (<55 y ♂ or <65 y ♀ in 1° relative), HTN, smoking, DM, obesity, HLD, exercise capacity (i.e., climbs stairs, runs)

**PE risk factors:** Immobility, hx clotting, long plane/car rides, malignancy

**Other:** Cocaine use, recent URI, hemoptysis, recent procedures/surgery

**Mindfulness:** ↑ Triage errors in women, minorities, elderly, diabetics, pts w/ dyspnea

- **Physical exam:** *VS:* Including $SaO_2$, BP in both arms (>10 mmHg difference → consider aortic dissection); ask pt to point where pain is; *CV* (JVP, heart murmurs, rubs, $S_3$, $S_4$, pulses), *pulm* (rales), *abdominal* (epigastric tenderness to palpation), *chest wall* (tender to palpation/reproducible, zoster), breast exam if sx, *ext* (edema, Homans sign) (pain in calf w/ dorsiflexion of foot)
- **Diagnostics:** CXR (PNA, widened mediastinum), ECG, labs (CBC, electrolytes, D-dimer, troponin/CK per clinical suspicion); CT scan, stress testing (if intermed pretest probability of CAD), TTE as needed
- **Management:** Immediate ED referral of pts w/ life-threatening causes of CP (aortic dissection, PTX, intermed or high pretest probability for ACS or PE)
- **Patient information:** *JAMA* 2009;301:1498

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## NONINVASIVE CARDIAC TESTING

### Indications

- **CAD diagnosis:** Stress testing beneficial in pts w/*intermediate* pretest probability of CAD to avoid false ⊖ in pts w/ ↑ pretest probability & to avoid false ⊕ in pts w/ ↓ pretest probability (*NEJM* 1979;301:230); Exercise ETT does not localize/quantify myocardial viability; pharmacologic/exercise imaging studies needed instead
- **Prognosis:** In pts w/ stable angina after dx or change in sx
- **Postrevascularization:** Can assist in activity counseling as part of cardiac rehab; consider in pts >5 y after CABG

## Screening

- **Asymptomatic patients:** In asx pts w/ low pre-test probability, routine screening *not* recommended unless pt is in a high-risk occupation (e.g., airline pilots); risk eval using Framingham model w/ aggressive risk factor modification more beneficial (*NEJM* 2003;349:465)
- **Diabetics:** No difference in cardiac events over ~5 y in asx DM2 pts who underwent adenosine-stress w/ imaging vs. no screening (DIAD, *JAMA* 2009;301:1547); ADA recs *against* screening asx pts w/ DM2 (*Diabetes Care* 2012;35:S11); AHA/ACC recommends consideration of ETT in pts who plan to initiate vigorous exercise (*JACC* 2002;40:1531) (see *"Sports & Exercise Clearance"*)
- **Prior to initiation of a rigorous exercise program:** Consider ETT in diabetics & in pts w/intermediate or high risk of CAD

## Pre-test Counseling

- **To establish diagnosis of CAD as cause of symptoms:** Hold βB, CCB, dypyridamole, & nitrates for 48 h & caffeine for 12 h prior to ETT/stress TTE (note: If concerns, discuss with cardiology prior to testing); ok to continue ACEI, statin
- **To determine if known CAD is cause of current symptoms, for prognosis, or post-revascularization:** Continue regular medications w/o interruption; βB/CCBs may limit ability to reach max HR

## Choice of Test

- **Screening ECG:** USPSTF & AHA recommended **against** ECG CAD screening in low-risk pts; insufficient evidence re: intermediate/high-risk pts (*Ann Intern Med* 2012;157:512; *Circulation* 2003;107:149)
- **ETT w/ ECG preferred for diagnosis,** but may be limited due to arthritis, claudication, poor functional status, pulmonary disease, or inability to achieve 85% predicted maximal HR
- **Imaging studies:** TTE or radionuclide myocardial perfusion imaging (rMPI) preferred in pts w/prior PCI or CABG
  **Radionuclide choice:** Thallium detects viable myocardium; sestamibi ("mibi") provides better images in ♀ or obese pts due to higher-energy photons, measures LVEF

- **"Stress testing":** Induces situation which (1) ↑ $O_2$ demand or ↑ coronary flow & (2) monitors for sx of ↓ supply; multiple combinations available; see table below
  ↑ **Myocardial $O_2$ demand:** Exercise (preferred, may be limited due to functional status, pulm disease, or inability to achieve 85% predicted max HR), chemical (adenosine, dobutamine)
  **Monitor supply:** ECG (often preferred, may be limited 2/2 abnl baseline ECG such as LBBB); TTE or radionuclide imaging (rMPI) preferred for pts w/prior PCI/CABG
- **Coronary artery calcium scoring:** Screening in low-risk populations not recommended due to ↓ Sp & ↑ false ⊕ rate (*AFP* 2012;86:405; *JACC* 2007;49:378; *NEJM* 2012;366:294); consider ETT in pts w/coronary Ca score >75th percentile

**Testing Modalities**

| Test | Comments (*AFP* 2007;75:2129) |
|---|---|
| **ETT** ~$160 (68% sensitive, 77% specific) (*Ann Intern Med* 1999;130:719) | **Pros:** Standard test for most pts; cost-effective, widely available, gives functional capacity, prognosis, & provides info on pt sx; **Cons:** Requires exercise to 85–90% maximal HR (220—age in y); avoid if ECG shows WPW, V-paced, >1 mm ST ↓ at rest, complete LBBB, LVH, or pt on digoxin; ECG changes in V1–V3 nondiagnostic in pts w/ RBBB; *does not localize/quantify ischemia or myocardial viability;* **Contraindications:** Recent MI (<2 d), unstable angina, sx valvular heart disease, severe CHF/arrhythmias, myocarditis/pericarditis, aortic dissection, PE, systemic infections; Left main disease (relative); **Risks:** 3.6 MI, 4.8 major arrhythmias, & 0.5 deaths/10,000 ETT (*Chest* 1980;77:94) |
| **Stress echo** ~$375 (76–85% sensitive, 77–88% specific) (*JAMA* 1998;280:913) | **Pros:** ↓ Cost compared to nuclear imaging; assesses functional capacity, EF, valve function, chamber size, myocardial viability, location, extent/severity of ischemia, & functional significance of CAD; **Cons:** Subjective interpretation, low-quality images in many pts, poor prognostic ability, avoid in LBBB, V-paced pts; ↓ Se/Sp in LVH; ↑ false ⊕ in pts w/ HTN response to exercise, ↓ Sp w/ prior MI |
| **Dobutamine echo** (80% sensitive, 84% specific) (*JACC* 1997;30:595) | **Pros:** No exercise involved, assesses myocardial viability, EF, chamber size, valve function, ↑ accuracy in pts w/ LBBB, best Se/Sp of pharmacologic tests, may be used for prognosis after MI; **Cons:** Does not measure functional capacity, ↓ Se for ECG Δs vs. ETT, subjective interpretation, risk of ventricular arrhythmia, contraindicated in aortic aneurysm, may cause coronary artery spasm; **Risks:** Rare (<0.2%) life-threatening complications (*Am J Cardiol* 2006;98:541) |
| **Exercise rMPI** (85% sensitive, 64% specific) (*JAMA* 1998;280:913) | **Pros:** Assess LV size, myocardial perfusion, functional significance of CAD, prognosis, & extent, location, & severity of ischemia, functional capacity, info on pt sx; ↑ accuracy w/ resting LV WMA; ↑ prognostic data compared to stress echo; **Cons:** Cost, radiation exposure, variability btw labs, high false ⊕ in pts w/ LBBB, or V-paced |
| **Vasodilator (dipyridamole or adenosine) rMPI** (89% sensitive, 75% specific) (*Circulation* 2003;108:1404) | **Pros:** No exercise involved, ↑ accuracy in pts w/ LBBB; useful for dx & prognosis of CAD in pts unable to exercise; **Cons:** Does not measure functional capacity, ↓ Se for ECG Δs compared to ETT, pts must d/c theophylline 72 h & caffeine 24 h prior; risk of ischemia due to coronary steal w/ dipyridamole; ↓ accuracy w/ RV PPM, CCB, βB, nitrates; may have ↓ Se for 3V disease ("balanced ischemia")<br>**Contraindications:** COPD/asthma, SSS, heart block; Dobutamine rMPI may be used in pts w/ COPD or w/ adenosine/dipyridamole allergy |
| **Coronary CTA** (Se for ≥50% stenosis 85–98%, Sp 88–96% (*Am J Med* 2008;121:715) | **Pros:** May be useful in sx pts of intermediate risk or w/ equivocal stress test results (*Circulation* 2008;118:586); useful to eval for anomalous coronary arteries<br>**Cons:** AHA recommends against CTA screening in asx pts; incidental findings (i.e., pulm nodules) ↑ pt anxiety & further diagnostic testing; radiation exposure; HR must be btw 60–70 bpm or IV βB used; pts w/ renal dysfunction, cardiac stents, severe calcification, & AF may be ineligible; cardiac MRI may be used in pts w/ contrast allergy or coronary artery calcification (*Am Heart J* 2006;151:404) |

## Preferred Testing Modalities by Population

| Patient Characteristic | Test Choice & Comments (*Circulation* 2007;116:e418) |
|---|---|
| Dx of CAD in pt w/ intermed pretest probab (10–90%) w/o factors below | Exercise ECG treadmill test |
| WPW or >1 mm ST ↓ at rest | Exercise perfusion or echocardiogram |
| Hx PCI or CABG | Exercise perfusion or echocardiogram |
| V-paced | Adenosine/dipyridamole rMPI |
| LBBB | Adenosine/dipyridamole rMPI, dobutamine echo |
| Digoxin/LVH w/ <1 mm ST ↓ | Exercise rMPI, echo, or dobutamine echo |
| Unable to exercise | Adenosine/dipyridamole perfusion, dobutamine echo |

- **Management of results:** Cardiology consultation advised for intermed- & high-risk stress test results; low-risk results may be medically managed
- **Patient information:** *Ann Intern Med* 2012;157:1; *JAMA* 2008;300:1836

# HEART FAILURE

## Background (*NEJM* 2003;348:2007; *AFP* 2006;73:841; 2004;69:2609; *JACC* 2009;53:e1; *J Card Failure* 2010;16:475)

- **Definition:** HF is a clinical syndrome of dyspnea, fatigue, & fluid retention; result of the inability of the heart to pump sufficient blood to meet the body's metabolic needs

  **Asymptomatic LV dysfunction:** ↓ EF noted on echo done for other reasons (i.e., post-MI, revascularization); no prior hx clinical HF sx; progresses to sx HF ~10%/y (*NEJM* 1992;327:685)

  **HF w/ reduced LVEF (systolic or congested HF, HF w/ a dilated LV):**

  Sx of HF & abnl EF (i.e., ≤50%) or systolic dysfunction; *Causes:* Ischemia/CAD, valvular disease, HTN, PE, HIV, peripartum CMP, cardiotoxic agents (doxorubicin), EtOH/substance abuse, infiltrative disease, CTD, thyroid disease, myocarditis

  **HF w/ preserved EF (HFpEF, aka diastolic HF):** Nl/near nl EF (≥40–50%) w/ sx of HF (*Ann Intern Med* 2013;158:ITC5–1); 40–60% of pts p/w HF; most are elderly, ♀, & have HTN; ↓ diastolic relaxation, ↓ ventricular filling most commonly due to hypertrophy, ischemic damage, or restrictive/infiltrative CM; asx diastolic dysfunction assoc w/ progression to diastolic HF (*JAMA*

2003;289:194; 2011;306:856); other causes include valvular/pericardial/congenital disease (*NEJM* 2008;359:2456; *Lancet* 2003;362:777); survival similar to slightly better than HF w/ ↓ EF (*NEJM* 2006;355:260; 355:251)

**High-output HF:** ↑ CO & ↓ SVR due to AV fistulas, pregnancy, hyperthyroidism, anemia, $B1_2$ deficiency, liver/renal disease, Paget disease, Beriberi, VSD

- **Epidemiology:** 5.8 million adults in US, ~2.2% prevalence which ↑ w/ age; accounts for 20% of all hospitalizations in pts >65 y (*JAMA* 2003;289:194; *Circ* 2010;121:e46)
- **Risk factors:** DM, EtOH, smoking, obesity (*NEJM* 2002;347:305), prior chest radiation, rheumatic fever, vitamin deficiencies, ↑ risk if parents had HF (*NEJM* 2006;355:138)

## Evaluation (*AFP* 2004;70:2145; 2006;74:1893)

- **History:** *Sx:* Dyspnea, fatigue, PND ("Do you wake up at night short of breath, coughing, or choking?"), orthopnea (dyspnea lying flat), ↑ wt, weakness, edema, palpitations, CP, ↓ exercise tolerance/functional level; duration of sx; *Etiology/Comorbidities:* Risk factors (above), depression, FHx; hx SUD, esp EtOH, cocaine, chemotherapy, alt medicines; *HF regimen:* Review log of daily wt, diet & med adherence; can pt afford medication or healthy foods?

  **Exacerbation triggers:** Infection, medication/diet adherence, arrhythmia (esp AF), anemia, EtOH, renal dysfunction, ischemia
- **Exam:** Establish & document dry wt; ✓ BMI, orthostatics; Lung crackles (not always present), S3 and/or S4, displaced apical impulse, LV/RV heave, JVP, peripheral edema, ascites; Pulsus alternans (alternating strong/weak peripheral pulses), peripheral vasoconstriction, ST; signs of CAD/PAD (peripheral pulses, carotid bruits)
- **Labs:** CBC, electrolytes, BUN/Cr, Ca, Mg, A1c, BNP/NT-proBNP, LFTs (↑ in hepatic congestion), lipids, TSH, UA; if anemic ✓ iron studies, $B1_2$, folic acid

  **BNP:** ProBNP released by ventricles → cleaved to BNP (active) & NT-proBNP (inactive); useful along w/ other factors in diagnosing CHF as cause of dyspnea in emergency & primary care settings (*NEJM* 2002;347:161; *J Am Coll Cardiol* 2003;42:1793);Nl values ↑ w/ age;

falsely low in obesity; ↑ trend assoc w/ worse prognosis (*BMJ* 2005;330:625); target value to guide tx remains controversial (*Circulation* 2013;127:500, 509)

- **Studies:** ECG, echo, CXR (r/o pulmonary causes of dyspnea); *Consider based on pt hx:* cath, stress test, sleep study, 6 min walk test, ✓ HIV, iron/ferritin, ACE level, SPEP, serum free light chains, ANA, dsDNA, urine metanephrines, selenium/thiamine level, Chagas, Lyme, carnitine, α-galactosidase

## Classification (*NEJM* 2010;362:228; 1992;327:685; 1991;325:293; 1987;316:1429)

**Heart Failure Classification**

| NYHA | | ACC/AHA Task Force | |
|---|---|---|---|
| I | Sx w/ greater than nl activity | A | CHF risk factors; No sx or structural abnorm |
| II | Sx w/ nl activity | B | ⊕ Structural disease; No sx |
| III | Sx w/ minimal activity | C | ⊕ Structural disease; Current or prior HF sx |
| IV | Sx at rest | D | End-stage HF, sx at rest |
| **Mortality w/o Rx:** NYHA **I:** 5% 1 y, 19% 4 y; **II or III:** 15% 1 y, 40% 4 y; **IV:** 63% 1 y | | | |

## Treatment of Heart Failure with Reduced Left Ventricular Ejection Fraction (*Circulation* 2009;119:e391; *AFP* 2004;70:2157; 2008;77:957; *JACC* 2009;53:e1; *J Card Failure* 2010;16:475)

- **Treat reversible causes:** Thyroid disease, AF, anemia, hemochromatosis, HTN, renovascular disease, CAD, valvular disease, EtOH/cocaine abuse, malnutrition, SLE, sarcoid; CPAP in OSA & HF ↑ EF & exercise tolerance but no effect on survival (*NEJM* 2005;353:2025)

  **Medications to avoid/use cautiously in HF pts:** NSAIDs, corticosteroids, CCB (except amlodipine, felodipine (*NEJM* 1996;335:1107; *Br Heart J* 1995;73:428)), thiazolidinediones, metformin (can ↑ HF sx; *JAMA* 2003;290:81), cilostazol, class I & III antiarrhythmics (except amiodarone), anagrelide, amphetamines, carbamazepine, dronedarone, clozapine, ergots, β2−agonists (i.e., albuterol), herbal agents (*Arch Intern Med* 2004;164:709)

  **Atrial fibrillation:** No survival benefit for rate vs. rhythm control in HF pts (*NEJM* 2008;358:2667), but pts w/ persistent HF sx should

be considered for a rhythm control strategy (*Circ* 2004); in pts w/ HFpEF, a rhythm strategy is often preferred as most do not tolerate the assoc reduced diastolic filling; if rhythm control used, amiodarone (*Circulation* 1998;98:2574) & dofetilide (*NEJM* 1999;341:857) preferred; dronedarone assoc w/ ↑ mortality in severe systolic HF (*NEJM* 2008;358:2678)

- **Lifestyle:** Smoking/EtOH cessation, salt restriction (2–3 g/d), wt loss; nutrition referral; cardiac rehab & supervised exercise (*JAMA* 2009;301:1439; 2009;301:1451)
- **Prevention:** Influenza & pneumococcal vaccination
- **Medications and order of therapy (varies by stage):**
  1. Loop diuretics to optimize volume status
  2. ACEI (or ARB if ACEI not tolerated)
  3. βB once euvolemic, stable, & on an ACEI/ARB
  4. Consideration of spironolactone, digoxin, and/or hydralazine/nitrates in select pts who remain sx (below); digoxin beneficial regardless of rhythm (AF or SR)

  **Titration:** βB/ACEI/ARB should be started low & ↑ q1–2 wks as tolerated

  ≠ **Survival:** ACEI, βB, ARB, hydralazine/nitrates, aldosterone antagonists

  **Ø Sx:** Digoxin, diuretics, βB, ACEI, ARBs

**Treatment of Systolic Heart Failure by ACC/AHA Stage**

| Stage | Intervention (*NEJM* 2003;348:2007) |
|---|---|
| A | Treat HTN, DM, HLD, CAD, AF, obesity, metabolic syndrome, thyroid disease; risk factor reduction & healthy lifestyle (*JAMA* 2009;302:394); ACEI or ARB in appropriate pts |
| B | Above interventions + ACEI/ARB and/or βB in appropriate pts; consider AICD in select pts (see below) |
| C | Above interventions + diuretics/salt/fluid restriction in appropriate pts; ACEI in all pts, βB in stable pts; avoid drugs that may worsen HF; consider specialist referral, aldosterone antagonists, digoxin, hydralazine/nitrates, & CRT/AICD in select pts |
| D | VAD, transplantation, or hospice |

**Medical Management of Systolic Heart Failure** (*NEJM* 2010;362:228)

| Rx Class, starting dose | Notes |
|---|---|
| Loop diuretics<br>Furosemide 20 mg QD<br>Bumetanide 0.5 mg QD<br>Torsemide 5 mg QD | Titrate to wt ↓ 1 kg/d until euvolemic; monitor for ↓ $Mg^{2+}$; If lack of diuresis, ↑ dose rather than freq; oral absorption of bumetanide/torsemide more predictable than furosemide; PO Bumetanide 1 mg = torsemide 20 mg = furosemide 40 mg; thiazides enhance diuresis by blocking distal Na reabsorption but may further ↓ $K^+/Mg^{2+}$ (*NEJM* 1998;339:387) |
| ACEI*<br>Enalapril 2.5 mg BID<br>Lisinopril 5 mg QD | ↑ Survival in asx or sx pts w/ EF ≤35% (*NEJM* 1992;327:685; 1991;325:293), NYHA class IV (*NEJM* 1987;316:1429) |
| βB*<br>Bisoprolol 1.25 mg QD<br>Carvedilol 3.125 mg BID<br>Metoprolol ER 12.5 mg QD | ↑ Overall & event-free survival in NYHA II–IV & EF ≤35–40% (*Lancet* 1999;353:9; 2001;353; *NEJM* 1996;334:1349; *JAMA* 2000;283:1295; 2002;287:890; 2002,287:883); improvement additive to ACEI (*Ann Intern Med* 2001;134:550); pts w/ low BP less likely to tolerate vasodilatory activity of carvedilol; pts should be on an ACEI prior to initiation, be stable & euvolemic to avoid worsening sx; cardioselective βB (i.e., metoprolol) safe in pts w/ mild–mod reactive airway disease (COPD, asthma) (*Ann Intern Med* 2002;137:715) |
| Aldosterone antagonists<br>Spironolactone 25 mg QD<br>Eplerenone 25 mg QD (in pts w/ nl GFR) | ↑ Survival in NYHA II & EF ≤35% (*NEJM* 2011;364:11), NYHA III–IV & EF ≤35% (*NEJM* 1999;341:709); monitor closely for ↑ $K^+$; avoid in pts w/ baseline Cr ≥2.5 ♂, 2.0 ♀, or GFR ≤30 or $K^+$ ≥5.0; eplerenone ↓ endocrine s/e (i.e., gynecomastia) |
| Angiotensin receptor blocker (ARB)<br>Candesartan 4 mg QDLosartan 50 mg QDValsartan 20 mg BID (*NEJM* 2001;345:1667) | ↑ Survival in pts intolerant to ACEI w/ sx CHF & EF ≤40% (*Lancet* 2003;362:772); ↑ survival w/ high dose losartan (150 mg QD) compared to low dose (50 mg QD) in pts w/ NYHA II–IV HF, EF ≤40%, & intolerant to ACEI (*Lancet* 2009;374:1840); candesartan ↓ risk of CV death or nonfatal MI in NYHA II–IV pts & is assoc w/ ↓ mortality risk compared to losartan (*JAMA* 2005;294:1794; 2011;305:175); ↑ adverse effects w/ combination of ACEI & ARB in pts w/ sx systolic HF (*Arch Intern Med* 2007;167:1930); use *very cautiously* in pts w/ hyperkalemia, HoTN, or renal insufficiency due to ACEI |
| Hydralazine 25 mg TID + nitrate (isosorbide mononitrate 30 mg QD) | ↑ Survival in African-Americans w/ EF ≤40% & persistent NYHA III to IV HF despite optimal medical Rx (*NEJM* 2004;351:2049); consider in pts intolerant of ACEI/ARB; hydralazine assoc w/ lupus-like syndrome |
| Digoxin 0.125 mg QD (in pts w/ nl GFR) | Provide sx control in pts w/ EF ≤40% & NYHA II–IV despite optimal medical Rx; ↓ hospitalization for HF but not mortality (*NEJM* 1997;336:525); goal serum digoxin 0.5–0.8 ng/mL; ↑ levels ↑ toxicity & mortality (*JAMA* 2003;289:871); ✓ levels 6 h after dose |

*Double dose every 2 wks in stable HF pts; target max dose for each drug, or highest dose tolerated; some ACEI or βB is better than none (*Eur J Heart Fail* 2005;7:712)

- **Automatic implantable cardioverter defibrillator (AICD):** ↓ mortality by 23% in pts w/ persistent LVEF ≤35%, ischemic or nonischemic CMP, NYHA II or III HF despite optimal medical Rx for ≥3 mos (ischemic: >40 d post-MI) (*NEJM* 2005;352;222;

2005;352:225); candidates should have >1 y expected survival w/ good functional status

- **Cardiac resynchronization therapy (CRT, biventricular pacing):** ↑ NYHA functional status, ↓ sx, ↓ hospitalizations, ↓ all cause mortality in NYHA III & IV pts w/ ↓ EF & ↑ QRS (*JAMA* 2007;297:2502; *NEJM* 2002;346;1845); recommended in pts w/ QRS >120 ms, LVEF ≤35%, SR, NYHA II, III or ambulatory class IV despite medical Rx (best responders: LBBB + QRS ≥150 ms, women)
  **CRT + AICD benefits:** (vs. AICD alone)
  *NYHA III/IV:* Ischemic or nonischemic CMP pts w/ QRS >120 ms have ↑ QoL & functional status (*JAMA* 2003;289:2685)
  *NYHA II/III:* ↓ all-cause mortality or HF hospitalization (*NEJM* 2010;363:2385)
  *NYHA I/II:* ↓ ischemic or nonischemic CMP pts w/ QRS >130 ms and EF ≤30% have ↓ HF events but no mortality benefit (*NEJM* 2009;361:1329)
- **Revascularization:** For pts w/ EF ≤35% & CAD amenable to CABG, no difference in death from any cause btw medical Rx vs. CABG + medical Rx, although CABG pts had ↓ CV morbidity & mortality (*NEJM* 2011;364:1607)
- **Anticoagulation:** CHF pts w/o AF have ↑ risk of stroke, DVT, PE (*Circulation* 2007;115:2637); for pts w/ EF ≤35% in SR no benefit to anticoagulation w/ ASA, clopidogrel, or warfarin (*Am Heart J* 2004;148:157; *Circulation* 2009;119:1616); major society guidelines recommend against anticoagulation for systolic CHF unless hx previous thromboembolism
- **Referral:** HF specialist/transplant center for pts w/ severe disease
- **Asymptomatic left ventricular dysfunction:** Initiate Rx (ACEI + βB as tolerated) when EF ≤40%
- **HFpEF/Diastolic dysfunction:** Focus on tx of underlying conditions; salt restriction & cautious use of diuretics; control HTN & rate in AF; ACEI/ARB if tolerated to ↓ mortality (*JAMA* 2012;308:2108), use βB if hx ischemia (*NEJM* 2004;351:1097)
- **Care coordination/self-management:** Daily wts (pt to call if ↑ >2–3 lb), edema check, symptom log; prompt f/u appt after d/c for CHF flares (*JAMA* 2010;303:1716); involvement of cardiology, RNs, social

workers, nutrition; frequent pt education & clinician contact

- **Correction of anemia:** Controversial; IV iron in NYHA II or III pts w/ iron deficiency ± anemia ↓ sx, ↑ QoL (*NEJM* 2009;361:2436); darbepoetin in pts w/ sx HF, anemia not assoc w/ clinical benefit (*Circulation* 2008;117:526; *NEJM* 2013;368:1210) while meta-analysis of erythropoiesis-stimulating agents suggests otherwise (*Am Heart J* 2011;161:822); further studies needed; ESAs typically Rx'ed by hematology
- **Patient information:** *JAMA* 2011;306:2175; *AFP* 2008;77:967; 2003;68:339

# DYSLIPIDEMIA

## Background (*JAMA* 2011;305:1086; *NEJM* 2005;353:1252)

- Dyslipidemia is a common problem affecting >1/3 of US adults; proper management can ↓ risk of stroke & CAD; high-risk pts receive greatest benefit from tx
- **Total cholesterol (TC)** = LDL + HDL + VLDL (VLDL ≈ TG/5); formula valid if TG <400 mg/dL
  - **Low density lipoprotein (LDL):** "Bad cholesterol"; transports cholesterol to tissue; taken up by Mφ & endothelium → atheromas, endothelial dysfunction, & PLT aggregation → CAD/PAD; strong relationship w/ stroke/CAD risk (↑ 30 mg/dL LDL → 30% ↑ in CAD)
  - **High-density cholesterol (HDL):** "Good cholesterol"; HDL reverses cholesterol transport, removing it from tissue; ↓ HDL in familial syndromes, drugs (βB, BZD, steroids); ↑ HDL w/ aerobic exercise, wt loss, medications, smoking cessation, diet, niacin, fibrates
  - **Triglycerides (TG):** Fatty acids from diet released by enterocytes into bloodstream; ↑ TG due to genetic disease, EtOH, smoking, DM2, obesity, hypothyroidism, pregnancy, medications (tamoxifen, CsA, βB, estrogens, PI)
- **Etiology:** Most dyslipidemia 2/2 combination of diet, lifestyle, wt, & genetics
  - **1°:** Diet (saturated fat), sedentary lifestyle/obesity, heredity, ♂ gender, age

**2°:** Hypothyroidism, DM, nephrotic syndrome, CKD, liver disease, medications (progestins, estrogens, anabolic steroids, corticosteroids, protease inhibitors, atypical antipsychotics, retinoic acid derivatives, thiazides, βB, CsA)

- **Screening:**
  ♂ >35 y, ♀ >45 y; If risk factors for CAD then ♂/♀ >20 y; may ✓ nonfasting TC & HDL in pts at ↓ risk of CAD (*JAMA* 2009;302:1993); ✓ q5y if TC <200, sooner if RFs

## Evaluation (*JAMA* 2001;285:2486)

- **History:** Lifestyle (activity), diet, ⊕ FHx premature CAD; risk factors (above); ask about muscle sx prior to statin Rx to establish baseline
- **Exam:** BMI, carotid bruits, peripheral pulses, xanthoma, xanthelasma, corneal arcus
- **Labs:** ✓ TC, HDL, LDL; HDL & LDL levels vary 2–10% w/ fasts of various durations; ∴ **fasting unnecessary** unless info on TG (which vary up to 20% w/ fasting time) is needed (*Ann Intern Med* 2012;172:1707;1710); consider ✓ TSH, BUN/Cr, U/A (for nephrotic syndrome), A1c in pts w/ HLD
  **Monitoring therapy:** Fasting lipids q6–8wks until goals reached, then q6–12mos
  **Very high LDL (>190 mg/dL):** Consider familial hypercholesterolemia, familial combined hyperlipidemia (1–2% population); lipid specialist referral

**ATP III Cholesterol Classification (mg/dL)**

| **LDL** < 100 | Optimal | **TC** < 200 | Optimal | **TG** < 150 | Normal |
|---|---|---|---|---|---|
| 100–129 | Above optimal | 200–239 | Borderline | 150–199 | Borderline |
| 130–159 | Borderline | ≥240 | High | 200–499 | High |
| 160–189 | High | **HDL** < 40 | Low | ≥500 | Very high |
| ≥190 | Very high | ≥60 | High | | |

## Treatment (*AFP* 2011;84:551; *NEJM* 1999;341:498)

- **General approach:** LDL is 1° target to ↓ CV risk; lifestyle & statins are 1° therapy
- **Lifestyle:** Aerobic exercise 30 mins 3–4×/wk; some benefit after ~6–

12 mos; wt loss (2% wt loss ≅ 6% ↓ in LDL)

- **Diet:** ↓ LDL ~13% (*JAMA* 2011;306:831); ↑ fruits/veg, ↓ saturated fats & trans-fatty acids, 50% of total calories from complex carbs; AHA diet (heart.org); nutrition referral

**ATP III/NCEP LDL Goals** (*NEJM* 2004;350:1495; *JACC* 2004;44:720)

**CAD equiv:** DM (most pts), PAD, AAA, carotid disease (TIA/stroke of carotid origin or >50% obstruction), Framingham 10 y risk >20%, consider CKD (Cr >1.5 or GFR <60)
**Risk factors:** Smoking, HTN or anti-HTN Rx, HDL <40 mg/dL, FHx CAD (1° relative ♂ <55 or ♀ <65), age (♂ >45, ♀ >55); subtract 1 risk factor if HDL >60 mg/dL
**Framingham:** 10 y risk for MI/coronary death (hp2010.nhlbihin.net/atpiii/calculator.asp)
**UKPDS:** 10 y risk of MI or stroke in diabetic pts (www.dtu.ox.ac.uk/riskengine)

| Risk Category | LDL Goal (mg/dL) | LDL for Lifestyle Δ | LDL to Rx |
|---|---|---|---|
| CAD or equivalent | <100 (consider <70) | ≥100 | ≥100–130 |
| ≥2 risk factors and: | | | |
| Framingham 10 y 10–20% | <130 | ≥130 | ≥130 |
| Framingham 10 y <10% | <130 | ≥130 | ≥160 |
| 0–1 risk factors | <160 | ≥160 | ≥190 |

- **Statins:** HMG-CoA reductase inhibitors; ↓ cardiac & overall mortality in pts w/ or w/o CAD (*Arch Intern Med* 2005;165:725); **consider Rx regardless of LDL in pts w/ DM, CAD risk equiv, or 10 y CAD risk >20%** (*NEJM* 2004;350:1495; *Lancet* 2004;364:685)
  **Initial choice:** Simvastatin 20 mg/d in pts requiring <35% ↓ in LDL; consider fluvastatin or pravastatin in pts likely to have musculoskeletal complaints; uptitrate to ↓ LDL
  **Timing:** QHS (liver cholesterol synthesis mostly at night when dietary intake lowest)
  **Contraindications:** Liver disease, pregnancy (category X), breastfeeding
  **S/e:** HA, nausea, myalgias (~5%), ↑ LFTs (0.5–2%), sleep disturbance; rhabdomyolysis/myositis (0.1–0.5%, ↑ risk if CKD, hypothyroid, >65 y, or given w/ gemfibrozil, macrolides, itraconazole, HIV PIs or CsA) (*JACC* 2002;40:567); fluvastatin & pravastatin have lowest risk of muscle injury
  **Simvastatin:** FDA recommends against starting at 80 mg/d due to risk of muscle injury; Continue in pts who have tolerated 80 mg/d for >1 y
  **Interactions:** Digoxin, warfarin (see table); grapefruit: Up to 8 oz or ½ a fruit QD OK

**Monitoring: Baseline LFTs & CK; LFTs 12 wks after start;** no need to ✓ LFTs/CK unless per sx; d/c if CK >10× or LFTs >3× ULN

**Pleiotropic effects:** Atherosclerotic plaque stabilization/reduction (*JAMA* 2007;297:499), anti-inflammatory, ? prevention of dementia; no benefit in cancer prevention

### Selecting a Statin

| Statin | Dose (mg) | LDL ↓ | Comments |
|---|---|---|---|
| Atorvastatin | 10–80 | 38–54% | Preferred in CKD |
| Fluvastatin | 20–80 | 17–33% | Preferred in CKD; ↓ muscle toxicity; OK w/ warfarin |
| Lovastatin | 20–80 | 29–48% | Generic; take in evening |
| Pitavastatin | 1–4 | 31–41% | May be taken at any time; OK w/ warfarin |
| Pravastatin | 10–80 | 19–40% | Preferred in liver disease; OK w/ warfarin; ↓ muscle toxicity; generic; ↓ interaction w/ fibrate; take in evening; least drug–drug interactions |
| Rosuvastatin | 5–40 | 52–63% | May be taken at any time; ↑ HDL; ↓ drug–drug interactions |
| Simvastatin | 10–80 | 28–41% | Generic; take in evening; highest drug–drug interactions |

- **Second-line agents:** If high LDL despite maximal statin therapy, consider statin + bile resin or niacin or ezetimibe; statin + ER niacin may ↓ risk of CV events in pts w/ CAD compared to ezetimibe combination (*NEJM* 2009;361:2113)

### Secondary Lipid Lowering Drugs

| Drug | Dosing | S/e & notes | LDL (%) | HDL (%) | TG (%) |
|---|---|---|---|---|---|
| **Gemfibrozil** | 600 mg BID | ↑ INR on warfarin; ↑ gallstones, ↑ rhabdo w/ statins | ↓ 10–15 | ↑ 5–20 | ↓ 35–50 |
| **Fenofibrate** | 145 mg/d nanocrystal 160–200 mg/d micronized | Rash, GI upset, myalgia, ↑ LFTs, ↑ CsA, avoid if CrCl <30; ↑ gallstones; use cautiously w/ statin | ↓ 6–20 | ↑ 5–20 | ↓ 41–53 |
| **Niacin** *Regular more effective than timed-release* | 1–4.5 g/d Start at 100 mg AC & ↑ or use ER | Flushing, HA, pruritus, GI upset; avoid in gout, PUD, liver disease; may worsen DM; pre-Tx w/ NSAIDs/ASA ↓ flushing | ↓ 5–25 | ↑ 15–35 | ↓ 20–50 |
| **Bile sequestrants** Cholestyramine Colestipol Colesevelam | Take w/ meals 2–24 g/d 5–30 g/d 1.5–4.5 g/d | GI upset, ↓ drug absorption; avoid in biliary/bowel obstruction; effect additive to statins | ↓ 15–30 | No Δ | No Δ |
| **Ezetimibe** (inhibits absorption) | 10 mg QD | ↑ LFTs w/ statins | ↓ 17 | No Δ | No Δ |
| **Fish oil** (Ω3-acid ethyl esters) | 4 g QD or 2 g BID | GI upset; useful in CAD pts intolerant of statins | May ↑ | No Δ | ↓ 20–50 |

- **Hypertriglyceridemia (mg/dL)** (*NEJM* 2007;357:1009; *J Fam Pract* 2006;55:S1; *AFP* 2007;75:1365):
  Screen pts w/ ↑ TG for metabolic syndrome; blood glucose control key to ↓ TG in diabetics
  **150–199:** Diet (fat <15% total cal, low sugar, ↓ EtOH), exercise (↓ TG up to 25%)
  **200–499:** Consider Rx ↑ risk pts (CAD or equiv); non-HDL cholesterol (TC − HDL) is a 2° target w/ a goal 30 mg/dL higher than LDL goal; statins ↓ TG 5–33%
  ≥**500:** Ω 3-acid ethyl esters (fish oil), fibrate, nicotinic acid to avoid pancreatitis
- **Complimentary and alternative therapies:**
  **Plant sterols** (i.e., Benecol, Promise active)**:** ↓ LDL 8–20%; consider in pts w/ CAD or equiv; use in general population not recommended pending long-term studies
  **Soy:** Low in saturated fat, useful in substitution for animal protein, ↓

LDL

**Other:** Fiber (psyllium, oatmeal), nuts, green tea, DASH, & Mediterranean diets

- **Patient information:** *JAMA* 2001;285:2536; 2004;291:2276; 2013;309:1419; *AFP* 2003;67:1775; 2005;71:1147; 2010;81:1103

# HYPERTENSION

## Background (*JAMA* 2010;303:2043; *NEJM* 2010;362:2102)

- **Definition:** Elevated BP on ≥2 separate visits spaced >1 wk apart unless signs of end-organ damage or stage II HTN (below)
- **Epidemiology:** HTN affects ~50% pts >60 y; only ~50% pts w/ HTN at BP goal
- BP control ↓ risk of stroke by 35–40%, MI by 20–25%, CHF by 50%; to prevent 1 death/y from stage I HTN, NNT = 11
- Each 20 mmHg ↑ in SBP over 115/75 doubles risk of CV complications (stroke, MI, heart/renal failure, PVD) (*Lancet* 2002;360:1903)

## Evaluation (*Ann Intern Med* 2011;154:781; *NEJM* 2003;348:610; 2006;355:385)

- **History:** Duration of HTN, comorbid conditions (CAD, CKD, stroke, DM, OSA, PAD, thyroid), evidence of end-organ damage, FHx, medication use, lifestyle

  **Adherence:** Ask pts not at goal BP: "Did you take your meds today, & at what time? Thinking over the past 2 weeks, were there any days when you did not take your blood pressure medicine?"
- **Exam:** Cardiac exam (LVH, murmurs, volume status), fundoscopic, neuro, thyroid, BMI, auscultation for bruits (carotid, renal); average several BP measurements;

  **BP measurement:** Pt seated, arm supported & level to heart, measured in both arms unless contraindicated (i.e., HD fistula, axillary LN dissection in breast CA); proper cuff size key: Improperly small cuffs overestimate SBP by up to 10 mmHg; check supine + standing BP in elderly, fall risk, or diabetics to detect/avoid orthostatic HoTN w/ tx (difference in SBP >20 mmHg, HR >20, or sx such as dizziness); check leg BP in young

(eval for coarctation)

**Home BP monitors:** Should be calibrated in office; pts may keep daily log

- **Initial workup:** CBC, Chem-12, lipids, TSH, U/A w/ protein:Cr ratio, ECG, HbA1c

## Treatment

**Treatment of Hypertension by Stage**

| Definition | Treatment (see below for compelling indications) |
|---|---|
| **Normal** | Encourage healthy lifestyle |
| **Pre-HTN:** SBP 120–139 or DBP 80–89 | Lifestyle modification for 3 mos (*NEJM* 2010;362:2102):<br>• Wt loss (SBP ↓ 0.5–2 mmHg/kg lost)<br>• DASH diet rich in fruits, vegetables, low fat (SBP ↓ 8–14 mmHg) (http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf)<br>• $Na^+$ reduction <2.4 g/d (SBP ↓ 2–8 mmHg), avoid canned, packaged, processed foods as high in Na<br>• Aerobic exercise >30 mins/d, minimum 5 d/wk; intensity more effective than freq (SBP ↓ 4–9 mmHg)<br>• Mod EtOH consumption <2 drinks/d men, <1 drink/d women (SBP ↓ 2–4 mmHg) |
| **Stage I:** SBP 140–159 or DBP 90–99 | Lifestyle modification & in pts w/o compelling indication: Hydrochlorothiazide 12.5 mg PO QD |
| **Stage II:** SBP >160 or DBP >100 | Lifestyle modification & in pts w/o compelling indication: ACEI + CCB (ACCOMPLISH, *NEJM* 2008;359:2417) |
| **HTN urgency:** >180/>120 | Tx for stage II plus close f/u (1–3 d); consider home BP monitoring |
| **Hypertensive emergency** (e/o end-organ damage) | HA, CP, visual changes, altered mental status, stroke, neuro sx, pulm edema, bleeding, aortic dissection, renal failure, CHF, pre-eclampsia/eclampsia; requires ED referral for IV agents |

(Adapted from JNC VII; *JAMA* 2003;289:2560)

- **General principles:** 1st-line drugs (ACEI, thiazides, CCB, βB) have equal efficacy (*BMJ* 2009;338:b1665; *JAMA* 1993;270:713); degree of CV benefit related to how well BP is controlled & compelling indication (below table) (*Arch Intern Med* 2005;165:1410)
- **Treatment failure:** 50–60% of pts w/ HTN will achieve BP control w/ a single agent; 50–80% of pts who fail a 1st agent will achieve BP control by switching to a different agent in a different class, ∴ a sequential single agent approach may be preferable to initial combination Rx (*Arch Intern Med* 1995;155:1757); may consider

switching to a stronger drug within class if applicable; (e.g., not at goal on HCTZ → switch to chlorthalidone, which is a longer-acting and more potent thiazide)

- **Secondary causes:** ~2–5% pts, esp in pts w/ refractory HTN, or onset <20 y (*NEJM* 2006;355:385)
  **CKD:** Proteinuria, elevated Cr, volume overload
  **Renal artery stenosis:** Carotid/abdominal bruits; ↑ Cr w/ ACEI/ARB; resistant HTN in young (fibromuscular dysplasia); renal artery U/S, CT angio, or MRA
  **Sleep apnea:** "Do you snore, wake up tired, fall asleep during the day?" (see "*Obstructive Sleep Apnea*")
  **White coat HTN:** Seen in 10–20% of patients; consider in refractory HTN; ✓ home BP log (*NEJM* 2006;354:2368)
  **Medications:** Antidepressants, NSAIDs, celecoxib, estrogen-OCPs, steroids, decongestants, diet pills, CsA, tacrolimus, herbal medications (ephedra, ginseng)
  **Endocrine:** Cushing syndrome, hypercalcemia, hyperthyroidism, hyperparathyroidism
  **Hyperaldosteronism:** ↓ K suggestive, but >50% pts normokalemic; ratio of plasma aldosterone:renin activity >20; confirm w/ saline infusion test; eval for adrenal adenomas or bilateral adrenal hyperplasia w/ CT (see *"Adrenal Nodules"*); Rx aldosterone antagonist
  **Pheochromocytoma:** Palpitations, diaphoresis, pounding HA, episodic HTN; 24 h urine fractionated metanephrines, catecholamines
  **Pseudo-HTN:** Inability to compress stiff brachial artery; assoc w/ orthostatic sx
  **Aortic coarctation:** Discrepancy in BP btw arms/legs, ↓ femoral pulses

**Compelling Indications** (*NEJM* 2006;355:385)

| |
|---|
| **AF:** βB or CCB (i.e., diltiazem) for rate control |
| **DM2:** ACEI (renoprotective) or ARB; ACEI + CCB for combined therapy (ACCOMPLISH, *NEJM* 2008;359:2417). Goal BP <140/90 in absence of nephropathy/CKD (ACCORD, *NEJM* 2010; 362:1575) |
| **High CAD risk:** βB (1st line), ACEI, CCB, thiazide<br>**Hx MI:** ACEI, βB, ± aldosterone antagonist |
| **CKD:** ACEI/ARB plus a loop diuretic |
| **CHF:** ACEI or ARB, βB, diuretics, aldosterone antagonist, avoid CCB in pts w/ ↓ EF |
| **Hx stroke:** Thiazide, ACEI |
| **Hx thoracic aortic aneurysm:** βB or losartan |

## Special populations

| |
|---|
| **African ancestry:** Response rate by agent: diltiazem (64%), HCTZ (58%), clonidine (45%), prazosin (38%) (*NEJM* 1993;328:914) |
| **Angina:** βB (1st line) or CCB |
| **BPH:** αB |
| **Elderly:** Thiazide or CCB (*JACC* 2011;57:2037; *NEJM* 2007;357:789); tx of HTN in pts >80 y resulted in ↓ stroke & CHF, ↓ in death from CV, stroke, & any cause (HYVET, *NEJM* 2008;358:1887) |
| **Migraines, essential tremor, significant anxiety/phobia, hyperthyroid:** βB (i.e., propranolol) |
| **Nephrolithiasis or osteoporosis:** Thiazide (↓ renal Ca clearance) |
| **Pregnancy:** Methyldopa (Pregnancy risk factor B), hydralazine or nifedipine sustained release (Pregnancy risk factor C), βB used in some situations |
| **Younger pts (<50 y):** ACEI or ARB |

- **Refractory hypertension:** Persistent HTN despite 3 meds; discuss adherence, titrate meds to max dose, & consider w/u of secondary causes + home BP monitoring before moving onto 2° agents (below)
- **Second-line agents:**
  **Aliskiren:** Oral renin inhibitor; assoc w/ diarrhea; limited outcomes data
  **αB:** Doxazosin, prazosin
  **Aldosterone antagonists:** Spironolactone, eplerenone (↓ gynecomastia)
  **Clonidine:** Available in transdermal dosing; anxiolytic; taper if discontinuing
  **Combined aB & bB:** Carvedilol, labetalol
  **Combinations:** (Diltiazem/verapamil + amlodipine) or (ARB + ACEI) w/ careful K/Cr monitoring; avoid in HF due to ⊖ inotropy
  **Hydralazine:** TID or preferably QID dosing; may cause rebound tachycardia
  **Loop diuretics:** Furosemide, bumetanide, torsemide; useful in

refractory HTN w/ CKD (Cr >1.5/CrCl <30)

**Triamterene:** $Na^+$ channel antagonist; available in combo pill w/ HCTZ for 1° tx

- **Medication side-effects:**

**aB:** ↑ risk of CHF (doxazosin), postural HoTN

**ACEI:** Cough (~15% pts); ↑ K in CKD; angioedema, contraindicated in pregnancy

**Aldosterone antagonists:** Hyperkalemia, esp w/ ACEI, DM, renal insufficiency; Gynecomastia & breast pain (less so w/ eplerenone)

**ARB:** Contraindicated in pregnancy

**bB:** Angina/rebound HTN on abrupt discontinuation; may mask hypoglycemic sx in DM; may exacerbate asthma, COPD, impotence; caution in pts w/ conduction disease (heart block), pheo (unopposed α-stimulation); can → nightmares, fatigue, ↓ exercise tolerance

**CCB:** Peripheral edema (esp amlodipine); verapamil/diltiazem are nodal agents & ⊖ inotropes & contraindicated if low EF or heart block

**Clonidine:** Rebound HTN on discontinuation

**Thiazides:** Hypokalemia, most common in 1st wks of tx, prevent by dietary salt restriction; hyperglycemia, esp in diabetics; hyponatremia; may exacerbate gout & erectile dysfunction; ineffective in pts w/ CrCl <30

- **Patient handouts:**
  www.nlm.nih.gov/medlineplus/highbloodpressure.html

# LOWER EXTREMITY EDEMA & ULCERS

## LOWER EXTREMITY EDEMA

### Background (*AFP* 2005;71:2111)

- **Causes:** Δ in hydrostatic or oncotic pressure, ↓ lymph drainage, ↑ capillary permeability
- **Unilateral/asymmetric Ddx:** DVT, cellulitis, lymphedema, venous insufficiency, popliteal (Baker) cyst, ruptured muscle/tendon

- **Bilateral/symmetric** D**dx:** CHF/RHF, nephrotic syndrome, cirrhosis, venous insufficiency, malnutrition, hypothyroidism, lymphatic disease, IVC thrombosis, lipedema, pregnancy/premenstrual or idiopathic, vasculitis (rare)
  **Meds:** CCB (**amlodipine**), steroids, estrogens, hydralazine, thiazolidinediones, diazoxide, pramipexole, minoxidil, NSAIDs (in CHF or cirrhosis)

## Evaluation

- **History:** Onset (acute vs. chronic), location, assoc sx (dyspnea, orthopnea, pain, urinary), hx CAD/CHF/HTN/DM/EtOH/clotting, medications; hx immobility, malignancy, surgery (i.e., LN dissection venous harvest for CABG), radiation or cath, filariasis (where endemic), recurrent cellulitis/lymphangitis, prior DVT; consider OSA → pHTN
- **Exam:** HEENT (periorbital edema), lungs (crackles), CV (JVP, $S_3/S_4$), abdominal (HSM, ascites); lower extremities (✓ limb circumference, ✓ peripheral pulses, e/o venous insufficiency); pattern of edema involving dorsal foot & toes (Stemmer sign) suggests lymphedema; sharp demarcation at ankle, sparing the foot suggests lipedema
- **Diagnostics:** As dictated by hx; consider BUN/Cr, LFTs including albumin, U/A for protein, blood, D-dimer or venous duplex U/S for unilateral/bilateral disease; TTE, CXR, BNP, D-dimer, TFTs, CBC, per clinical suspicion

## Treatment

- **General measures:** Treat underlying etiology; low salt diet (<2 g/d), properly fitted compression stockings (>20 mmHg), fluid restriction limb elevation (30 mins QID)
- **For hypervolemic states:** Loop diuretics (+ spironolactone in cirrhosis)
- **Diuretics:** *Not* effective in venous insufficiency; benefit limited to hypervolemic states; 1st line is loop diuretic (+ spironolactone in cirrhosis); monitor for ↓ K, AKI, dehydration
- **Patient information:** *AFP* 2005;71:2118

## Lymphedema (*BMJ* 2000;320:1527; *Am J Med* 2001;110:288)

- **Causes:** ↓ Lymphatic flow due to LN dissection, XRT, malignancy, filariasis, recurrent cellulitis, obesity, congenital, RA, psoriasis
- **Diagnosis:** Localized, *nonpitting*, gradual swelling/heaviness of limb, including involvement on the dorsum of the foot, worse at day's end; does not improve w/ recumbency; cutaneous fibrosis, dry/scaly skin, peau d'orange, ⊕ Stemmer sign (unable to lift skin at base of upper surface of 2nd digits); edema may be monitored by measuring limb circumference at set points (i.e., wrists); MRI or CT helpful if dx unclear; consider malignant lymphatic obstruction in new or worsening lymphedema
- **Complications:** Discomfort > cellulitis >> lymphangiosarcoma (particularly in LE)
- **Prevention:** Skin/nail care to prevent infection; avoid tight clothing, dependent positioning for long periods; avoid phlebotomy, vaccination, IVs in affected limb; Hot climates, baths, & saunas may exacerbate; wt loss; ROM & wt exercises
- **Treatment:** Manual lymph drainage/compression (bandages, hose, intermittent pneumatic compression); for severe cases, surgery & cold laser tx (data unclear); **Diuretics not beneficial**

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## Chronic Venous Disease (*JAMA* 2012;308:2612)

- **Definition:** Clinical syndrome due to ↑ pressure in venous system, 2/2 obstruction/reflux
- **Pathophysiology:** Incompetent valves/thrombosis → reflux → stasis → pain, edema, dermatitis, lipodermatosclerosis (circumferential hyperpigmentation, induration), ulcers
- **Epidemiology and risk factors:** Overall prevalence of 50% in adults (*NEJM* 2006;355:488; 2009;360:2319; *BMJ* 2007;335:83); incidence ↑ w/ age, pregnancy, ⊕ FHx, obesity, hx LE trauma, DVT; Cumulative rates 7% at 1 y, 14% at 5 y, & 20% at 10 y following DVT

### Venous Disease Spectrum (*BMJ* 2007;335:83; *NEJM* 2009;360:2319)

| Signs | Disease | Prevalence |
|---|---|---|
| Telangiectasias | Dilated dermal veins ("spider veins") | 50–85% |
| Varicose veins | Dilated, tortuous, SC veins | 10–40% |
| Edema, pain, ulcers | Deep, usually w/ venous reflux | 1–16% |

- **History:** Pain (↑ at night, ↓ w/ elevation, exercise), heaviness/achiness, cramps, itching
- **Exam:** Erythema, lipodermatosclerosis (hyperpigmentation + induration), ulcers (above ankle, classically medial, w/ irregular/sloped borders), bleeding
- **Varicose veins:** SC, tortuous dilated veins >3 mm; may hemorrhage, thrombose, or → thrombophlebitis; cosmetically distressing
- **Stasis dermatitis:** Eczematous reaction: pruritic, erythematous, papular rash w/ overlying scale; simultaneous contact dermatitis (from topical agents) or infection possible
- **Evaluation:** Clinical dx; severity of s/sx correlate w/ degree of venous incompetence; refer symptomatic pts for duplex U/S to assess acute vs. remote DVT, reflux severity/site, as this guides tx options
- **General treatment:** Walking, seated ankle flexion, stockings & massage to promote $O_2$ transport, prevent edema & progression to venous insufficiency
  - **Compression stockings:** Effective but poor compliance; avoid in pts w/ PAD (ABI < 0.5); ↑ pressures work better; *Class I:* DVT ppx 10–18 mmHg, *Class II:* ↓ edema (20–30 mmHg), *Class III:* Control venous dermatitis, ulcers (>40 mmHg); high likelihood of recurrent edema, ulcers, if compression stockings d/c'ed
  - **Skin care:** Nonsoap cleansers, emollients, short course of topical corticosteroids
  - **Medications:** Pentoxifylline + compression effective at ulcer healing; escin & stanozolol ↓ sx; ASA may help ulcer healing: abx not useful unless e/o systemic infection (↑ pain, ↑ redness, fever)
- **Intervention:** Consider ablation after 6 mos failed med Rx; ablation contraindicated in pregnancy, thrombosis, PAD, joint disease
  - **Chemical ablation:** Foam or liquid sclerosing agent → endothelial damage/scarring; preferred for telangiectasias, reticular & small varicose veins; contraindicated if PFO
  - **Thermal ablation:** Laser delivers heat to veins; surface tx used for

telangiectasias/reticular veins; endovenous lasers/RF probes used for saphenous vein

**Mechanical ablation:** Vein ligation, stripping, phlebectomy

**Other:** Percutaneous iliac stenting, deep valve reconstruction

- **Patient information:** *AFP* 2010;81:1003; *JAMA* 2012;308:2638; 2013;309:1306; vascularweb.org; vdf.org

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## LOWER-EXTREMITY ULCERS

- **Differential:** Venous or arterial insufficiency, neuropathic (i.e., diabetic), pressure (i.e., decubitus), rheumatologic disease, malignancy, calciphylaxis, thromboembolism, Buerger disease, pyoderma gangrenosum, necrobiosis lipoidica, sickle cell
- **Workup:** Assessment for osteomyelitis (i.e., wound probes to bone or has bone visible), infection (erythema, warmth, tenderness, swelling), screen for neuropathy (monofilament, tuning fork); ✓ pulses: If not palpable → ABI; segmental Doppler pressures & volume plethysmography once PAD diagnosed; duplex imaging, ESR/CRP, CTA/MRA, MRI for osteomyelitis as indicated; consider plain films for foreign body; biopsy ulcers present >3 mos

### Clinical Features of Ulcers, by Etiology

| Ulcer Types | Arterial | Venous | Diabetic/ Neuropathic |
|---|---|---|---|
| Location | Toes/heel/pressure points | Malleolar, lateral, posterior calf | Plantar region/bony prominences |
| Appearance | Irregular, pale/cyanotic | Irregular, pink base, exudative, shallow | Punched out, deep |
| Foot temp | Cold | Warm | Warm |
| Pain | + (worse lying flat) | None/mild | – |
| Pulses | – | + | ± |
| Veins | Collapsed | Varicosed | Dilated |
| Sensation | Variable | + | – |
| Deformities | – | – | + |
| Skin | Shiny, taut, pallor | Erythema, edema | Shiny, taut, doughy |

(Adapted from: *J Vasc Surg* 2000;31:S1; *AFP* 2010;81:989; *Ann Intern Med* 2003;138:326)

- **Treatment** (*AFP* 2010;81:989; 1998;57:1325; 1999;59:1899; 2002;66:1655; *Cochrane Database Syst Rev* 2007;CD001733; *JAMA*

2005;293:217; *NEJM* 2004;351:48; *Wound Rep Regen* 2006;14:649): Debridement of necrotic tissue (surgical vs. enzymatic); consider tetanus vaccination; daily self-inspection, elevation, avoid walking barefoot; smoking cessation; control HTN, HLD, DM2; keep wounds moist; osteomyelitis → hospitalization; wound care/podiatry/vascular referral

**Arterial:** Anti-PLT medications; vascular specialist referral for revascularization; debridement should be performed after vascularization; consider hyperbaric $O_2$ if wound does not heal despite revascularization or if revascularization not possible

**Venous:** ASA; compression stockings (30– >40 mmHg—contraindicated if ABI <0.7) + pentoxifylline; worn indefinitely to prevent recurrence; abx only if infection present; elevation 30 mins QID & o/n; skin grafting in chronic ulcers

**Diabetic/neuropathic:** Pressure off-loading w/ a contact cast/cast walker; ⊖ pressure therapy; revascularization of PAD; becaplermin gel (PLT-derived growth factor); consider tissue-engineered skin; role of hyperbaric $O_2$ unclear; prevention includes regular foot inspection, custom footwear, debridement of calluses, treating fungal infection, f/u q6mos for neuropathy, q1–3mos if hx ulcer; for ulcer; (see "Diabetic Foot Infection" subsection of *"Skin & Soft Tissue Infection"*)

- **Wound dressings:** See *"Wound Care"*

# PALPITATIONS

## Background (*AFP* 2005;71:743)

- **Definition:** Sensation that the heart is beating abnormally; common complaint in ambulatory setting, ~16% of outpt visits (*Arch Intern Med* 1990;150:1685)
- **Premature ventricular contractions (PVCs):** Found in ~6% of middle-aged pts (*Am Heart J* 2002;143:535); may manifest as a skipped beat or palpitation
- **Premature atrial contractions (PACs):** Activation of the atria from site other than SA node; may manifest as a skipped beat or

palpitation

- **Etiology:** 43% cardiac, 31% Ψ, 10% unknown (*Am J Med* 1996;100:138); may have >1 etiology (2/3 of pts dx w/ SVT meet criteria for panic d/o) (*Arch Intern Med* 1997;157:537)

## Evaluation (*AFP* 2011;84:63; *JAMA* 2009;302:2135)

- **History:** Ask pt to "tap out" rhythm; onset, duration, provocative factors (anxiety, exercise, EtOH, caffeine), palliative factors; Has this ever happened before? *Assoc sx:* CP/pressure, neck pulsations, syncope/pre-syncope (most likely CHB or ventricular arrhythmia, rare in SVT); review medications, supplements, illicits, EtOH; screen for depression (see *"Depression"*), anxiety/panic attacks (see *"Anxiety Disorders"*)

### Medical Causes of Palpitations (*AFP* 2005;71:743)

| Diagnosis | Clinical Features |
|---|---|
| Anemia | Fatigue, pica, pallor (see *"Anemia"*) |
| Depression | Lack of energy, suicidal ideation, disrupted sleep, guilt, inability to concentrate (see *"Depression"*) |
| Dehydration/orthostasis | Assoc w/ standing, ⊕ orthostatic VS |
| Panic/anxiety d/o | Situational triggers (i.e., crowds), paresthesias, fear of losing control/dying, derealization, sweating (see *"Anxiety"*) |
| Hypoglycemia | Diaphoresis, relieved by eating |
| Medications/habits | Assoc w/ taking medication or habit (i.e., caffeine) |
| Thyrotoxicosis | Insomnia, weakness, frequent BM, brittle hair, wt loss (see *"Thyroid Disorders"*) |
| Postural tachycardia syndrome | Chronic fatigue/dizziness/lightheadedness, unexplained spells, inappropriate sinus tachycardia (*Mayo Clin Proc* 2012;87:1214) |
| Pheo | HA, HTN, orthostasis, wt loss, hyperglycemia |

### Arrhythmic Causes of Palpitations (*NEJM* 2006;354:1039; 2012;367:1438)

| Diagnosis | Clinical Features |
|---|---|
| AF/AFL | Older age at presentation, "irregular/fluttering" sensation; may p/w presyncope, but syncope rare |
| Atrial tachycardia (AT) | Similar to ST but w/o appropriate stimulus |
| AV node-dependent tachycardia (AVNRT, AVRT) | Younger at presentation, abrupt onset/termination; provoked by exercise; terminates w/ vagal maneuvers (carotid massage, valsalva); AVNRT may be provoked by bending over → standing; may manifest as "pounding in neck" due to AV dissociation |
| Left or right ventricular outflow tract tachycardia/VT | Younger pts; rapid palpitations w/ dizziness, syncope, provoked by exercise, ↑ catecholamines<br>RVOT may terminate w/ vagal maneuvers |
| PACs | "Skipped" beat or "flip-flop" sensation, usually at rest (↑ incidence at ↓ HR) |
| PVCs | Similar to PACs; more common in pts w/ CMP, CAD; pt may report flip-flopping, pause, or forceful contraction (i.e., after PVC) |
| Sinus tachycardia (ST) | Gradual onset, regular/fast, assoc w/ exercise/stress |
| Valvular heart disease | Murmurs heard on exam (see *"Valvular Heart Disease"*) |
| Ventricular tachycardia (VT), nonsustained VT | More common in high-risk pts (CMP, CAD) & older pts; rapid palpitations w/ dizziness, presyncope, syncope; can be postexertion (long QT) |

- **Exam:** Heart sounds for signs of structural/valvular heart disease; assess JVP, edema, & pulm exam for CHF; mid-systolic click assoc w/ MVP
- **Workup:** Electrolytes incl Mg, ECG; further studies as directed by sx; consider HCT, TSH serum/urine catecholamines/metanephrines (pheo), glucose

  **ECG:** Baseline rarely documents culprit arrhythmia, but should be obtained on all pts w/ palpitations since can help w/ dx of ischemic heart disease (see table below)

  **Continuous (Holter) monitoring:** 24–48 h; best for pts w/ frequent sx or sx w/ activity; requires pts to keep log of sx/activities for best interpretation; 48–96 h monitors available, as well (*Circulation* 1999;100:886)

  **Event monitor/loop recorder:** Intermittent or continuous recording; pt can activate during sx; good for those w/ infrequent episodes

  **Implantable loop recorders:** Best for those w/ particularly infrequent episodes; can stay in place for up to 36 mos

  **Exercise treadmill test:** Useful for provoking arrhythmias that occur during exercise, including SVT & the idiopathic outflow tract tachycardias

  **EP testing (referral):** Consider in pts w/ palpitations → syncope or

serious sx, in pts who have known structural heart disease, or who are at risk for structural heart disease (*Circulation* 1995;92:673)

- **Risk stratification** (*NEJM* 1998;338:1369):
  **High risk:** ⊕ FHx of SCD, AF, CAD, arrhythmia; personal hx HTN, syncope or presyncope, valvular heart disease, CAD, CMP, HOCM, recurrent sx → ambulatory ECG monitoring; if ambulatory ECG ⊖ but arrhythmia still suspected → EP referral
  **Low risk:** No e/o structural heart disease/arrhythmia → H&P + ECG is sufficient

**Resting ECG Findings and Potential Etiology**

| ECG Finding | Etiology |
|---|---|
| Short PR, delta-wave | WPW, AVRT |
| Long QT (often + bradycardia) | Polymorphic VT |
| Q-wave (prior MI) | PVCs, NSVT, VT |
| Q-wave in I, aVL, V4–V6 + LVH | Hypertrophic cardiomyopathy |
| P mitrale, LVH, PACs | Large LA → AF |
| PVCs w/ LBBB morphology & ⊕ axis | Right ventricular outflow tract tachycardia |
| PVCs w/ RBBB morphology & ⊖ axis | Left ventricular outflow tract tachycardia |
| Mobitz II | Complete heart block |
| Inverted T-wave in V2, ± ε-wave | Arrhythmogenic right ventricular dysplasia |

(Adapted from *NEJM* 1998;338:1369)

## Management (*AFP* 2011;84:63)

- **Emergency department referral:** (1) Syncope/near syncope w/ high-grade AV block; (2) Syncope in pts w/ known or high risk for cardiac disease (i.e., ⊕ FHx for SCD); (3) Concern for VT; (4) AF w/ slow or rapid ventricular response; (4) Symptomatic bradycardia
- **Electrophysiology/cardiology referral:** (1) Sustained or poorly tolerated palpitations; (2) High likelihood of structural heart disease in an o/w stable pt; (3) Persistent SVT or PVCs not managed w/ βB; (4) Unclear dx
- **PVCs or SVT:** Some studies observed assoc w/ ↑ mortality, even for pts w/o heart disease (*Heart* 2012;98:1290), however, ↓ PVCs in pts w/o heart disease not shown to ↓ mortality (*JACC* 2006;48:e247), consider βB & eval for structural heart disease (i.e., TTE and/or stress test) if risk factors present; if sx persist despite βB or assoc w/ syncope, consider cards referral for anti-arrhythmic Rx or EP eval (*NEJM*

2006;354:1039)

- **Premature arterial contractions:** Reassurance; d/c triggers (i.e., caffeine, nicotine, EtOH, avoid stress); consider βB for persistent sx

# PERIPHERAL ARTERY DISEASE

## Background (*JAMA* 2006;295:547; *Am J Med* 2010;123:790)

- **Definition:** Obstruction due to atherosclerosis, most commonly found in the aortic, iliac, & LE arteries (*JAMA* 2006;295:547)
- **Epidemiology:** Affects ~20% of adults >55 y & is assoc w/ ↑ risk for CV events & all-cause mortality
- **Risk factors:**
  **Age:** Gradual ↑ in prevalence w/ each decade over age 40
  **Race:** Non-Hispanics & pts of African ancestry disproportionately affected, even after controlling for risk factors
  **Smoking:** 5-fold ↑ in PAD compared to lifetime nonsmokers
  **Diabetes:** Risk doubles w/ impaired glucose tolerance, up to 4-fold ↑ w/ DM
  **HTN:** Independent risk factor, ↑ severity assoc w/ ↑ risk
  **Dyslipidemia:** ↑ TG, ↓ HDL-C, ↑ apo A-I/A-II
  **Inflammation:** Assoc w/ ↑ CRP, fibrinogen, & D-dimer
  **Elevated homocysteine:** Present in 30–40% of PAD vs. 3–5% in non-PAD pts

## Evaluation (*N Engl Med* 2001;344:1608, *Am J Med* 2010;123:790)

- **History:** *Claudication:* Exertional leg pain relieved w/ rest; 50% of PAD pts asx; atypical sx (exercise intolerance joint pain or limb numbness) more common in women; Pain at rest suggests critical limb ischemia = 50% risk of amputation or death at 1 y
- **Exam:** ↓ or absent distal pulses, bruits, but can also be nl; ulcers
- **Ankle–brachial index (ABI):** Systolic ankle to systolic arm pressure; simple, inexpensive, noninvasive SBP of dorsalis pedis or posterior tibial arteries divided by higher SBP of brachial arteries
  **ABI < 1.00:** 95% sens & 99% spec for the dx of PAD
  **ABI 0.4–1.0:** Claudication, **£0.4:** Critical limb ischemia, **>1.3:**

Peripheral artery disease (calcified arteries won't compress w/ cuff; ∴ falsely ↑ SBP reading)

- **Other studies:** Duplex U/S, CTA, & MRA used more for endovascular or surgical revascularization planning
- **Contrast angiography:** Gold standard, only performed if plan for endovascular tx

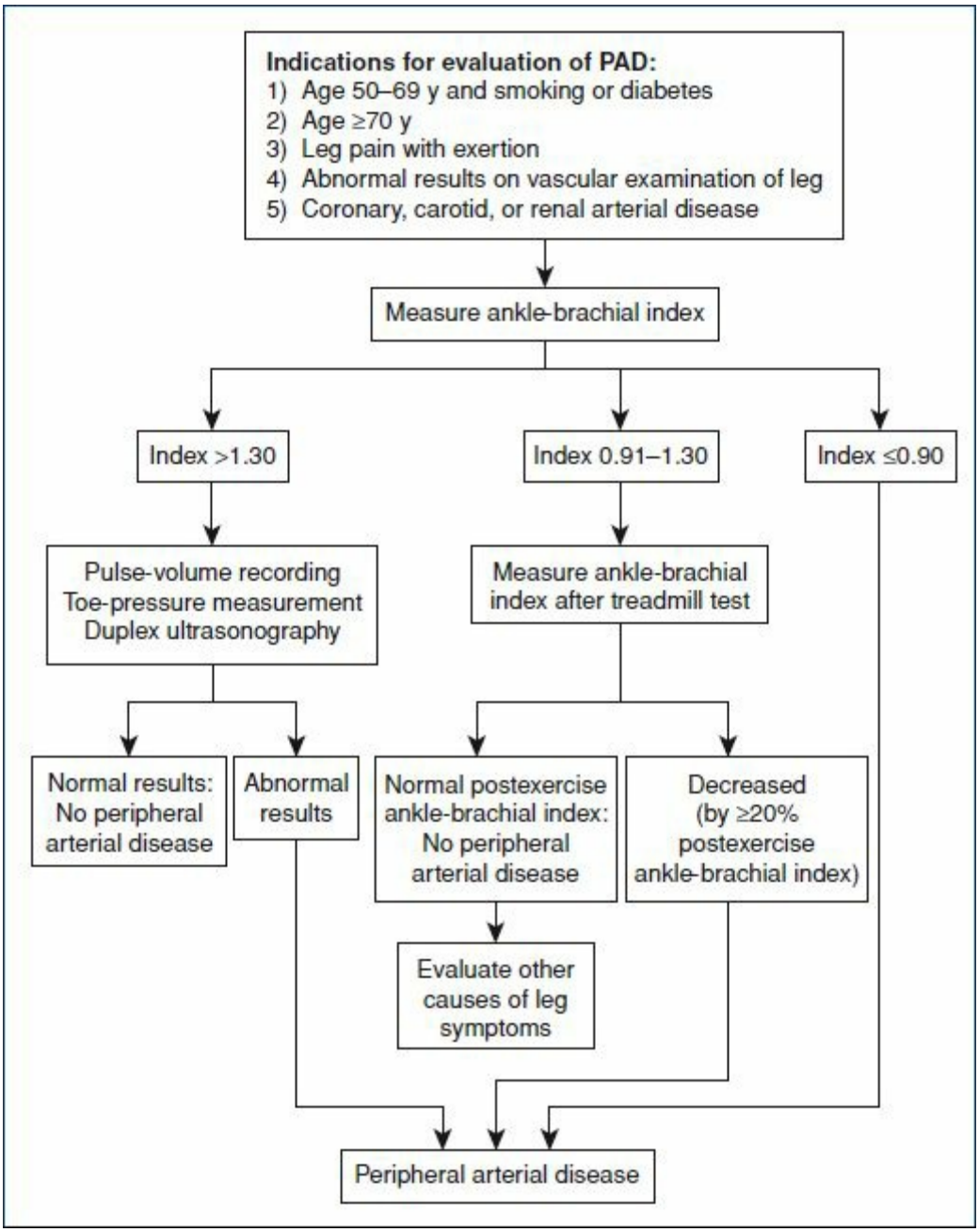


Figure 2-1 Evaluation of PAD (Adapted from *NEJM* 2001;344:1608)

## Treatment (*Circ* 2006;113:1474; *J Vasc Surg* 2007;45:S5; *Mayo Clin Proc* 2008;8:944)

- **Goals:** Sx relief, mgmt of related CV diseases (CAD, stroke)
- **Risk factor modification:**
  **Smoking:** Cessation ↓ progression, rates of amputation, incidence of rest ischemia
  **DM:** Goal A1c <7%
  **HTN:** Goal BP <140/90, <130/80 in diabetics; consider ACEI & βB therapy
  **Dyslipidemia:** Target LDL-C <100 mg/dL, <70 mg/dL in pts w/ PAD/CAD
  **Rehab:** Exercise program can ↑ walking distance by 100–150%, comparable to surgery
- **Pharmacologic therapy**
  **Anti-PLT:** ASA 81 mg or clopidogrel (CAPRIE suggests clopidogrel superior (*Lancet* 1996;348:1329))
  **Cilostazol (PDE inhibitor):** Indicated for critical limb ischemia, refractory claudication
  **Naftidrofuryl:** ↑ the time to initial pain development in pts w/ subclinical disease
- **Revascularization:**
  **Indications:** Claudication that interferes w/ activity, ischemic rest pain, nonhealing ulcer/gangrene
  **Endovascular:** 1st choice due to ↓ morbidity/mortality compared to surgery
  **Surgery:** Indicated if endovascular approach is not possible or if recurrent failure of endovascular approach occurs
- **Patient information:** *JAMA* 2009;301:236

# PRE-FLIGHT ASSESSMENT

## Background (*AFP* 1999;60:801; *NEJM* 2000;342:1716; 2002;346:1067; *Lancet* 2003;361:1368)

- **Pathophysiology:** Air travel = physiologic stress: ↓ $PaO_2$ + ↓ cabin pressure by ~30%, dehydration, relative immobility, ↓ sleep, ↑ stress
- **General advice:** Most pts w/ well-compensated or stable disease can tolerate air travel w/o difficulty; see "*Travel Medicine*" for advice re: meds, jet lag, travel safety, etc

## Cardiovascular Disease (*Ann Intern Med* 2004;141:148)

- **Contraindications:** Recent ACS/PCI (<3 wks), unstable angina, decompensated HF, sx valvular disease (given ↓ $PaO_2$ in-flight), severe arrhythmias
  **AICD:** Pts should request hand search (theoretical risk screening wands may → firing)
- **Bring recent ECG** for cardiac disease, PPM or ICDs (w/ & w/o magnet) & recent office visit note w/ summary of medical hx (prior interventions etc.)
- **Indications for in-flight oxygen:** NYHA class III CHF, angina, cyanotic congenital heart disease, pulm HTN/right HF (*Can J Cardiol* 2004;20:1314)

## Pulmonary Disease (*Aviat Space Environ Med* 2003;74:A1)

- **Contraindications:** Recent pneumothorax, severe hypoxia; stable disease may require prearranged in-flight $O_2$ (*Thorax* 2002;57:289)

### Oxygen Saturation at Rest and Room air

| | |
|---|---|
| >95% | Supplemental $O_2$ not indicated |
| <92% | Supplemental $O_2$ indicated |
| 92–95% | W/o risk factors: supplemental $O_2$ not indicated |
| 92–95% | W/ risk factors: supplemental $O_2$ indicated |
| **Risk factors:** Hypercapnia, FEV1 <50%, severe cardiopulmonary disease, pHTN, recent hospitalization for pulm disease, inability to walk <50 m, cardiac/pulm/CVD | |

- **Home oxygen:** ↑ flow rate 1–2 L/min (*Chest* 2008;133:1002)

- **Asthma:** Carry β-agonist rescue inhalers & a course of steroids on the person
- **Cystic fibrosis and bronchiectasis:** May need abx & secretion-clearing medications; counsel to stay well-hydrated

## Thromboembolic Disease (*Chest* 2004;126:338; *JGIM* 2007;22:107)

- **Risk:** 2–4 × ↑ risk w/ prolonged air travel (↑ in flights >4 h): ↑ Venous stasis ± hemoconcentration, coagulopathy (*Ann Intern Med* 2009;151:180)
- **Prophylaxis:** For high-risk pts: Fitted compression stockings or single dose of LMWH; ASA alone ineffective; encourage frequent movement, adequate hydration, & ankle/knee exercises in all passengers; advise to request seats w/ more leg room (i.e., bulkhead or aisle)

## Infectious Disease (*Lancet* 2005;365:989)

- **Contraindications:** Active/contagious respiratory infections (e.g., TB, PNA, flu) & untreated severe sinusitis (i.e., ⊕ cultures) (*Lancet Infect Dis* 2010;10:176)
- **Uncomplicated URI/mild sinus infections:** Consider prophylactic decongestant due to pain, vertigo, even TM perforation

## Neurologic (*Aviat Space Environ Med* 2003;74:A1)

- **Contraindications:** Stroke <2 wks, uncontrolled seizure d/o
- **Migraines:** Can be triggered by air travel; carry prophylactic & rescue medications

## Other Considerations

- **Pregnancy:** No contraindication for uncomplicated pregnancies <36 wks gestation;
  pregnancy ↑ risk for DVT; prevention as described above (*Obstet Gynecol* 114:954)
- **Procedures:** Wait 2 wks for open surgery, 1 day for uncomplicated laparoscopic procedures or colonoscopy (*AFP* 1999;60:801)
- **Scuba diving:** Wait 12–24 h prior to flying if 1 dive/d, 24–28 h if multiple dives/d (*Aviat Space Environ Med* 1990;61:1130)

- **Immunizations and ID ppx:** See *"Travel Medicine"*
- **Patient information:** *AFP* 2006;73:1807

# PRE-OPERATIVE RISK ASSESSMENT

## Background (*NEJM* 2005;353:412)

- **Epidemiology:** 27 million pts undergo surgery each y in US; ~50K have peri-op MI
- **Pathogenesis:** (1) Volume shifts; (2) ↑ $O_2$ demand (stress); (3) Post-op ↑ PLT reactivity

## Evaluation (*Ann Intern Med* 2009;151:ITC1; *Circulation* 2009;120:e169; *JACC* 2007;50:e159)

- **History:** Hx heart disease, angina, CHF, AS, HTN, PAD, OSA, exercise capacity; meds (alt meds, NSAIDs, ASA, anti-PLT drugs), tobacco use, EtOH, drug/opiate abuse to prevent withdrawal; hx XRT to chest or cardiotoxic (i.e., doxorubicin, trastuzumab) or pulm toxic (e.g., bleomycin) medications; anesthesia reactions
  **Screening for bleeding d/o:** Easy bruising, profuse bleeding from minor injuries, FHx of bleeding d/o, bleeding into muscles/joints, epistaxis, bleeding w/ dental work, menorrhagia → if screen ⊕ consider hematology referral

**Functional Capacity** (*Circulation* 1981;64:1227)

**1 MET:** Independently eat, dress, toilet **4 METs:** Climb flight of stairs or hill, walk 4 mph, sex
**4–10 METs:** Heavy housework (scrubbing floors), moving heavy furniture, jog 5 mph
**>10 METs:** Swimming, tennis, basketball

- **Exam:** Carotid bruits, BP both arms, peripheral pulse, LE edema, JVP, wheezes, crackles
- **Workup: ECG** in high-risk pts (hx DM, CHF, CAD, stroke, PAD, CKD) undergoing high-/intermed-risk surgery or pts w/o risk factors undergoing vascular surgery; **CXR** if obese, hx cardiopulmonary dz, or if >50 y undergoing thoracic/abdominal surgery (*Ann Intern Med* 2006;144:581); ✓ **b-hCG;** other pre-op lab testing, including coags, generally not indicated in healthy pts <50 y undergoing low-risk

elective surgery (*Lancet* 2003;362:1749); ✓ **aPTT, PT, PLT** in surgery w/ ↑ bleeding risk (i.e., prostate, neurosurgery, ophthalmic, intrabdominal/thoracic, mastectomy, laparoscopy, arthroscopy); consider **PFTs** in pt w/ dyspnea of ? origin, hx COPD or asthma; consider **echo** if pt has dyspnea of ? origin or hx CHF w/ change in clinical status (including concern for severe pHTN or severe AS) & no echo in past 12 mos

## Assessment of Peri-operative Risk (*AFP* 2007;75:656; *Circulation* 2009;120:e169; *Eur Heart J* 2009;30:2769; *JACC* 2007;50:e159)

- **General rule:** Assessment incorporates predictors of cardiac risk: Revised Cardiac Risk Index (RCRI) or Gupta, functional capacity, surgery-specific risk, & results of stress testing/echo (when appropriate)
  **Emergency surgery:** Proceed to OR
  **Low-risk surgery:** Proceed to OR provided no cardiac contraindications (table below)
  **Mod-high risk surgery & functional capacity ≥4 METs, asx:** Proceed to OR provided no cardiac contraindications
  **Mod-high risk surgery & functional capacity <4 METs or unknown:**
  **No RCRI risk factors:** Proceed to OR provided no cardiac contraindications
  **1–2 RCRI RF:** Consider **b**B or stress test if it will Δ mgmt
  **>3 RCRI RF: Intermed-risk surgery:** Consider βB or stress test if it will Δ mgmt; **Vascular surgery:** Consider stress test if it will Δ mgmt

**Cardiac Contraindications to Nonemergent/Elective Surgery**

| | | | |
|---|---|---|---|
| **CAD:** Unstable/severe angina or recent MI (within 4–6 wks) | | | |
| **CHF:** Decompensated CHF, NYHA class IV CHF, worsening or new-onset CHF | | | |
| **Arrhythmias:** High-grade AV block, sx ventricular arrhythmias, supraventricular arrhythmias w/ rate >100 bpm at rest, sx bradycardia, new VT | | | |
| **Valvular heart disease:** Severe AS (i.e., sx or <1 cm), symptomatic MS | | | |
| **Cardiac Risk by Type of Surgery** (% cardiac death/nonfatal MI) | | | |
| **High risk (≥5%):** Aortic/major vascular surgery, peripheral arterial surgery | | | |
| **Intermed (1–5%):** CEA, head & neck, intraperitoneal/thoracic, orthopedic, prostate surgery | | | |
| **Low risk (≤1%):** Outpt surgery, endoscopy, cataract & breast surgery, dental procedures | | | |
| **RCRI risk factors** | **Class** | **#Risk Factors** | **Cardiac Risk*** |
| Diabetes treated w/ insulin | I | 0 | 0.4% |
| Cr > 2.0 | II | 1 | 0.9% |
| Hx HF | III | 2 | 6.6% |
| Hx CVD | IV | ≥3 | 11% |
| High-risk surgery (intrathoracic/peritoneal, suprainguinal vascular) | | | |
| Hx MI or ⊕ ETT, current nitrate Rx, CP due to CAD, ECG w/ pathologic Q-wave† | | | |

*Cardiac death, nonfatal MI, nonfatal cardiac arrest; †Hx coronary revascularization does not count unless other criteria for ischemic heart dz present (*Circulation* 1999;100:1043)

**Cardiac risk by type of surgery (% cardiac death/nonfatal MI)**


| | | | |
|---|---|---|---|
| **High risk (≥5%):** Aortic/major vascular surgery, peripheral arterial surgery | | | |
| **Intermed (1–5%):** CEA, head & neck, intraperitoneal/thoracic, orthopedic, prostate surgery | | | |
| **Low risk (≤1%):** Outpt surgery, endoscopy, cataract & breast surgery, dental procedures | | | |
| **RCRI risk factors** | **Class** | **#Risk Factors** | **Cardiac Risk*** |
| Diabetes treated w/ insulin | I | 0 | 0.4% |
| Cr > 2.0 | II | 1 | 0.9% |
| Hx HF | III | 2 | 6.6% |
| Hx CVD | IV | ≥3 | 11% |
| High-risk surgery (intrathoracic/peritoneal, suprainguinal vascular) | | | |
| Hx MI or ⊕ ETT, current nitrate Rx, CP due to CAD, ECG w/ pathologic Q-wave† | | | |


- **Limitations:** Does not predict all-cause mortality, excludes emergency surgery; ↓ sensitive methods (CK-MB) used in MI dx; ↓ accuracy for AAA, vascular surgery
- **Gupta/NSQIP risk calculator:** surgicalriskcalculator.com/miorcardiacarrest; outperforms RCRI (*Circulation* 2011;124:381)
- **Stress testing:** ETT preferred; generally, stress testing has a high NPV for peri-op CV events & a low PPV → ⊖ testing identifies pts at low risk while ⊕ testing does not necessarily identify high-risk pts; see

*"Chest Pain & Noninvasive Testing"* for details

**Not indicated if:** No cardiac sx, functional capacity ≥4 MET undergoing low- or intermed-risk surgery; pre-op testing has not been shown conclusively to change outcomes & may lead to unnecessary testing & intervention for stable CAD

**Indicated if testing will change mgmt:** Pts w/ ≥1 RCRI risk factor & functional capacity ≤4 MET undergoing intermed risk or higher surgery; pts w/ ≥1 RCRI risk factor & functional capacity ≥4 MET undergoing vascular surgery

- **Echocardiogram:** Useful in pts w/ hx CHF, dyspnea, pHTN, valvular heart disease, or pathologic murmur
- **Angiography:** Decision based on results of stress test/echo, or if pt has an indication independent of need for surgery (i.e., ACS, uncontrolled angina)

## Management of Peri-operative Risk (*AFP* 2012;85:239; *JACC* 2007;50:e159; 2009;54:2102)

- **Revascularization:** Pts w/ UA, MI, left main/3v disease, or 2v disease w/ proximal LAD stenosis, LV dysfunction/ischemia on stress testing; benefit of revascularization weighed against risk of d/c anti-PLT agent peri-op; cardiology consultation advised

### Management of Recent Percutaneous Coronary Intervention

| |
|---|
| **Balloon angioplasty:** <14 d → delay surgery >14 d → ASA |
| **Bare mental stent (BMS):** < 30–45 d → delay surgery >30–45 d → ASA |
| **Drug-eluting stent (DES):** <1 y → delay surgery when possible<br>>1 y → if low bleed risk & ↑ CV risk, continue ASA; o/w, hold ASA & clopidogrel 7–10 d prior to surgery & resume 24 h after surgery if sufficient hemostasis |

- **Beta-blockers:** Controversial (*Am J Med* 2012;125:953; *JAMA* 2010;303:551); ↓ peri-op MI, ↑ stroke & total mortality (POISE, *Lancet* 2008;371:1839); in retrospective cohort analysis of pts undergoing noncardiac, nonvascular surgery, peri-op βB ↓ all cause mortality in pts w/ >2 RCRI risk factors; for RCRI = 2, NNT = 105, RCRI = 3, NNT = 41, RCRI = 4 NNT = 18 (*JAMA* 2013;309:1714); consider initiating 2–4 wks prior to surgery in pts who should be on a βB or who have CAD, stable angina, or >1 RCRI risk factor undergoing intermed or high-risk surgery (*NEJM* 2005;353:349); discuss

risks/benefits w/ pt & document; continue βB in pts already on; titrate to HR 60–70 bpm; continue for 1 mo after & taper carefully if discontinuing; β1 selective agents preferred due to less HoTN

- **Statins:** Continue if pt already on & initiate early in surgery in pts who should be on (see *"Dyslipidemia"*); consider initiating in pts undergoing vascular surgery regardless of risk factors
- **Congestive heart failure:** Typically continue ACEI & diuretics; consider short-acting ACEI (i.e., captopril)
- **Diabetes mellitus:** Pts should hold PO DM2 medications the morning of surgery; insulin requirement varies w/ length of surgery/NPO status, whether IV or SC sliding scale insulin is used intraoperatively (*AFP* 2003;67:93); pts w/ DM1 require basal insulin to prevent DKA even if not eating–dose often halved
- **History of stroke:** Incidence of peri-op stroke varies w/ type of surgery (0.08–0.7% general surgery to 8.7% aortic repair) (*NEJM* 2007;256:706); >2 wks should pass between stroke & surgery
- **Herbal meds:** ↑ Bleeding w/ garlic, ginkgo, ginseng; ↓ glucose w/ ginseng; CV complications w/ ephedra; interaction w/ sedatives & other drugs by kava, valerian, St. John's Wort (*JAMA* 2001;286:208)
- **Tobacco:** Meta-analysis shows cessation prior to surgery ↓ post-op complications by 41% & each add'l wk of cessation ↑ effect by 20% (*Am J Med* 2011;124:144); breathing exercises, incentive spirometry
- **Pacemakers:** Consult cardiology for programming during surgery & post-op interrogation
- **Rheumatoid arthritis, ankylosing spondylitis, or chronic steroids:** Risk of C-spine injury during intubation 2/2 atlantoaxial instability; consider flex/ext C-spine films (*Ann Intern Med* 2009;151:ITC-1)

## Medication Management (*Chest* 2008;133:299; 2012;141:e326S; *NEJM* 1997;336:1506)

- **Anticoagulation:** Risk of thromboembolism balanced against risk of bleeding

  **High risk of thrombosis:** AF &: Valvular heart disease, CHF, EF <35%, hx clot, HTN, DM2, or age >75 y; mechanical valves in mitral position or prior clot; coronary stent in last y, recent MI, non-stented PCI after MI (*Gastrointest Endosc* 2009;70:1060)

**Low risk of thrombosis:** DVT, chronic/paroxysmal AF w/o valvular disease or risk factors above, bioprosthetic valves, aortic mechanical valve

**Low-risk surgery (i.e., arthrocentesis, cataract surgery, outpt dental surgery, minor dermatologic procedures):** Continue warfarin w/ INR goal at low end of therapeutic goal (*Arch Intern Med* 2003;163:901); continue ASA (*Chest* 2012;141:e326S)

**High-risk surgery (i.e., neurosurgery, urologic procedures), low risk of thrombosis:** D/c warfarin 5 d prior to surgery to allow INR to fall ≤1.5, & resume when safe, ideally 12–24 h post-op; consider *prophylactic* heparin/LMWH bridge to prevent rebound hypercoagulability when warfarin d/c'ed or hypercoagulability due to surgery

**High-risk surgery, high-risk clotting:** Therapeutic LMWH/heparin bridge

**Interrupting dabigatran:** Hold 1–2 d pre-op for CrCl ≥50, 3–5 d for CrCl <50; when ready to resume, onset of action is rapid (2–3 h) (*Thromb Haemost* 2010;103:1116)

**VTE:** Postpone elective surgery for 1st mo on warfarin, when recurrence risk highest

- **Antihypertensives:** Generally continued until time of surgery; clonidine & βB assoc w/ withdrawal syndrome (*JAMA* 2002;287:2043)
- **Aspirin:** Pts on ASA for CAD, stents, or PAD or at mod/↑ risk of peri-op CV mortality should generally **continue ASA**; hold for surgery w/ ↑ bleeding risk (neurosurgery, prostate surgery); pts w/ ↓ peri-op CV risk should d/c ASA 7–10 d prior to surgery; resume 24 h after surgery if sufficient hemostasis (*Chest* 2008;133:299; 2012;141:e326S)
- **Clopidogrel:** Pts at low risk of CV events should d/c 7–10 d prior to surgery; resume 24 h after surgery if sufficient hemostasis
- **Oral contraceptive pills:** Consider holding 4–6 wks prior to surgery w/ ↑ risk of VTE (use alt contraception)
- **Corticosteroids:** Generally, pts on chronic steroids should continue on day of surgery; consider stress dosing if pt on >20 mg prednisone/equiv for >3 wks & major surgery
- **Steroid stress dosing** (Adapted from: *Ann Intern Med* 2009;151:ITC-1)
  **Major surgery (CT surg, oncologic, intra-abdominal):**

Hydrocortisone 100 mg IV q8h × 3 doses → 50 mg IV q8h × 3 doses → 25 mg IV q8h × 3 doses → outpt dosing

**Intermediate-risk surgery (orthopedic, urologic, ENT):** Hydrocortisone 50 mg IV q8h × 3 doses, then 25 mg IV q8h × 3 doses, then outpt dosing

**Minor surgery (cataract, outpt):** Outpt dosing day of surgery, double 1st post-op dose

- **Patient information:** *JAMA* 2007;297:2158; *Ann Intern Med* 2009;151:ITC-15

## Commenting on Peri-operative Risk

| |
|---|
| [Pt's name] is seen for peri-operative risk stratification. [Pt] reports no sx of CP at rest or w/ exertion, dyspnea at rest or w/ exertion, PND, LE edema, claudication, & palpitations. [Pt] has no history of (ischemic heart disease, CHF, CVD, diabetes, EtOH/drug abuse, recent anticoagulant or antithrombotic use, personal or FHx of coagulopathy, or CKD). [Pt] reports no hx (undergoing a stress test, cardiac cath, or coronary revascularization either percutaneously or surgically). [Pt] reports being able to achieve __ METs of activity during (describe activities). |
| This pt's cardiac risk factors include __. According to the RCRI, this number of risk factors stratifies the pt to Class __, which carries w/ it a __ percent risk of major CV complications, such as MI, CHF, or malignant arrhythmia (*Circulation* 1999;100:1043). In this case, however, the RCRI likely under- (or over-) estimates the pt's true cardiac risk given his/her history of __. |
| These risks, along w/ the risk of peri-operative stroke, were discussed w/ the pt, in light of the benefits of possible surgery. [Pt] wishes to proceed w/ the operation. This assessment was conveyed to the surgery & anesthesia teams. |

# SPORTS AND EXERCISE CLEARANCE

## Background (*AFP* 2010;81:55; *JAMA* 2003;289:2913; 2005;294:3011)

- **Exercise recommendations:** 30 mins of physical activity on most days & preferably all days, or 20 mins of vigorous physical activity 3×/wk (*JAMA* 1995;273:402); ~50% of adults in US participate in regular physical activity (*JAMA* 2008;299:30)
- **Benefits of exercise:** Pts w/ highest level of physical activity have a 30–40% ↓ in the risk of CV disease compared to pts w/ lowest level, regardless of age, race, or gender (*Circulation* 2010;122:743); exercise ↓ risk of HTN, HLD, DM2, obesity, osteoporosis, stroke, depression, anxiety, & some cancers; inactivity → 5.3 million deaths annually worldwide (*Lancet* 2012;380:219)
- **Risks of exercise:** Risk of SCD in healthy pts is ~1/1.51 million episodes of vigorous exertion (*NEJM* 2000;343:1355); ~1/200,000 young athletes/y (*Circulation* 2007;115:1643), perhaps higher in college athletes (*Circulation* 2011;123:1594)
  **Long-distance running:** Cardiac arrest rate of 0.54/100,000 marathon & half-marathon participants, majority due to CAD or HOCM (*NEJM* 2012;366:130)
- **Common pathologies encountered with physical activity:**
  **Young adults:** (HOCM, 0.2% prevalence in population), coronary artery anomalies, ostial malformations, aortic aneurysms, bicuspid AV, myocarditis, undiagnosed Marfan, congenital aortic/pulmonic stenosis; arrhythmias (long QT, Brugada, WPW)
  **Older adults (>35 y):** CAD → MI or ischemic arrhythmia
  **Exercise-induced bronchoconstriction:** Asthma spectrum (see *"Asthma"*) (*AFP* 2011;84:427)
  **Concussion:** Immediate, reversible LOC after head trauma w/ brief period of amnesia (see *"Concussion"*)
  **Commotio cordis:** Blunt impact to chest (hockey puck, baseball, bodily collision) → V-Fib & SCD; prevent w/ chest protection, access to AEDs (*NEJM* 2010;362:917)

## Evaluation (*NEJM* 2003;349:1064)

- **Guidelines:** ACC/AHA recommend 12-step hx/exam (below)

**ECG:** Adding ECG is cost-effective ($42,900/y of life saved) (*Ann Intern Med* 2010;152:276); European society of cardiology & Olympic committee recommend ECG (*Eur Heart J* 2005;26:1422); adding ECG to H&P improves Se (99.8%) but ↓ Sp (false ⊕ rate 9.6%) (*Heart* 2011;97:1573)

- **History:** Exercise hx, current peak activity level, hx heart disease, syncope, pulm disease, dyspnea, injuries, surgery, concussion; medications (incl OTC, herbal, supplements); illicits; screen for eating d/o; FHx of cardiac disease, arrhythmia, SCD
- **Exam:** Major joints, scoliosis, Marfan features, cardiac exam (esp listening for murmurs)

**AHA 12-step Preparticipation Screening of High-school & College Athletes**

| | |
|---|---|
| **Personal History** (*Circ* 2007; 11512: 1643) | **(1)** Exertional CP/discomfort; **(2)** Syncope or near syncope; **(3)** Excessive exertional or otherwise unexplained dyspnea/ fatigue; **(4)** Hx heart murmur; **(5)** HTN |
| **Family History** | **(6)** Premature death related to heart disease or SCD; ask about drownings, car accidents, specific syndromes to ↑ recall; **(7)** Disability from heart disease in close relative <50 y; **(8)** Knowledge of FHx of hypertrophic/dilated CMP, ion channelopathy, long QT, Marfan, or arrhythmias |
| **Physical Exam** | **(9)** Murmur (listen supine & sitting, looking for signs of LVOT obstruction); **(10)** Femoral pulses to r/o aortic coarctation **(11)** Stigmata of Marfan; **(12)** Brachial artery BP (seated) |

- **Cardiology referral:** If abnl exam, FHx suspicious for SCD, or concerning factors found in 12-step exam; consider noninvasive testing (echo); pt should not be cleared to participate prior to cardiology clearance; recommendation for sports clearance & allowed sports for pts w/ cardiac disease vary by condition (*Am J Med* 2012;125:742)
- **Documentation:** Screening exam should be complete prior to signing any clearance paperwork (*JAMA* 2005;294:3011); document: "Pt is seen in consultation for exercise/sports clearance, & underwent the 12-step AHA preparticipation screening which revealed (no abnormalities) that would preclude participation in (sport); pt was counseled in preventative measures specific to sport, i.e., wearing a helmet." HIPAA-compliant release necessary for provider to disclose

info to party other than pt

## Evaluation of Specific Populations

- **Physical activity prescription or clearance** (*JAMA* 2003;289:2913):
  **Previously inactive pts:** Begin w/ short duration, moderate-intensity exercise & ↑ duration as tolerated; pts w/ DM2 or cardiac risk factors (♂ >40 y, ♀ >55 w/ >2 CAD risk factors (see "*Coronary Artery Disease*")): ETT prior to vigorous exercise program
  **Chronically ill:** Initiate exercise as for previously inactive pts *unless:* Severe HTN, arrhythmias, uncontrolled metabolic disease, high-degree AV block, UA, severe AS, recent ECG changes/cardiac events, acute myocarditis/pericarditis, DM2 starting vigorous exercise, or fall risk
  **Pts w/ cardiac disease (EF <50%, ischemia/arrhythmia w/ exercise, >50% stenosis coronary artery):** Cards eval prior to exercise (*JACC* 2005,45:1348); pts s/p MI or PCI can return to sports after 4–6 wks, specific cardiac rehab program recommended for all; post-CABG pts may exercise after 4–6 wks provided sternal wound is stable
  **Mitral valve prolapse (MVP):** May participate in all competitive sports, *provided* (1) No hx syncope due to arrhythmia; (2) No FHx of SCD; (3) No recurrent arrhythmias; (4) Absence of mod to marked MR; (5) No prior embolism (*JACC* 1994;24:845)
  **Known predisposition to SCD, arrhythmia, Brugada syndrome, HOCM, long-QT, Marfan:** Detailed recommendations by 36th Bethesda Conference (*JACC* 2005;45:1313); cardiology consultation advised

## Counseling (*JAMA* 2003;289:2913)

- **Moderate-intensity exercise** defined as (1) Able to speak but not sing while exercising; (2) Maximum HR 65–75% of age-adjusted maximal HR (220-age) (*AFP* 2006;74:437)
  **Potential activities:** Brisk walk (i.e., outside or in the mall during winter), YMCA, yoga, tai chi, stair climbing, stationary bike, arm curls w/ wt every time there is a TV commercial, dancing, golf, tennis, vacuuming, jogging, calisthenics

**5A's of Provider Exercise Counseling***

| |
|---|
| **Assess:** Eval pts current level of exercise/activity |
| **Advise:** Relate current health to activity benefit (i.e., exercise will help your BP) |
| **Agree:** Agree w/ pt if they are planning exercise plan & address barriers; set goals for duration, intensity of exercise |
| **Assist:** Help pt in developing strategies to achieve goals; involve nutrition, PT |
| **Arrange f/u:** Either appt or have someone from the office call to check how pt is doing & if there is anything that can be done to optimize care |

*see "*Patient Counseling*" for further strategies

- **Patient education:** *AFP* 2006;74:2095; 74:2097 (getting started w/ exercise), *JAMA* 2011;306:114 (concussion); *JAMA* 2005;294:3048 (fitness), shapeup.org

# SUDDEN CARDIAC DEATH

## Background (*Circulation* 1998;98:2334; *NEJM* 2001;345:1473)

- **Definition:** Unexpected natural death from a cardiac cause occurring soon (≤1 h, typically) after the onset of sx in an individual w/o other cause of death
- **Epidemiology:** 300,000–400,000 cases/y, accounts for >50% of all cardiac deaths in US; in pts <35, usually 2/2 congenital heart disease; If >35, usually due to CAD
- **Risk factors:** CAD, CHF, inherited d/o (e.g., WPW, long QT)
- **Pathophysiology:** Predisposing condition (anatomic, functional) + transient factor (electrolytes, ischemia); 1° arrhythmia is typically VF, VT, or VT → VF; bradyarrhythmias are thought to cause only 7% of SCD

## Evaluation

- **Evaluation: Sx:** Palpitations, CP, **syncope** (esp exertional syncope or syncope from a nonvagal mechanism), **PMHx;** CHF, CAD or s/sx of these; tx w/ QT-prolonging meds, **FHx** SCD, ventricular arrhythmia, structural heart disease, drowning, or unexplained car accidents
- **Exam:** Signs of HF, valvular disease, hypertrophic changes, particularly HOCM
- **Initial workup: ECG** (prior MI, conduction delays [incl LBBB ≠ QT],

LVH, vs. ectopy); **TTE:** (If ↑ suspicion for HF or HOCM), **stress test** (if intermediate prob CAD, see *"Chest Pain and Noninvasive Testing"*, or if indicated for sports clearance (see *"Sports and Exercise Clearance"*); further w/u per cardiology may include cardiac MRI for arrhythmogenic right ventricular CMP (ARVC)

## Management

### Acquired Disorders

| |
|---|
| **HF:** Many pts w/ EF ≤35% qualify for ICDs; cards consultation advised |
| **Drug-induced QT prolongation:** azcert.org contains a continually updated list of drugs known to affect the QT interval; if QT prolonged at baseline, d/c culprit medication |
| **CAD or hx MI:** See *"Coronary Artery Disease"* for 2° prevention |
| **Electrolyte abnormalities:** Monitor Mg, K in pts w/ renal failure or on diuretics, esp if baseline ECG is abnl (see *"Potassium disorders"*) |

### Inherited disorders (cardiology or EP consultation advised)

**HOCM:** Asymmetric septal hypertrophy → outflow tract obstruction; prevalence of 1/500, yearly incidence of SCD of 2–4% in adults & 4–6% in children (*NEJM* 1997;336:775); *S/sx:* Palpitations, syncope (often exertional), & classic HF sx, but may be asx
**Exam:** Diffuse, laterally displaced PMI, S4, paradoxically split S2, harsh crescendo–decrescendo systolic murmur at the left sternal border (w/o radiation to neck or axilla) worsened by Valsalva & standing, often w/ an assoc MR murmur
**ECG:** LVH & other chamber enlargement, Q-wave in I, aVL, V4–V6; abnl ECG found in 95% of pts (*JAMA* 2002;287:1308)
**TTE:** Asymmetric LVH, systolic anterior motion of the posterior mitral leaflet, & dynamic LVOT obstruction induced during vagal maneuvers in ¼ pts
**Mgmt:** AV nodal agents to improve diastolic filling & ICDs in selected pts

**WPW:** Accessory tract bypasses AV node → substrate for SVT; when in AF, risk of rapid conduction down the bypass tract → VF; *S/sx:* sustained palpitations, anxiety, occasionally syncope or SCD; exam typically unrevealing
**ECG:** Shortened PR interval & slurred upstroke of the QRS (δ waves); risk stratification may require EP study
**Mgmt:** RF catheter ablation of the accessory tract in selected individuals

**Congenital Long QT Syndrome (LQTS):** Mutations in Na or K channels → prolonged myocyte depolarization (↑ QT) → *torsades de pointes;* p/w syncope or may be asx
**ECG:** Prolonged QT/QTc (>440 ms ♂, >460 ms ♀); pts w/ baseline QTc >500 are considered at high risk for SCD
**Mgmt:** βB & ICD implantation in sx or high-risk pts

**Arrhythmogenic right ventricular dysplasia:** Fibrous replacement of the RV → dilatation & failure; 1% of adults (*Am J Med* 2012;125:742); *S/sx:* Dizziness, palpitations, syncope, or CP
**ECG:** TWI in V1–V3, ε waves, RBBB, & prolonged QRS
**Cardiac MRI:** E/o fatty infiltration, scarring, dilation/dysfunction of RV
**Mgmt:** ICD implantation ± antiarrhythmic drugs

**Brugada Syndrome:** Mutations → ↓ Na current; *S/sx:* Syncope, palpitations, SCD, polymorphic VT, or asx, may have ⊕ FHx
**ECG:** Pseudo RBBB in w/ ST ↑ in V1–V3 (type 1) or a "saddle-back" morphology, most prominent in V2 (types 2 & 3); may be transient/only in context of inciting factors: Meds (antiarrhythmics, antidepressants, βB), fever, EtOH, cocaine, electrolyte disturbances
**Mgmt:** EP referral for risk stratification & possible ICD implantation

# SYNCOPE

## Background (*Eur Heart J* 2009;30:2631; *NEJM* 2000;343:1856; 2002;347:878)

- **Definition:** Abrupt, brief, total LOC & postural tone w/ spontaneous recovery **Presyncope:** Prodrome to LOC, lightheadedness **Reflex/neurocardiogenic syncope "fainting":** Includes vasovagal, situational syncope (i.e., in relation to blood draw, micturition, or cough) & carotid hypersensitivity; neurally mediated vasodilatation/bradycardia → HoTN
- **Epidemiology:** 1–3% of ED visits, 11–33% lifetime risk, ↑ w/ age; orthostatic HoTN found in up to 20% pts >65 y w/ incidence ↑ w/

age (*Am J Med* 2007;120:975)

- **Etiology:** Unexplained (34–39%), vasovagal (14–21%), cardiac (10–18%), orthostatic (10%), neuro (7–10%), situational (3–5%), medications (3%), Ψ (1–2%), carotid hypersensitivity (1%) (*Ann Intern Med* 1997;126:989; *Med Clin North Am* 2001;85:423)
- **Pathogenesis:** ↓ Perfusion to cerebral cortex or reticular activating system → LOC
- **Differential diagnosis:** *CV:* Valvular heart disease (i.e., AS), PE, CAD, pHTN, subclavian steal, aortic dissection, CMP, arrhythmia, tamponade, PPM failure;

*Neuro:* TIA/stroke, seizure, atypical migraine, SAH, cataplexy, drop attacks;

*Other:* Falls, hemorrhage (GIB, ruptured aortic aneurysm, spleen, ectopic pregnancy, or ovarian cyst), orthostasis, reflex/vasovagal, hypoglycemia, Ψ, anaphylaxis, meds, EtOH, illicit, hyperventilation/hypocapnia, postexercise HoTN

## Evaluation (*AFP* 2011;84:640; *Ann Intern Med* 2011;155:543; *Circulation* 2006;113:316)

- ***Hx/PE:*** Does episode meet definition of syncope? Prior episodes? What was pt doing before episode? Does pt remember hitting ground? *Assoc sx:* CP, dyspnea, palpitations, prodrome; *Provocative factors:* exertion, changing position, eating, coughing, sneezing, swallowing, anxiety, pain, defecation/micturition; collateral historians; medication Δs; FHx of cardiac disease, SCD

### Clues for Syncope in the Patient History (*Eur Heart J* 2009;30:2631; *JACC* 2002;40:142)

| |
|---|
| **Reflex (vasovagal):** Nausea, warmth, diaphoresis, pallor, lightheaded, fear, pain, emotional distress, instrumentation (i.e., blood draw), or prolonged (>20 mins) standing |
| **Seizure:** Aura, injury, tongue biting, incontinence, postictal state, seizure activity |
| **Arrhythmia:** Palpitations; syncope while sitting or supine; usually sudden & unheralded |
| **Orthostatic HoTN:** ↓ volume (diarrhea, GIB, vomiting, fever), dysautonomia (DM2, amyloid, Parkinson, Shy–Drager, EtOH, prolonged bed rest), adrenal insufficiency, POTS; may present as fatigue/cognitive impairment in elderly |
| **Drugs:** Medication changes or new medications? Vasoactive (αB & βB, CCB, nitrates, anti-HTN), diuretics, digoxin, EtOH, antidepressants, sedatives, erectile dysfunction medications, insulin; antiemetics, anti-arrhythmics, or antipsychotics (↑ QT) |

- **Exam/workup:** Orthostatic VS, cardiac, pulm, neuro exam; survey body for trauma; ✓ tongue for injury; ✓ for carotid bruits; ✓ volume status (JVP, mucous membranes, skin tenting); consider rectal exam & FOBT if GIB suspected; ✓ UE vs. LE BP & pulse if subclavian steal suspected
  **Orthostasis:** ↓ SBP by ≥20 mmHg or ↑ HR ≥20 bpm from supine to standing; Standing → pooling of 0.5–1 L blood in LE/splanchnic circulation
  **Carotid massage:** Consider in pts >40 y (avoid in pts w/ hx carotid stenosis/bruits, severe arrhythmia, acute MI or TIA/stroke); *Unilateral* pressure to angle of jaw for 5–10 s; ⊕ test: relative ↓ SBP ≥50 mmHg (vasodepressor), asystole ≥3 s (cardioinhibitory), or both (mixed); perform in monitored setting w/ IV access (*JAMA* 2004;292:1221)
  **ECG findings:** Bradycardia, tachycardia (usually assoc w/ palpitations), AF/flutter, VT, AVB or BBB, abnl PR, QT, or QRS intervals, pauses, Brugada syndrome (RBBB + STE in V1–V3), Q-wave, low voltage, WPW (short PR + upsloping QRS); Δ from prior ECGs; **PE:** Right heart strain, S1, QIII, TWI in III
  **Tilt table testing:** Used to differentiate reflex syncope vs. orthostatic HoTN; First exclude arrhythmias in pts w/ heart disease

### Approach to Diagnostics in Syncope Evaluation

| Study | Yield | Patient Population (*Med Clin North Am* 2001;85:423) |
|---|---|---|
| H&P | 45% | Everyone |
| ECG w/ rhythm strip | 5% | Everyone |
| Echocardiogram | 5–10% | Known or suspected heart disease |
| ETT | 1% | Suspected CAD or exertional syncope; perform after ECHO |
| Holter | 19% | Heart disease, suspicion for arrhythmia, abnl ECG |
| Event recorder | 34% | Frequent syncope, suspicion for arrhythmia, ⊖ cardiac w/u |
| Implanted recorder | 59% | ⊖ cardiac w/u & tilt table, infrequent syncope |
| EP studies | 60% | Heart disease & suspicion for arrhythmia |
| EEG | 1–2% | Witnessed seizure, hx seizure, postictal state |
| Head CT | 4% | Focal neuro deficits, seizure, head trauma, suspected TIA |
| Tilt testing | 49% | Unexplained syncope, w/u o/w ⊖ |
| Labs (based on hx) | | INR if on warfarin, U/A + UCx if elderly consider β-hCG, CBC, Chem-12, $B_{12}$, AM cortisol, syphilis, HIV, HbA1c, BNP, 24 h urine Na |

## Management (based on cause) (*AFP* 2011;84:527; *NEJM* 2005;352:1004; 2008;358:615)

- **Red flags to consider hospitalization or intensive workup:** Known or suspected heart disease (CAD, CHF, AS); abnl ECG (see above); severe lab abnorm; FHx of SCD; syncope w/ exertion or when supine; syncope w/ palpitations, HA, CP, neuro deficits, or dyspnea; older age & multiple comorbidities; abnl exam; injury; absence of prodrome; new onset seizures; (*AFP* 2005;72:1492; 2011;84:640; *Ann Intern Med* 1997:127:76; *NEJM* 2000;343:1856)
- **Reassurance:** Pts w/ single reflex syncopal episode, normal ECG, & no red flags
- **Electrophysiology referral:** Pts w/ hx ischemic heart disease & arrhythmia, indication for ICD (see *"Congestive Heart Failure"*), bundle branch block w/ otherwise ⊖ w/u, or recurrent syncope w/ cardioinhibitory response on carotid massage
- **Neurology referral:** If seizure suspected
- **Orthostatic hypotension:** Hydration (2–2.5 L/d) & drink water rapidly (0.5 L in 5–15 mins → up to 20 mmHg ↑ SBP that lasts 1–2 h), stand slowly & in stages, avoid overheating, sleep w/ head of bed at 10–20° (useful in supine HTN), compression hosiery, exercise, tense legs while standing; respiratory measures & handgrips (*Lancet* 1992;339:897; *Neurology* 2007;69:582); if HoTN is postprandial, pts should avoid EtOH & large or carbohydrate-rich meals, & not stand or do vigorous activities after eating (*NEJM* 1983;309:81); d/c precipitating meds & use short-acting anti-HTN Rx (i.e., nitropaste) QHS when supine (*Lancet Neurol* 2008;7:451)
  - **Fludrocortisone:** ↑ Fluid retention & blood volume; titrate dose in 0.1 mg increments each wk; pts should keep log w/ orthostatic BPs; check supine BPs for HTN, monitor for edema & hypokalemia, avoid in ESRD, CHF (*Lancet Neurol* 2008;7:451); low-dose NSAIDs may augment effect
  - **Midodrine:** α1-agonist; monitor for supine HTN; pts should keep log w/ orthostatic BPs; monitor for anxiety, GI upset, urinary retention, tachyphylaxis, avoid in CAD; combination w/ fludrocortisone → synergistic effect (*JAMA* 1997;277:1046)
  - **Dietary Na/salt tabs:** Up to 10 g/d, esp if 24 h urine Na <170 mmol (goal = 150–200); contraindicated in hypervolemic states,

avoid in HTN

**Caffeine:** Administer in morning 100–250 mg (equiv to 2–4 cups of coffee); esp useful for postprandial HoTN (*NEJM* 1985;313:549)

**Erythropoietin:** May be useful in pts w/ anemia & low Epo levels; administer w/ iron supplementation (*NEJM* 1993;329:611); see *"Anemia"*

**Ephedrine/pseudoephedrine:** Do not take w/in 4 h of lying down

- **Preventing recurrent vasovagal syncope:** Physical counterpressure (cross legs & tense, abdominal, & gluteal muscles, grip 1 hand w/ another & pull away, leg pumps, squeeze objects w/ hands), avoid triggers, lie down w/ legs elevated when sx occur (*JACC* 2006;48:1652); role of support stockings, abdominal binders, liberalized fluid/salt intake, midodrine, & fludrocortisone unclear, but may be considered on case basis; paroxetine found in a small RCT to ↓ recurrent syncope (*JACC* 1999;33:1227)
- **Driving:** Document pt was counseled; DMV reporting requirements vary by state

**Driving Recommendations for Syncope**

| Etiology | Private Drivers | Commercial Drivers |
|---|---|---|
| Unexplained syncope (single episode) | No restriction unless absence of prodrome, occurrence during driving, or heart dz | After dx & tx established |
| Single reflex syncopal episode | No restrictions | No restriction unless during high-risk activity |
| Recurrent/severe reflex syncope (i.e., no prodrome, syncope during driving, no provocative factors) | Until sx controlled | Permanent restriction unless effective tx established |

(Adapted from: *Eur Heart J* 2009;30:2631; *Circulation* 1996;94:1147)

- **Prognosis:** Cardiogenic syncope assoc w/ 2-fold ↑ CV & all cause mortality, up to 10% in 6 mos & 50% in 5 y; no ↑ risk of CV or all-cause mortality w/ vasovagal syncope (*NEJM* 2002;347:878)
- **Patient information:** *JAMA* 2004;292:1260

# VALVULAR HEART DISEASE

## Mitral Stenosis (*NEJM* 1997;337:32; *Lancet* 2009;374:1271)

- **Etiology:** Rheumatic; calcification (ESRD or calciphylaxis); post-MV repair/replacement; congenital (mitral ring, parachute); rarely, myxoma; valvulitis (SLE, RA, amyloid, carcinoid); infiltration (e.g., mucopolysaccharidoses)

### Classification of Mitral Stenosis (*JACC* 2006;48:e1)

| Stage | Mean Gradient (mmHg) | MVA ($cm^2$) | PA Systolic (mmHg) |
|---|---|---|---|
| Normal | 0 | 4–6 | <25 |
| Mild | <5 | 1.5–2 | <30 |
| Moderate | 5–10 | 1–1.5 | 30–50 |
| Severe | >10 | <1 | >50 |

- **History:** *Pulm congestion:* Dyspnea, hemoptysis; volume overload, tachycardia (↓ diastolic filling), ↓ exercise tolerance (can't ↑ CO); *AF:* Loss of "atrial kick" (essential w/ ↑ LA pressure) can precipitate HF
- **Exam:** Soft, low-pitched mid-diastolic rumble at apex or in L lateral decubitus; loud, delayed S1 + opening snap (early diastolic, in expiration); **Maneuvers:** ⊕ by rapid exercise (e.g., sit-ups)
- **Workup: ECG:** Left atrial abnorm, AF, RVH (late stage); **CXR:** LA dilatation = straight upper L heart border, pulm congestion, ↑ main PA size; **Echo:** Transvalvular peak & mean gradients, valve area, restriction, & thickness of leaflets
- **Treatment:** Dietary (Na restriction), diuresis for pulm congestion; rate control to ↑ diastolic filling time (longer diastole)
  **Mechanical intervention:** Only in sx (NYHA Class II–IV) pts; success defined as 50% reduction of mean MV gradient & doubling MVA
  **Percutaneous balloon valvotomy:** Better w/ isolated MS w/ MVA $<1$ $cm^2/m^2$ BSA or $<1.5$ $cm^2$, contraindicated if heavily calcified valve & ≥mod MR
  **Surgical:** Valves generally replaced (not easily repairable); MVR indicated in pts w/ significant MR, severe valve distortion not amenable to percutaneous intervention; 10 y survival 70%; worse outcomes if ↓ CO, pHTN, & RV dysfunction

## Mitral Regurgitation (*NEJM* 1997;337:32; 2001;345:740)

- **Etiology:** Damage or distortion of MV apparatus; *Ischemic:* Acute, assoc w/ papillary muscle rupture; *Other:* Myxomatous/degenerative, MVP, IE, blunt trauma, rheumatic (33%), mitral annular calcification, congenital (mitral cleft), HOCM, DCMP
- **Presentation: AF** (↑ LA pressure); **Pulm congestion/CHF** (LA pressure → ↑ pulm pressures → fatigue, dyspnea); **RHF** (↑ LA pressure → pHTN → ↑ RV pressure)
- **Exam:** Loud, holosystolic, decrescendo murmur, radiating to the axilla; w/ posterior mitral leaflet prolapse or flail, regurgitant jet is eccentric & directed anteriorly, striking the LA wall adjacent to the aortic root, transmitting sound to the base; soft S1, low-pitched $S_3$ (tensing of papillary muscles & chordae tendineae), acute MR: S4, shorter murmur
  **Maneuvers:** ↑ w/ isometric exercise (e.g., handgrip); ↓ by strain phase of Valsalva
- **Diagnostic workup: ECG:** LAE, AF ± LVH, if pulm HTN may have RV strain pattern (late stages); **Echo:** Est of severity based on color Doppler, regurgitant volume/fraction
- **Treatment:** Avoid isometric exercises, keep BP low nl
  **Medical:** Dietary (Na restriction), BP control, diuresis; if AF, digoxin, βB
  **Anticoagulation:** Indicated if AF or prior thromboembolic events
  **Surgical:** Indicated (repair > > replacement) in sx disease, or consider if progressive LV dilation/dysfunction, recent-onset AF, pHTN; if AF, may have valve reconstruction + annuloplasty ± LA Maze procedure or RFA

## Mitral Valve Prolapse (*NEJM* 1997;337:32; *Circ* 2002;106:1355; *NEJM* 2010;363:156)

- **Etiology:** Thick, redundant myxomatous mitral leaflets & chordal elongation, if both leaflets involved/thickened: Barlow valve; **Bimodal distribution:** ♀ 15–30 y; ♂ >50 y
- **Presentation:** Often asymptomatic but can be assoc w/ syncope, atypical CP, SCD (rare); **Palpitations:** Related to PVCs, paroxysmal SVT & VT, AF
- **Exam:** Mid or late systolic click, after S1 (sudden tensing of slack,

elongated chordae tendineae or prolapsing mitral leaflet); **Maneuvers:** Earlier with standing, strain portion of Valsalva (↓ LV volume), diminishes w/ squatting & isometric exercises

- **Workup: ECG:** LA enlargement, nl, biphasic, or inverted Tw in II, III, or aVF; **Echo:** Quantify MR, est PA pressure, LV size/function
- **Treatment:** βB for CP & palpitations; **Surgical:** Valve repair if presence of significant MR & sx (or if ASx) (*NEJM* 2009;361:2261)

## Aortic Stenosis (*NEJM* 1997;337:32; *NEJM* 2002;346:677)

- **Etiology:** Represents 20% of all pts w/ chronic valvular disease, ♂ predominance
  **Valvular:** Calcific (age-related degenerative, most common), congenital (bicuspid or unicuspid); rheumatic (usually w/ AR & MV involvement)
  **Subvalvular:** LVOT obstruction, (i.e., HOCM or discrete congenital subaortic membrane)
  **Supra-valvular:** Ascending aortic narrowing (e.g., William syndrome)
- **Presentation and prognosis:** If AVA $<1$ cm$^2$, average survival time (AST) by symptoms:
  **Angina pectoris** (35% of pts)**:** $O_2$ mismatch due to ↑ myocardial mass; **AST:** 5 y
  **Exertional syncope** (15%)**:** Sudden ↓ in CO due to mechanical obstruction or arrhythmia; **AST:** 3 y
  **Exertional dyspnea** (50%)**:** Due to ↑ pulm capillary pressure; **AST:** 2 y
  **CHF:** Systolic & diastolic dysfunction; **AST:** 1.5–2 y
  **Cardiac cachexia:** Marked fatigability, weakness, peripheral cyanosis, orthopnea, PND, pulmonary edema; severe pHTN leading to RV failure
- **Exam:** Systolic *crescendo–decrescendo* ejection murmur (also consider PS); timing of murmur peak & not volume determines valve severity (early peaking → mild, late peaking → severe), murmur best heart at the base of the heart & radiated along the carotids; *Gallavardin phenomenon:* Radiation to apex *Pulsus parvus et tardus* w/ slow rise & delayed sustained peak (severe disease only)

Paradoxic splitting of $S_2$ w/ eventual loss of $S_2$ w/ severe disease; $S_4$ due to LVH

- **Workup: ECG:** LVH, ST-depression, TWI ("strain pattern") in I, aVL & V5–6; **Echo:** Serial evaluations of severity; natural progression w/ reduction of 0.1 $cm^2$/y & ↑ in mean gradient of 7 mmHg/y (*Circ* 2008;118:e523)

  **Dobutamine stress echo:** Eval of pts w/ sev AS & low gradients (low SV, usually due to LV systolic dysfunction) to determine LV myocardial reserve, confirm dx

  **Cath:** Eval for CAD prior to surgical intervention (incidence >50% in age >45 y), or confirm severity of AS if echo & PE or clinical findings do not correlate

**Classification of Aortic Stenosis** (*JACC* 2006;48:e1)

| Stage | Aortic Jet Velocity (m/s) | Mean gradient (mmHg) | AVA ($cm^2$) |
|---|---|---|---|
| Aortic Sclerosis | <2.6 | — | — |
| Mild | 2.6–3 | <20 | >1.5 |
| Moderate | 3–4 | 20–40 | 1–1.5 |
| Severe | >4 | >40 | <1 |

**Sclerosis:** Focal thickening or calcification of valve cusps w/ a peak transaortic velocity ≤2.5 m/s; determination of valve area, jet velocity; precursor to mild AS

- **Treatment:** Avoid strenuous activity, isometrics (even if asx); dehydration/hypovolemia

  **Medical:** βB, ACEI for HTN & CAD; NTG for angina (if not hypovolemic); statins do not ↓ progression or diastolic dysfunction (*Circ* 2010;121:306; *Cardiovasc Ultrasound* 2011;9:5); *Caution* w/ antihypertensive Rx in severe AS; stenosis limits cardiac ability to ↑ BP

  **Surgical:** Indicated in **symptomatic**/severe disease, or if progressive LV dilation, LVEF <50%, or aneurysmal, expanding aortic root or ascending aorta

  **Percutaneous valvuloplasty:** Temporary bridge to surgery for severely ill pts

  **Percutaneous valve replacement:** Only offered for high-risk

surgical pts; ↓ mortality but ↑ incidence of stroke & vascular events (*NEJM* 2010;363:1597; *AIM* 2010;153:314)

## Aortic Regurgitation (*NEJM* 1997;337:32; *NEJM* 2006;355:385)

- **Etiology:** Valvular vs. aortic root disease; *Valvular:* Congenital (bicuspid, VSD), myxomatous degeneration, endocarditis, rheumatic (usually w/ assoc MV disease), nonpenetrating trauma; *Aortic rooot:* Cystic medial degeneration & aortic dilation → leaflet malcoaptation, idiopathic, annuloaortic ectasia, osteogenesis imperfecta, severe HTN; retrograde type A aortic dissection, syphilis, ankylosing spondylitis
- **Presentation:** *Acute:* Pulm edema ± cardiogenic shock, diffuse ST changes on ECG; *Chronic:* Palpitations, exertional dyspnea, orthopnea, PND, excessive diaphoresis; anginal CP (usually unresponsive to NTG)
- **Exam:** Wide pulse pressure if severe; high-pitch, decrescendo diastolic murmur (shorter murmur w/ more severe AR); **Austin–Flint murmur:** Soft, low-pitch rumbling mid-diastolic murmur; Corrigan pulse ("water-hammer"), capillary pulsations if severe & chronic
  **Maneuvers:** Intensified w/ handgrip or squatting (↑ peripheral vascular resistance)
- **Workup: ECG** LVH, if severe → global ST depressions, TWI ("strain pattern") in I, aVL & V5–6; LA dilatation, QRS prolongation (assoc w/ poor prognosis); **Echo:** If severe, monitor LV function q6–12mos
- **Treatment:** Avoid isometric exercises; diuretics, vasodilators (ACEI, dihydropyridine CCB, hydralazine); SBP <140; Surgical replacement > repair (rare), indications: severe/symptomatic or if asymptomatic w/ LV dilation or dysfunction

# APPROACH TO SKIN LESIONS

## Background

- Being able to concisely characterize lesions is important for communicating w/ your colleagues & formulating your differential
- A complete cutaneous exam includes skin, mucosal surfaces, nails, hair, & LN (when appropriate)

## Approach to Describing Skin Lesions

- Every description must include a **primary lesion** (see below); 2° characteristics can be helpful, if applicable (e.g., scale/crust, desquamation)
- **History:** Duration, timing, sx, where/how did lesion(s) start, PMHx, medications
- Description should include **color, distribution,** and **grouping**
- Example: "The patient is a 46 year-old man w/ well-demarcated erythematous plaques w/ silvery scale on his extensor surfaces, scalp, & gluteal cleft" (psoriasis)

## Primary Lesions

- **Macule:** A small flat, nonpalpable lesion $<1$ cm (denotes color change or min textural change)
- **Patch** (or large macule): A flat, nonpalpable lesion $>1$ cm
- **Papule:** A small, palpable, solid lesion $<1$ cm
- **Plaque:** A larger elevated or depressed, often flat, palpable lesion $>1$ cm
- **Nodule:** A palpable rounded lesion that usually denotes deep dermal or SC process $>1$ cm
- **Tumor:** A palpable solid lesion either above or beneath skin's surface, usually $>2$ cm
- **Vesicle:** An elevated lesion that contains clear fluid $<0.5$ cm
- **Pustule:** An elevated lesion that contains purulent fluid $<1$ cm
- **Bulla:** A lesion that contains clear fluid $>0.5$ cm

## Distribution

- Generalized, flexural (AD), extensor (psoriasis), seborrheic: chest, scalp, upper back (tinea versicolor), acral (2° syphilis, RMSF), dermatomal (VZV), photoexposed (cutaneous lupus), follicular (folliculitis), bilateral LE (stasis dermatitis) vs. unilateral (cellulitis)
- Also consider areas of sparing (e.g., sparing of intertriginous folds can suggest contact dermatitis)

## Color

- White (milium), yellow (sebaceous hyperplasia), gray (argyria), blue (blue nevus), green (pseudomonas), violaceous (Kaposi sarcoma), red or erythematous
- Consider quality of erythema: Violaceous erythema (DM), beefy red erythema (candidiasis), bright red erythema (drug eruptions), dusky erythema (SJS–TEN)

## Secondary Lesion(s)—what are other components/descriptors?

- **Scale:** Quality (e.g., silvery: psoriasis, greasy: seb derm)
- **Lichenification:** Thickening of epidermis due to persistent scratching or rubbing, characterized by hyperpigmentation & marked hyperlinearity; implies chronicity
- **Erosion:** Loss of epidermis ± superficial dermis → dyspigmentation
- **Ulcer:** Loss of significant dermis or SC tissue → scar
- **Other:** Excoriations, fissures, exudate/crust, desquamation or "peeling"

## Grouping

- Linear (contact dermatitis), Herpetiform (herpes simplex), Annular: Ring-like w/ central clearing (tinea corporis), Polycyclic: Coalescing annular lesions (urticaria)

## Morphologic Warning Signs

- **Dusky (grayish to violaceous) erythema:** Impending necrosis esp of lesions w/ stellate or sharp borders (i.e., SJS/TEN, calciphylaxis, angioinvasive fungi)
- **Purple or violaceous nodules:** Leukemia, lymphoma, malignant

vascular tumors, Merkel cell, melanoma
- **Black lesions:** Cutaneous necrosis, melanoma

## The ABCs of Dermatology: A list of additional terms

- **Atrophy:** Thinned epidermis = cigarette paper-like skin (e.g., chronic corticosteroid use)
- **Blaschkoid:** Lesions that follow the "lines of Blaschko" or migration of embryonic cells; often represent genetic mosaicism
- **"Collarette of scale":** Thready ring of scale around a lesion implying previous pustule (e.g., folliculitis) or vesicle
- **Comedo:** Plugged follicular units; "open" or "closed" (the defining lesion of acne)
- **Dermal:** Denotes papules or nodules w/o surface change or scale
- **Dermatographism:** Linear, erythematous edematous plaques in places where skin is firmly stroked or scratched (form of mechanical urticaria)
- **Depigmented:** Absence of pigment (e.g., vitiligo) vs. hypopigmented (decreased pigment)
- **"Eczematous":** Definition of a reaction pattern; aka "dermatitis"; poorly defined erythematous patches w/ xerotic or waxy scale
- **Ephelides:** "Freckle"; small brown macule in sun-exposed areas in pts w/ fair skin; caused by ↑ melanogenesis
- **Erythroderma:** Generalized, occasionally confluent redness ± scaling of the skin; often w/ systemic sx
- **Folliculitis:** Inflammation of hair follicle, often manifesting as a pustule (e.g. Staph folliculitis)
- **Hyperkeratotic:** Hypertrophy of the stratum corneum marked by thickened scale
- **Induration:** Palpation reveals firm skin caused by inflammation of dermis ± fat
- **Impetigo:** Superficial skin infection caused by *S. aureus* toxin manifesting as honey-colored crusting or as bullae ("bullous impetigo")
- **Keloid:** Elevated, irregular (often "claw-like") firm scar, often pruritic or painful

- **Koebner phenomenon:** Skin trauma that induces new lesions (e.g., psoriasis)
- **Morbilliform:** Generalized, often blanchable & coalescing erythematous macules or thin plaques, w/o scale (classically viral exanthems or hypersensitivity drug eruptions); more specific/preferable to "maculopapular"
- **Nevus:** Lesion characterized by proliferation of melanocytes
- **Onychodystrophy:** Broad term to describe dystrophy of nail plate
- **Onycholysis:** Separation of nail bed from nail plate
- **Petechiae:** Pinpoint nonblanchable erythematous macules caused by extravasation of RBCs into the skin (thrombocytopenia)
- **Pedunculated:** Lesion on a thin stalk (neurofibroma)
- **Poikiloderma:** Hyperpigmentation + hypopigmentation + atrophy + telangiectasias
- **Purpura:** Nonblanchable; macular (RBC extravasation w/o inflammation → traumatic or hematologic issue) vs. palpable (inflammation of blood vessels → vasculitis)
- **Reticulate:** "Net-like" (livedo reticularis)
- **Sebaceous:** Denotes involvement of sebaceous glands (palms & soles lack them); all sebaceous glands (except ectopic glands) are assoc w/ hair follicles ("pilosebaceous")
- **Solar lentigo:** Brown macule in sun-exposed areas caused by melanocytic proliferation
- **Target lesion:** Erythematous round plaque w/ 3 zones of color Δ, center of lesion can be deeply erythematous or bullous (erythema multiforme)
- **Targetoid plaques:** Erythematous round plaque w/ 2 zones of color Δ
- **Telangiectasia:** Small dilated blood vessels (rosacea, CTD)
- **Verrucous:** Wart-like architecture (seborrheic keratosis, verruca vulgaris)
- **Xerosis:** Dry skin

# ACNE

## Background (*JAAD* 2009;60:S1)

- **Definition:** Chronic disease of pilosebaceous follicle, characterized by comedo formation & assoc inflammatory lesions
- **Epidemiology:** Affects nearly all adolescents; can persist into adulthood in up to 50%, particularly in ♀; severity ♂ > ♀ in adolescence; ♀ > ♂ postpubertal
- **Pathogenesis:** Multifactorial & includes aberrant follicular keratinization, hormonal influences, ↑ sebum production, colonization w/ *Propionibacterium acnes* → follicle rupture → inflammatory host response
- **Severe disease has significant psychosocial impact:** Similar to that of epilepsy, asthma, DM, can → 2–3× ↑ in suicidal ideation (*Br J Dermatol* 1999;140:672; *J Invest Derm* 2011;131:363)

## Evaluation (*JAMA* 2004;292:726)

- **Diagnosis:** Clinical, w/ wide range in severity of presentation
- **History:** Eval for triggers (below); dietary triggers not well defined

**Acne Vulgaris Triggers (*NEJM* 2005;352:1463)**

| | |
|---|---|
| **Cosmetic** | Occlusive creams/makeup/pomades |
| **Mechanical** | Friction/pressure (e.g., helmets) → "acne mechanica" |
| **Drug-induced** | **Glucocorticoids** (monomorphic papules & pustules), phenytoin, **lithium, INH**, iodides, bromides, androgens, Vits $B_2$, $B_6$, & $B_{12}$, AZA, CsA, disulfiram, psoralens, thiourea, & EGFR inhibitors |
| **Hormonal** | Flares w/ menses, significant jawline/chin acne → **eval for signs of hyperandrogenism** (see *"Polycystic Ovary Syndrome"*) |
| **Occupational** | Insoluble cutting oils (machinery), coal tar, chlorinated hydrocarbons (e.g., dry cleaning) |
| **Radiation** | Radiation acne |

- **Exam:** *Morphology:* Closed ("whiteheads") & open ("blackheads") comedones; erythematous papules, pustules, nodules, & cysts
  *Healed lesions:* Postinflammatory hyperpigmention ± "ice-pick" (deep, punctate) & "boxcar" (wider/shallower) scarring
  *Distribution:* **Face**, back, chest
- **Differential diagnosis: Rosacea** including perioral dermatitis (no comedones), sebaceous hyperplasia (yellowish papules w/o comedones), folliculitis, **gram ⊖ folliculitis** (after prolonged oral

abx), keratosis pilaris (on trunk/extremities), pseudofolliculitis barbae/acne keloidalis nuchae, ("razor bumps" on shaved areas, ↑ prevalence African-American ♂), Favre–Racouchot (comedones from photodamage)

### Classification

| Severity | Description |
|---|---|
| Mild | Primarily open & closed comedones; <10 papules & pustules |
| Moderate | Mod (10–40) of comedonal & inflammatory lesions present; mild disease of the trunk |
| Mod-Severe | Numerous papules & pustules (>40), occasional tender nodules & cysts; ⊕ truncal involvement, ± scarring |
| Severe | Many large, painful nodules & cysts, **significant scarring** |

## Treatment (*NEJM* 2005;352:1463; *J Am Acad Dermatol* 2009;60:S1)

- Aimed at correcting follicular keratinization, ↓ sebum production, ↓ bacterial colonization, & ↓ inflammation
- Treatment algorithm largely divided into topical ± systemic tx based on severity

### Acne Treatment

| | Dosage | Side Effects |
|---|---|---|
| **Topical Tx:** 1st line for **mild** comedonal or inflammatory acne **w/o scarring** | | |
| **Retinoids** | **Tretinoin 0.025–0.1%** (C,G) QHS | **Irritation**, photosensitivity; Tazarotene preg category X |
| | Adapalene 0.1–0.3% (C,G,L) QHS | |
| | Tazarotene 0.05–0.1% (C,G) QHS | |
| **Topical antimicrobials** | **Benzoyl peroxide** 2.5–10% (C,G,L,W) QD–BID | Irritation, bleaches clothing/ linens |
| | Clindamycin, Erythromycin (G,L,S) QD–BID (2nd line) | ↑ Bacterial resistance |
| | Dapsone (G) QD—BID (2nd line) | Irritation |
| **Other agents** | Azelaic acid 15–20% (C,G) QD–BID | Irritation |
| | Salicylic acid OTC QD–BID | Irritation, dryness |
| | Sulfur/Na sulfacetamide (C,W) QD–BID | Unpleasant odor |
| **Systemic therapy: Mod–severe** inflammatory acne ± **scarring** | | |
| Antibiotics (1st line) | **Tetracycline 25–500 mg QD–BID** | GI upset |
| | Doxycycline 50–100 mg QD–BID | GI upset, photosensitivity |
| | Minocycline 50–100 mg QD–BID | Hyperpigmentation, HA, SLE-like reaction, hypersensitivity |
| (2nd line) | TMP–SMX DS BID | Hypersensitivity, photosensitivity, TEN |
| Hormonal agents (♀ only) | Spironolactone 50–200 mg | Menstrual irregularities, breast tenderness, teratogenicity |
| | Estrogen-containing OCP | see *"Contraception"* |
| Oral retinoids | Isotretinoin 0.5–1 mg/kg/d | Teratogenicity, xerosis, ↑ LFTs, visual changes |

*Formulations: C, cream; G, gel; L, lotion; S, soln; W, wash* (Data from: *NEJM* 2005;352:1463)

- Combination therapy with topical retinoid + antimicrobial agents preferred approach for almost all pts w/ acne
- Use of topical or oral antibiotics should be combined w/ benzoyl peroxide or retinoid to limit incidence of abx resistance
- Oral isotretinoin most effective medication for acne; federally mandated regulation program (www.ipledgeprogam.com) implemented due to risk of teratogenicity
- **Adjunctive treatments:** Include extractions/peels & laser/light-based therapies (e.g., photodynamic Rx); no dietary modifications definitively improve acne

## When to Refer

- **Systemic/severe variants:** Acne fulminans (typically adolescent ♂ w/

fever, arthralgias, large inflamm nodules, ↑ WBC, ↑ ESR, proteinuria, osteolytic lesions); acne conglobata (typically adolescent ♂ w/ severe nodular acne, draining lesions, & sinus tracts)

- **Rare disorders:** SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis); PAPA syndrome (sterile pyogenic arthritis, pyoderma gangrenosum, acne)
- **Treatment-refractory:** Consider referral for severe disease or initiation of oral retinoids

# ALOPECIA

## Background (*NEJM* 1999;341:491; 2007;357:1620; *Clin Exp Dermatol* 2002;27:389)

- **3 phases in hair cycle: Anagen** (growth phase, ~2–6 y, ~90–95%) → **catagen** (involutional phase, ~2–3 wks, <1%) → **telogen** (resting phase, ~2–3 mos, 5–10%)
- **Number of hairs on scalp:** ~100,000; **nl scalp loss:** ~100 telogen hairs/d
- **Hair loss:** Abnormalities in cycling ± inflammation; **thinning** (c/w androgenetic alopecia) **vs. shedding** (c/w alopecia areata or telogen effluvium) **vs. both**
- **Nonscarring alopecia:** Follicular openings visible on exam

## Etiologies (*NEJM* 2007;357:1620)

- **Androgenetic alopecia: Most common**; occurs after puberty; genetic, hormonal (DHT) etiologies; early-onset/vertex assoc w/ ↑ incidence CAD (*J Cardiovasc Risk* 2001;3:147; *BMJ Open* 2013;3:e002537)
  *S/sx:* Progressive **follicular miniaturization** & shortening of anagen phase; location → ♂ : Frontotemporal & vertex; ♀ : Crown/widened part w/ preserved frontal hairline "Christmas tree" pattern ("Ludwig pattern")
  *Tx:* Must be used indefinitely or progression will resume; Minoxidil 5% soln BID or 5% foam QD in ♂, 2% in ♀ (s/e: facial hypertrichosis, irritant dermatitis); Finasteride 1 mg PO QD daily in men (s/e: sexual dysfunction) (*JAAD* 2012;67:379); hair transplant

- **Telogen effluvium:** Premature shift to telogen → diffuse shedding; starts 2–4 mos after trigger (*J Invest Dermatol* 2003;121:985)
  *Causes:* Stress, wt loss, infection, fever, hypothyroidism, new medication, **Fe deficiency**
  *Meds:* Minoxidil (wks); heparin, coumadin, ramipril, βB, lithium, IFN-α, TCAs, oral retinoids, terbinafine, VPA, OCPs, postpartum (2–5 mos postdelivery)
  *S/sx:* **Hair pull test** → grab ~60 hairs, tug the group of hairs proximally to distally, ⊕ if >6 hairs are released (*NEJM* 1999;341:491; *Clin Exp Dermatol* 2002;27:389)
  *Tx:* Reversal of trigger, if possible (*Arch Dermatol* 1993;129:356; *JAAD* 1996;35:899)
- **Anagen effluvium** (*NEJM* 2007;357:1620; *JAAD* 2011;64:604); hair matrix arrest → tapered fractures of the hair shaft; starts 7–14 day after thallium or chemotherapy (cyclophosphamide, doxorubicin, taxanes); can → permanent alopecia (taxanes, busulfan, cyclophosphamide, tamoxifen)
  *Tx:* Counseling before starting Rx; scalp cooling, minoxidil, wigs if pt preference
- **Alopecia areata** (*NEJM* 2012;366:1515; *JAAD* 2009;60:85; 2010;62:177; 2010;62:191); Aberrant HLA expressed by hair bulb; lifetime incidence 1.7%; 16% of pts also have other autoimmune disease; chronic, relapsing course, but spontaneous remission possible; ↑ risk of severe disease if hx atopic dermatitis, juvenile onset, widespread, duration >5 y, onychodystrophy
  *S/sx:* Discrete circular bald patches w/ "**exclamation point**" hairs (proximal narrowing); *Totalis* (scalp only) or *Universalis* (scalp + body); 60% w/ nail pitting
  *Tx:* Intralesional corticosteroids (s/e: Dermal atrophy); topical immunotherapy
  *Pt information:* www.naaf.org
- **Other:** *Trichotillomania* (OCD spectrum, repetitive pulling of hair, often unconscious);
  *Traction alopecia* (↑ prevalence in African-Americans, tight hairstyles → recession of frontal hairline, can be scarring); *Tinea capitis* (hair breakage, may be assoc w/ LAD)
- **Scarring (cicatricial) alopecia: No follicular ostia**, **tufted hairs**

("doll's hairs"), characterized by 1° vs. 2° process or infiltrate type (*JAAD* 2005;53:1)
*Primary*: Inflammatory follicular destruction; e.g., discoid lupus erythematosus, lichen planopilaris, dissecting cellulitis, folliculitis decalvans
*Secondary*: Indiscriminate follicular damage from 1° process; e.g., burns, sarcoid, malignancy

- **Hair shaft disorders:** Acquired & congenital etiologies

## Evaluation (*NEJM* 2007;357:1620)

- **History:** Med review, infections, stressors, surgeries, pregnancy, wt loss, use of hair straighteners, braids, rollers; ⊕ FHx of alopecia; duration/pattern; menstrual cycle irregularities
- **Exam:** *Scalp:* ⊕ Scale, crust, pustules, erythema; *Hair shaft:* Note length, diameter, texture; distribution; hair breakage; ± follicular ostia intact; skin & nails, hair pull test
- **Labs:** Consider CBC w/ diff, iron studies, TSH, free & total testosterone, DHEA-S, PRL, ANA, Vit. D, zinc
- **Biopsy:** 4 mm punch bx is standard (*J Cutan Pathol* 2008;35:82)

## When to Refer

- **Scarring alopecia** or unclear etiology, consider for alopecia areata/androgenetic alopecia

# ATOPIC DERMATITIS

## Background (*J Invest Dermatol* 2011;131:67; *Lancet* 2001;357:1076; *NEJM* 2008;358:1483)

- **Definition:** Common, chronic relapsing dermatitis, assoc w/ xerosis & IgE-mediated sensitivities; often called eczema (due to classic "eczematous" pattern of dermatitis)
- **Epidemiology:** Prevalence 11% in US; **childhood onset** (90% by age 5); sx often improve w/ age (*JACI* 2004;113:832); "Atopy": 30% of pts w/ AD also have asthma, 35% have AR
- **Pathophysiology:** Thought to be combination of environmental exposures & genetic predisposition; Epidermal barrier dysfunction

2/2 *filaggrin* mutation → ↑ transepidermal water loss → dry skin

- "**Hygiene hypothesis**": ↑ Atopy assoc w/ ↓ microbial exposure early in life, esp in developed countries; food allergies & AD are assoc in minority of pts but causal relationship has not been established; IgE dysregulation in subset of pts
- **Complications:** 2° infection common
  *SSTI:* Common, esp *S. aureus:* Pts w/ AD have ↓ human defensin-2 → ↑ *S. aureus* colonization → inflammation → ↑ flares
  *HSV:* "Eczema herpeticum" (punched-out hemorrhagic erosions; see *"Herpes Simplex Virus"*)

## Evaluation

- **History:** Location, duration, triggers (irritant, allergic, infection, food, stress, season, temperature, sweating, wool clothing), severity of itch (incl sleep disturbance), past tx, personal or ⊕ FHx of atopy (AR, asthma)
- **Exam:** *Acute:* Poorly defined, excoriated erythematous patches, vesicles, serous exudates, & crusts; *Chronic:* Lichenified (↑ skin markings) & hyperpigmented plaques, prurigo nodules; *2° characteristics:* Excoriations, punctate erosions, ± honey-colored crust (impetigo)
- **Labs:** Low threshold to culture crust or punctate erosions

**Atopic Derm Diagnostic Criteria** (*Acta Derm Venereol* 1980;S92:47; *Lancet* 1996;348:769)

| | |
|---|---|
| **≥3 of the following major criteria** | 1. Pruritus<br>2. Typical morphology & distribution (flexural)<br>3. Chronic or relapsing dermatitis<br>4. PMHx or ⊕ FHx of atopy |
| **≥3 of the following minor criteria** | **"Atopic facies":** Facial pallor or erythema, hypopigmented patches, periorbital hyperpigmentation, infraorbital folds or wrinkles, cheilitis, recurrent conjunctivitis, anterior neck folds |
| | **Triggers:** Foods, emotional factors, environmental factors, & skin irritants such as wool, solvents, & sweat |
| | **Complications:** ↑ Cutaneous viral & bacterial infections, ↓ cell-mediated immunity, immediate skin test reactivity, ↑ serum IgE, keratoconus, anterior subcapsular cataracts |
| | **Other:** Early age of onset, **dry skin/xerosis**, ichthyosis, **hyperlinear palms**, **keratosis pilaris**, hand & foot dermatitis, nipple eczema, white dermatographism, & perifollicular accentuation (*J Invest Dermatol* 2007;127:1667) |

- **Differential diagnosis:** *Inflammatory:* Seborrheic derm, irritant/ACD, psoriasis, hypersensitivity drug reaction, *Infections/infestations:* Scabies, HIV, tinea; *Malignancy*: Cutaneous T-cell lymphoma, Langerhans cell histiocytosis; *Immunologic*: GVHD, connective tissue disease

## Treatment (*NEJM* 2005;352:2314; *Pediatr Dermatol* 1997;14:321)

- **Emollients: Goal is to restore barrier function;** "Soak & seal" use of emollients → ↓ skin dryness, ↓ itching, protects from irritants, improves appearance; daily **lukewarm** (not hot) bath 15–20 mins, soap only where/when necessary, pat (not rub) to dry skin, followed by application of ceramide-containing moisturizer or petrolatum-based emollient (hydrolatum, aquaphor); **proper hydration Ø need for topical steroid by ~50%**
- **Antipruritics:** Antihistamines PRN day (nonsedating) ± night, esp if significant sleep disruption, allergic dermatographism, or AR (see *"Allergic Rhinitis"*) (*JAAD* 2004;50:391,404)
- **Topical corticosteroids: first-line** topical tx for mod/severe AD (see *"Topical Corticosteroids");* use lowest effective potency at lowest freq possible to prevent s/e; oints preferred (most hydrating); intermittent use (twice weekly) can ↓ potential for relapse (*Br J Dermatol* 2002;147:528); S/e: **Irreversible** atrophy, striae
- **Ø Staph colonization:** For severe cases, twice weekly **dilute bleach baths** (0.5 cup of 6% bleach to full bathtub, immerse × 5–10 mins, then rinse, pat dry, emollients) plus **intranasal mupirocin** oint 5 consecutive d/mo; oral abx *not* recommended for routine use

## When to Refer

- Severe or refractory disease, consideration of PO corticosteroids; erythroderma
- Consideration of topical calcineurin inhibitors, phototherapy, immunomodulators (CsA, MMF, MTX)
- Widespread bacterial superinfection or eczema herpeticum = dermatologic emergency: Prompt tx w/ abx or antivirals; may need ED/hospitalization

# COMMON BENIGN GROWTHS

## SEBORRHEIC KERATOSIS

### Seborrheic Keratosis (*Br J Dermatol* 1997;137:411)

- Benign cutaneous growth in >80% of adults aged 35–76; incidence ↑ w/ age, ♂ = ♀; ↑ frequency in areas of sun-exposure; unknown trigger → keratinocyte proliferation, altered EGFR distribution, *FGF3* mutation; no assoc w/ HPV
- *S/sx:* Skin-colored or brown macules or papules, often w/ "warty" & **"stuck on"** appearance; can be pigmented; horn cysts (keratin-filled depressions) can be helpful feature; often multiple lesions; spares palms, soles, & mucosa
- *Dx:* Clinical; referral to dermatology or excisional bx if uncertain; Ddx includes **melanoma**, verruca vulgaris (wart), squamous cell carcinoma, lentigo
- *Tx:* Reassurance; electrodessication & curettage or cryotherapy for irritated lesion

### Verucca Vulgaris (Common Wart) (*JAAD* 1990;22:547)

- Caused by various HPV subtypes; prevalence ↓ w/ age; spread by skin-to-skin contact, fomites (nongenital lesions), sexual contact, autoinoculation; ↑ in areas of skin trauma, incl shaving; ↑ severity/incidence in meat handlers, AD, immunosuppressed
- *S/sx:* Varies by subtype: **Common wart:** <1 cm, skin-colored/pink/brown hyperkeratotic papule w/ punctate hemorrhage; **Flat wart:** Sessile, skin-colored, smooth, <3 mm papules; often multiple lesions; **Plantar wart:** Scaly, rough papule on sole w/ punctate hemorrhage; **Genital wart:** Skin-colored/brown, macerated; sometimes polypoid smooth papules
- *Dx:* Clinical; biopsy for definitive dx/large lesions to exclude malignancy; Ddx includes SCC, verrucous CA, AK
- *Tx:* Warts difficult to treat & often spontaneously resolve; consider reassurance; **First line:** Salicylic acid + cryotherapy > salicylic acid alone > cryotherapy alone (*AFP* 2011;84:288)

*Cryotherapy:* Tx should be q3wks; limit to 3 treatments & if no improvement → dermatology referral

*Salicylic acid:* May be used as adjuvant (btw visits) for cryotherapy; instruct pt to soak area × 5 mins, gently exfoliate w/ pumice/file, then apply QHS; S/e: Irritation (d/c if severe), maceration

**Second line:** Other destructive modalities (curettage, electrodessication), immunomodulators (imiquimod, intralesional Candida Ag), podophyllin toxin, duct tape (*Br J Dermatol* 2011;165:432)

- **Secondary prevention:** HPV transmission from tx items possible; have pts reserve home pumice/files for this purpose alone, avoid shaving directly over lesions
- **When to refer:** Extensive/painful lesions, failure to improve w/ tx, dx uncertain, periungual location (assoc w/ SCC) (*JAAD* 2011;64:1147)

## Angioma (*JAAD* 1997;37:887)

- Most common acquired cutaneous vascular neoplasm, benign, present in most by age 60; ↑ in # & size w/ age; unknown etiology (hormonal influences); ↑ blood vessels seen on pathology
- *S/sx:* <5 mm bright red macules, dome-shaped papules; multiple on trunk & proximal extremities
- *Dx:* Clinical; bx for definitive dx; Ddx incl petechiae, Kaposi sarcoma (larger), pyogenic granuloma (solitary, friable), bacillary angiomatosis
- *Tx:* If symptomatic, can be electrocauterized ± shave bx

## Epidermal Inclusion Cyst (EIC)

- Most common cutaneous cyst; ↑ in hair-bearing areas (posterior neck of ♂), filled w/ keratinaceous debris; SC, soft, mobile nodule **often w/ punctum**, yellow/blue appearance; cyst rupture can → inflamed (sterile or bacterial)
- *S/sx:* Clinical; Ddx includes pilar cyst (scalp), dermoid cyst (eyebrow), lipoma, other dermal tumor
- *Tx:* I&D, intralesional steroids, abx if inflamed; refer for excision for definitive tx

## Lipoma

- Subcutaneous tumor composed of adipocytes; ♂ > ♀
- *S/sx:* Often solitary, mobile, soft nodules w/ predilection for trunk, arms, buttocks, & proximal lower extremities; can have multiple lesions
- *Dx:* Clinical; excisional bx for definitive dx; Ddx incl EIC, angiolipoma (painful), liposarcoma (malignant variant, often >10 cm, proximal extremities, rapidly growing), spindle cell lipoma (large, often found on neck of ♂)
- *Tx:* Referral for excisional bx if sx or dx uncertain
- **Angiofibroma:** "Fibrous papule," dermal tumor composed of fibroblasts & blood vessels; solitary (often on nose) or grouped, <5 mm dome-shaped, skin-colored papule(s); *Variant:* Pearly penile papules (translucent papules on penile corona, often misdiagnosed as genital warts); *Dx:* Clinical, bx for definitive dx; *Ddx:* Intradermal nevus, BCC (*JAAD* 1998;38:143)
- **Dermatofibroma:** Composed of proliferation of fibroblasts & histiocytes; idiopathic or 2/2 arthropod bite, local trauma; usually solitary, often on lower extremities of ♀; multiple eruptions can be seen in SLE, HIV; *Dx:* Clinical, ⊕ dimple sign (dimple w/ lateral compression), bx for definitive dx; *Ddx:* Melanocytic nevus, melanoma, seborrheic keratosis, dermatofibrosarcoma protuberans (malignant variant, often >2 cm); *Tx:* Reassurance, excisional bx if symptomatic (e.g., pruritus) or large (*J Eur Acad Dematol Venereol* 2009;23:371)
- **Neurofibroma:** Composed of neural mesenchymal tissue; 0.2–2 cm skin-colored to pink pedunculated papules, soft, often on a broad base; solitary lesions common; *Dx:* Clinical ± buttonhole sign (easily invaginates w/ pressure); *Ddx:* Dermal nevus, acrochordon, neuromas, intradermal nevus, nevus lipomatosis; multiple lesions → consider type 1 neurofibromatosis

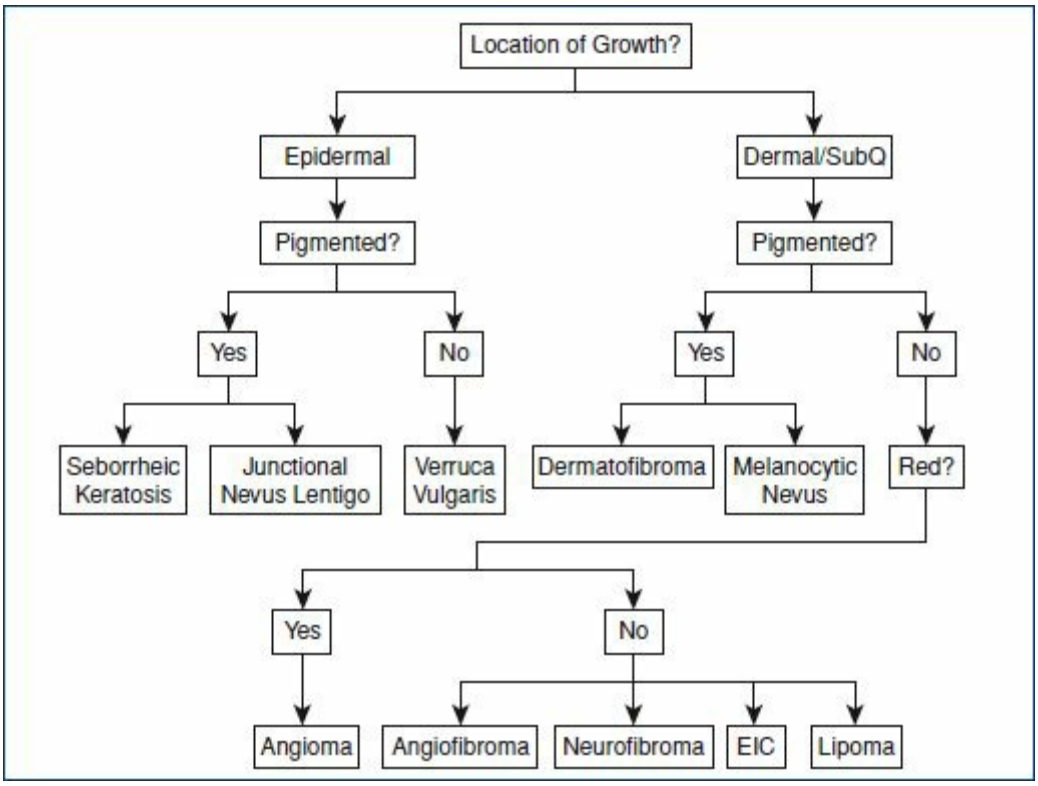

Figure 3-1 Diagnostic algorithm for common benign growths

# BURNS

## Background (*NEJM* 2009;360:893 ameriburn.org)

- **Epidemiology:** 450,000 people seek medical care for burns annually in US; majority of cases mild; most commonly 2/2 flame exposure, most commonly at home
- **Body surface area:** Reference is one palm (1% BSA); difficult in obese pts
- **Types of burns:** Can be thermal, electrical (often deeper than suggested by cutaneous findings, can → compartment syndrome), chemical (acids, alkali, solvents), radiation (fluoroscopy or XRT)
- **Sunburn:** Limited to partial-thickness; if severity >expected or focal/geometric distribution, consider:
  ***topical*** *phototoxic reaction:* Phytophoto dermatitis (**lime**, lemon), topical retinoids
  ***systemic*** *phototoxic agents:* Doxycycline, FQs, amiodarone, thiazides, naproxen, furosemide

## Diagnosing Burn Depth

| Burn depth | Level of injury | Clinical features |
|---|---|---|
| **Superficial** (1st-degree burn) | Epidermis | **Erythema** (e.g., mild sunburn)<br>No blisters, dry, painful |
| **Superficial partial-thickness burn** (formerly 2nd-degree) | Epidermis & superficial dermis | **Bullae** w/ serous fluid, erythema<br>+ **capillary refill, painful**<br>Heals w/ mild scarring |
| **Deep partial-thickness burn** (formerly 2nd-degree) | Epidermis & full-thickness dermis | **Bullae** w/ serous or hemorrhagic fluid<br>Pale white or yellow color<br>**No capillary refill**<br>Intense pain, ↓ sensation<br>Significant scarring |
| **Full-thickness burn** (formerly 3rd-degree) | Epidermis, dermis, SC fat, fascia, muscle, or bone | Blisters may be absent<br>Leathery, charred, wrinkled appearance over bony prominences<br>No capillary refill<br>**Pain absent,** hair pulls out easily |

(Adapted from: *NEJM* 1996;335:1581)

## Treatment (*NEJM* 1996;335:1581; 2008;359:1037; 2009;360:893)

- **General approach:** For PCP-appropriate mgmt, pain control, prevention of scar contracture & hypertrophic scars; *Dressing:* Moist environment, emollient use accelerates healing; *Cleaning:* Soap & tap water as needed
- **Superficial:** *Topical:* Aloe vera gel or other hydrophilic ointment; **no topical steroids** *Systemic:* Ibuprofen (800 mg q8h), ASA, or other NSAIDs
- **Superficial partial thickness:** Tetanus Ppx as appropriate (see *" Wound Care"*)
  Topical antimicrobial covered by occlusive dressing (see Table 1; *NEJM* 2008;359:1037)
- **Deep partial thickness:** Early surgical mgmt **standard of care Æ referral**
- **When to refer:** *If in doubt, call a burn center for phone triage;* list at *www.ameriburn.org;*
  **Partial-thickness burn:** If >20% BSA (refer if >10% BSA + pt >50)
  **Full-thickness burn:** If >5% BSA
  **Location:** Burns involving face, hands, feet, genitals, perineum, or major joints

# DERMATITIS

## SEBORRHEIC DERMATITIS (*NEJM* 2009;360:387)

### Background

- **Definition:** Chronic, relapsing inflammatory disease affecting sebaceous gland-dense skin (scalp, nasolabial fold)
- **Pathophysiology:** Unclear; suspected abnl immune response to *Malassezia* yeast (part of nl flora, but likely ↑ colony burden in seb derm pts)
- **Epidemiology:** 7–12% incidence in adults; most common in healthy 30–60 yo, ♂ > ♀ (*AFP* 2006;74:125)
- Severe, refractory disease assoc w/ **neuro d/o** (esp Parkinson), trisomy 21, **HIV/AIDS** (esp CD4 < 400); disease often ↑ w/ stress, dry/cooler mos

### Clinical Manifestations

- **Scalp:** Most commonly affected; fine scaling (“**dandruff**”) → more inflammatory disease w/ erythema, pruritus
- **Face/neck:** Erythematous, greasy, ± pruritic patch w/ yellowish scale involving forehead, **glabella, eyebrows, lateral nose/nasolabial fold**, retroauricular area, external auditory canal, & other hair-bearing skin of head & neck (e.g., beard)
- **Other forms:** Blepharitis (eyelids); otitis externa; involvement of central chest (can be psoriasiform, pityriasiform, “petaloid” variant resembles flower petals), umbilicus, intertriginous areas of trunk

### Evaluation

- Clinical diagnosis; KOH scraping can help r/o tinea; consider HIV testing if severe/refractory
- **Differential diagnosis:** Psoriasis, tinea, AD, contact dermatitis, impetigo, rosacea (⊕ telangiectasia), candidiasis, erythrasma, DM, & SLE (spare nasolabial folds)

### Treatment (*Br J Dermatol* 1995;132:441; *Arch Dermatol* 2005;141:47)

- Reactions may have antifungal, keratolytic, and/or immunomodulatory effects
- **Scalp: Ketoconazole 2% shampoo** 2×/wk until clearance then 1×/wk to 1×/every other wk for Ppx; similar regimen of ciclopirox 1% shampoo; OTC selenium sulfide, zinc pyrithione, coal tar, & salicylic acid shampoos also used solo or as adjuvant; topical corticosteroids may be useful for short-term control of sx but risk of adverse effects (e.g., atrophy, telangiectasia) & data lacking
- **Face/nonscalp areas:** 1st-line ketoconazole 2% crm or foam BID for at least 4 wks (*J Drugs Dermatol* 2007;6:1001); consider ciclopirox 1% crm BID as 2nd line (*Br J Dermatol* 2001:144:1033); topical corticosteroids & immunomodulators if unresponsive to antifungals

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# Allergic Contact Dermatitis (ACD)

## Background

- T-cell–mediated, delayed (type IV) hypersensitivity reaction; time interval to sensitization may be weeks to years; subsequent rechallenge may cause ACD w/in h to d
- **Epidemiology:** Prevalence ↑ w/ age (highest at age 60–69), ♀ > ♂ (*Dermatol Clin* 2012;30:87)
- Over 3000 chemicals assoc w/ ACD: Nickel, neomycin, bacitracin among most common

**Most Common Contact Allergens (*J Clin Aesthet Dermatol* 2010;3:36; *JAAD* 2004;51:S60)**

| | Examples |
|---|---|
| **Plant** ("Phyto-ACD") | Urushiol in poison oak/ivy/sumac |
| **Metals** | **Nickel**, gold (also can include nickel as alloy), cobalt |
| **Preservatives** | Formaldehyde, quaternium-15, parabens |
| **Cosmetics** | **Balsam of Peru**, fragrance mix, ***p*-phenylenediamine** |
| **Antibiotics** | **Neomycin**, bacitracin |
| **Textiles** | Potassium dichromate, disperse blue |

## Clinical Manifestations

- **Acute:** Well-demarcated, erythematous papules & plaques ± vesicles/bullae/exudate w/ prominent pruritus; often linear pattern

from transfer of allergen; allergen can be aerosolized presenting as facial/eyelid erythema & edema
- **Chronic:** Lichenified papules & plaques, + scaling, + erythema, + excoriations, + pigment Δ
- Often difficult to distinguish from Irritant Contact Dermatitis (ICD) (see below); ACD may be superimposed on ICD

## Evaluation

- **Hx/PE:** Hx of exposure to & withdrawal from allergens w/ emphasis on cosmetic/hygiene products, topical meds, **jewelry**, clothing, hobbies, plant contact, & occupation (hairdressers, construction workers, metalworkers)
- **Ddx:** ICD, AD, tinea, psoriasis, dyshidrotic eczema, scabies, stasis dermatitis, & cellulitis
- **Dx:** Patch testing gold standard; Thin-layer Rapid Use Epicutaneous (TRUE) test commonly used, FDA-approved; customized patch testing also available

## Treatment (*AFP* 2010;82:249; *JAAD* 2005;53:845)

- Avoidance of allergen; first-line tx is mid-to-high potency topical steroids (see *"Topical Corticosteroids"*)
- Severe disease: Prednisone taper over ~2 wks (short "dose pack" may result in rebound flare)
- Wet dressings, oatmeal baths, & oral antihistamines for sx relief

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# Irritant Contact Dermatitis (ICD)

## Background

- **Nonimmune-mediated** physical/chemical damage to epidermis → inflammation
- Most common (>>ACD) cause of **occupational** skin disease; highest prevalence in cosmeticians, also seen in health care, agricultural, custodial workers (*Dermatol Clin* 2012;30:87)
- May occur after single exposure to harsh chemical or chronic exposure to milder irritant (e.g., solvents, acids/bases, & detergents)

## Clinical Manifestations

- **Acute:** Well-demarcated erythematous papules & plaques, often w/ evolving vesicles/bullae & possible necrotic ulceration; usually painful, + pruritus; commonly involves hands, also face (esp thin eyelid skin) or any other area of contact w/ irritant
- **Chronic:** Poorly demarcated lichenified papules & plaques w/ scaling, crusting, & fissures; often painful & pruritic; typically involves hands

## Evaluation

- **Hx/PE:** Hx of exposure to & withdrawal from possible irritants, esp at home (e.g., laundry or dishwasher detergent) & workplace (hand sanitizer, occupational chemicals)
- **Dx:** Usually clinical, Ddx same as ACD; consider patch testing if concern of superimposed ACD

## Treatment (*JAAD* 2005;53:845)

- **Avoidance** of suspected irritant; short-term topical steroids ± occlusion, esp for severe disease, but data lacking; restoring dermal barrier: ↓ freq of exposure to water (e.g., handwashing) when feasible; lipid-rich moisturizers (*JAAD* 2005;53:845)
- **Prevention:** Barrier creams, lipid-rich moisturizers, & softened fabrics; nonlatex gloves w/ cotton liners & regular glove removal, substitution w/ nonirritant agents (*Br J Dermatol* 2009;160:946)

# CUTANEOUS DRUG ERUPTIONS

## Definitions and Epidemiology (*NEJM* 2012;366:2492; *JAAD* 2008;59:995)

- Reported for nearly all medications, rates up to 10 cases/1000 new users
- **Clinical presentation:** Majority of cases mild, but can be severe w/ systemic involvement; morbilliform (aka "exanthematous") most common (80%) followed by urticarial (5–10%)
- **Risk factors:** HIV, HSCT, connective tissue disease, autoimmune or viral hepatitis (*Br J Dermatol* 2003;149:1018)

## Evaluation (*NEJM* 2012;366:2492)

- **History:** Assess all pts for systemic, ocular, mucosal sx; obtain detailed med hx
  *Onset after starting new med:* <36 h (urticarial) 4–14 days (exanthem); 4–21 days (TEN/SJS) ~ 21 days (DRESS)
  *Course:* Peak w/in 2 d of stopping offending med; often fades by 1 wk after stopping
- **Exam:** Complete skin exam; evaluate mucosa in all pts

**Cutaneous Drug Eruptions**

| Reaction Type | Presentation | Classic "Culprit" Meds |
|---|---|---|
| **Morbilliform** "Exanthematous" (most common) Type IV hypersensitivity | Erythematous macules & papules coalescing into plaques; **symmetric**, widely distributed; ± pruritus Often w/ superficial exfoliation in resolution phase; mucous membranes spared | PCNs (amoxicillin w/ acute mononucleosis) TMP–SMX (↑ risk w/ HIV) FQs, anticonvulsants Allopurinol |
| **Urticarial** Type I hypersensitivity | Pink-to-erythematous edematous plaques ± soft tissue edema of lips, upper airway, eyelids, genitalia (angioedema); see *"Urticaria"* | ASA, NSAIDs, PCN |
| **Fixed drug eruption** (Occurs in same place each time) | Usually multiple, sometimes solitary, red/violaceous hyperpigmented plaques, often on acral surfaces, mucosa, or genitalia (glans penis) | NSAIDs, TMP–SMX Tetracyclines, pseudoephedrine |
| **Drug Rash w/ Eosinophilia and Systemic Symptoms (DRESS)** (*Arch Dermatol* 2010;146:1373) | Mortality up to 10% Eosinophilia common (but not necessary) Systemic sx: **Fever, facial edema, LAN; hepatic**, renal, pulm, cardiac, thyroid (delayed) involvement possible | Anticonvulsants (carbamazepine, lamotrigine, phenytoin) Allopurinol, sulfasalazine Nevirapine, dapsone (*Am J Med* 2011;124:588) |
| **SJS/TEN** (*NEJM* 1995;333:1600; *JAAD* 2008;58:25) | **Fever**, malaise, erythroderma, skin pain, dysphagia, dysuria, blisters, **mucosal involvement** = dermatologic emergency → ED | Allopurinol, TMP–SMX Carbamazepine β-lactam abx NSAIDs |

- **Labs:** If systemic sx, CBC w/ diff, LFTs, Cr
- **Differential diagnosis:** Viral exanthem (usually children, more abrupt onset & rapid resolution), GVHD in appropriate clinical setting, toxic shock syndrome

## Treatment

- **Identify and discontinue offending agent;** if simple morbilliform eruption (no systemic sx) & if drug necessary & temporary (e.g., chemotherapy), can consider "treating through" rash w/ close clinical & lab monitoring
- **Therapy:** Antihistamines for sx relief (nonsedating during the day, sedating at night); topical or systemic corticosteroids for sx relief, though little empiric evidence
- Rechallenge should generally be avoided as subsequent eruptions on re-exposure may be more severe (*NEJM* 2012;366:2492)

- If patient has allergy to one aromatic anticonvulsant, must also avoid others in same class (phenytoin, phenobarbital, carbamazepine)

## When to Refer

- **Immediate referral to emergency department:** Pustular lesions (acute generalized exanthematous pustulosis), duskiness, skin pain, blisters/epidermal desquamation, **ocular/mucosal involvement** (SJS/TEN) **systemic involvement** (e.g., DRESS)

# MELANOMA

## Background (SEER, http://seer.cancer.gov/statfacts/html/melan.html)

- **Epidemiology:** Melanoma lifetime probability 2.8% for ♂, 1.8% for ♀; incidence ↑ w/ age, but relatively common cause of cancer in the young; median age at dx: 61 y
- 75% of melanomas develop *de novo*, not from pre-existing nevi; high-risk sites: trunk of ♂, lower legs of ♀; **50% of all melanomas initially discovered by pt** (*JAAD* 1992;26:914)
- **Role of screening:** Cure rates much higher w/ earlier stage lesions (5 y survival 98% w/ localized disease) → theoretical, if unproven benefit, which is likely ↑ in high-risk population; currently insufficient evidence per USPSTF (*Ann Intern Med* 2009;150:188)
- **PCP detection:** Se 43–100%/Sp 93%; be alert for malignant features esp in ↑ risk groups

## Melanoma Risk Factors (*Arch Dermatol* 2006;142:433; *JAAD* 2005;52:197 *NEJM* 2004;351:998)

- **Strongest risk factors:** 1st-degree relative w/ melanoma, familial dysplastic nevi syndrome (*NEJM* 2004;351:998), multiple dysplastic nevi (if 5 atypical moles, 10× ↑ risk of melanoma (*Eur J Cancer* 2005;41:28), prior melanoma (up to 8% risk of 2nd melanoma at 2 y) giant congenital nevus >20 cm
- **Additional risk factors:** Inability to tan (only burn), freckles, blonde or red hair, blue eyes, tanning bed use, blistering sunburns, intermittent sun exposure (*Clin Dermatol* 1998;16:67)

- **Risk of recurrence:** Highest in first 2 y after initial dx (*Int J Cancer* 1997;73:198; *Cancer* 2003;97:639)

## Definitions (*NEJM* 2004;351:998)

- **Dysplastic nevi** (graded mild/moderate/severe atypia): Considered benign but for lesions w/ severe atypia (& sometimes mod) re-excision should be considered; low rates of clinical recurrence for benign to moderate atypical dysplastic nevi (*JAAD* 2010;62:591)
- **Melanoma types:**
  **Melanoma in situ:** No invasive component; include lentigo maligna
  **Superficial spreading melanoma:** 70%; median age: 50s, most common type to arise from pre-existing nevi, no preference for sun-damaged skin
  **Lentigo maligna melanoma:** 5–15%; irregular brown macules initially, often on head & neck; elderly pts w/ significant sun damage
  **Acral lentiginous melanoma:** 2–3%; *C-KIT* mutation; most common sites thumb & toe; more common in Asians, African-Americans; may present at later stages (*Arch Dermatol* 2009;145:427)
  **Nodular melanoma:** 10–15%; most arise *de novo;* more common in ♂
  **Other:** Polypoid, mucosal (*C-KIT* mutation (*J Clin Oncol* 2006;24:4340)), desmoplastic (↑ risk of local recurrence), amelanotic (erythematous eroded papule or nodule, often confused w/ basal cell or pyogenic granuloma), uveal (*GNAQ* mutation (*NEJM* 2010;363:2191))

## Evaluation (*JAMA* 2004;292:2771)

- **History:** PMHx or FHx of dysplastic nevi/melanoma? Blistering sunburns? Tanning bed use? **Changing moles**? Asx moles?
- **Exam:** Entire skin, nails, hair; LN exam (if hx of invasive melanoma); attention to: Fitzpatrick skin type/phototype, extent of photodamage, nevi density, atypical moles, "ugly duckling" nevi—moles that stand out from others, scars from prior melanoma/atypical nevus excision (risk of local recurrence)
- **ABCDEs of pigmented lesions:** Increased likelihood of malignancy
  **A**symmetry (of pigment or shape)

**B**order irregularity (Jagged or notched borders)
**C**olor variegation (≥**3 colors concerning**—in particular, **blue/gray/white**, light brown, dark brown, black, red)
**D**iameter (>6 mm)
**E**volving (or symptomatic—pain, pruritus, bleeding)

## Diagnosis/Treatment (*NEJM* 2004;351:998; *Crit Rev Oncol Hematol* 2010;74:27)

- **Biopsy:** If clinically suspicious for melanoma → **refer to dermatology**; if inadequate access for prompt referral, excisional bx w/ narrow 1–2 mm margins has least risk of tumor transection (to ensure accurate staging); alt: Deep shave bx; **avoid partial bx of lesion**
- **Treatment:** Refer to dermatology, surgical oncology (if sentinel node bx is needed) for excision, or medical oncology if appropriate
- **When to refer:** Clinically suspicious mole; bx shows atypical nevus or melanoma; hx melanoma (needs at least annual skin exam), or high-risk individuals (based on risk factors above)

## Prevention (*Lancet* 2007;370:528; *J Clin Oncol* 2011;29:257; *Br J Dermatol* 2001;144:288)

- **Sunscreen pearls:**
  1. SPF 30 or higher; daily use of SPF 16 assoc w/ 50% ↓ in melanoma & 73% ↓ in invasive melanoma
  2. Use products labeled "broad spectrum" covering UVA & UVB—physical blockers w/ zinc/titanium, ecamsule, oxy- or avobenzone
  3. Use enough—2 mg/cm$^2$—about 1 tsp to head & neck; underuse of sunscreen amount common
  4. Reapply at least every 2 hours
  5. Use cream or lotion; sprays likely less effective (*Br J Dermatol* 2007;156:716)
- **Sun protection:** Avoid or seek shade during peak h of sunlight btw 10AM–3PM; ~80% of UV rays can pass through clouds; wear sun-protective clothing esp during water sports (clothing w/ UPF), UVA protective sunglasses, hat w/ >4 in brim
- **Monthly self-skin checks:** Educate pts about ABCDEs
- **Pt information:** aad.org/media-resources/stats-and-facts/prevention-and-care/sunscreens

# PSORIASIS

## Background (*JAAD* 2008;58:826; *Ann Intern Med* 2011;155:ITC 2–1; *JAAD* 1999;41:401)

- **Definition:** Chronic inflammatory condition affecting skin, nails, & joints; assoc w/ multiple medical & psychiatric comorbidities; affect on quality of life ≈ major medical diseases
- **Pathophysiology:** Immune dysregulation (↑ Th1 & Th17 cytokines), keratinocyte hyperproliferation (↑ epidermal cycle, ↑ mitotic activity), & genetics (many associations)
- **Epidemiology:** Prevalence is 2% (US), onset 15–25 y, affects ♀ & ♂ equally; up to 30% of pts w/ mod–severe disease develop PsA; *Risk factors:* Tob, EtOH, obesity
- **Classification:** Multiple subtypes; plaque most common (80–90%), then guttate

## Evaluation (*Ann Intern Med* 2011;155:ITC2–1; *JAAD* 2008;58:851)

- **History** *Typical features:* Pruritus, disease remits in summer (likely 2/2 UV exposure)
  *Triggers*: **Infection**, including GAS (guttate "teardrop" psoriasis), **meds** (steroid withdrawal, βBs, lithium, ACEIs); provocation of lesions by skin **trauma** (Koebner phenomenon)
  *Complications:* **Psoriatic arthritis (see below)**; psychosocial morbidity
- **Skin exam**
  *Morphology:* Discrete erythematous plaques w/ adherent silvery scale; subtypes below
  *Distribution:* Asymmetric; **scalp** commonly involved (Ddx: seb derm, tinea); also lateral face, retroauricular areas; **extensor surfaces** (elbows, knees), back
  *Auspitz sign:* Scale removal → punctate bleeding
- **Nails:** 2/3 of pts w/ PsA have nail disease (*Br J Rheumatol* 1994;33:834); *Pitting*: Punctate depressions 2/2 nail matrix disease; *Oil spots:* Yellow-brown discoloration of nail bed
  *Onycholysis:* Separation of nail plate from bed (Ddx: onychomycosis)
- **Joints:** Hands/wrists most common (esp DIPs); tenosynovitis,

enthesitis, dactylitis ("sausage digits") w/ telescoping of digits in advanced disease

- **Subtypes** (*Ann Intern Med* 2011;155:ITC2-1)
  *Plaque:* Symmetric, over extensor surfaces (elbows, knees), scalp, penis, umbilicus, intergluteal cleft; Ddx: AD, tinea, cutaneous lupus, mycosis fungoides
  *Guttate:* Droplet-sized lesions on extremities/trunk, abrupt onset, spares palms/soles, often younger pts after GAS infection; Ddx: Pityriasis rosea
  *Palmar–Plantar:* Thick-fissured plaques + scale on palms/soles, or solitary pustules coalescing; assoc w/ tob; Ddx: Eczematous dermatitis, tinea manuum, reactive arthritis
  *Inverse:* Well-demarcated, erythematous thin plaques w/ min scale, inframammary, axillary, intergluteal distributions; Ddx: Intertrigo, tinea, erythrasma
  *Erythrodermic:* Confluent erythematous plaques/scale on >75% BSA ± systemic sx; can be triggered by PO steroid withdrawal → urgent derm referral vs. ED
  *Pustular:* Individual or coalescing sterile pustules—generalized or near existing plaques, assoc ↓ Ca → urgent derm referral vs. ED
- **Psoriatic arthritis:** Affects up to 30% of mod–sev psoriatic pts; 5 patterns of joint involvement, pattern can change over time for individual pt (*J Rheumatol* 2003;30:1022)
  Asymmetric oligoarthritis (usually hands/wrists, esp DIPs) most common; can also p/w symmetric polyarthritis (RA-like), distal arthritis (DIPs only), sacroiliitis & spondylitis, or "Arthritis mutilans" (severe, rapid joint destruction & deformity)
  *Studies:* **Dx is clinical;** consider labs to r/o RA
  *Imaging:* Obtain radiograph if suspected; acro-osteolysis, "pencil in cup deformity" classic

## Treatment (*JAAD* 2009;60:643; 2010;62:114; 2009;61:451)

- Initial management based on affected BSA (for BSA definition, see *"Burns"*)
- **Mild, limited disease (<3% BSA): Topical agents (below)**

**Topical Tx of Psoriasis**

| Class | E.g./Initial Dosing | Notes/Safety Monitoring |
|---|---|---|
| **Corticosteroids** | See *"Topical Corticosteroids"* Class I/II for torso or extremities; Class VI/VII for face, axilla, groin | Limit high dose to 3 wks; gradually ↓ use/potency to class IV for torso/ extremities, then to PRN as tolerated |
| **Vitamin D analogs** | Calcipotriene 0.005% oint, soln, crm<br>Calcitriol 3 µg/g oint | Transient irritation; inactivated by salicylic acid; <100 g/wk to avoid ↑ Ca; incompatible w/ some steroids |
| **Retinoids** | Tazarotene 0.05% crm, gel QHS | Irritation (gel > crm)<br>Pregnancy category X |
| **Coal tar** | Variety of preparations; apply QD | May stain skin & clothing; unpleasant odor; inexpensive |

(*Ann Intern Med* 2011;155:ITC2–1; *JAAD* 2009;60:643; 2011;65:137; 2010;62:114; 2009;61:451)

- **Moderate to severe disease** (incl PsA or disabling palmo-plantar): → Dermatology for consideration of phototherapy, systemic retinoids or immunomodulators; **avoid oral corticosteroids** (rebound, pustular, or erythrodermic flare)
- **When to refer:** Refractory, moderate, or severe disease; unable to wean high-potency corticosteroids; consideration of systemic tx, phototherapy; dx uncertain → Dermatology; erythrodermic or pustular subtypes → Dermatology (or ED if severe)
- **Pt information:** National Psoriasis Foundation, www.psoriasis.org/about-psoriasis

# RHEUMATOLOGIC SKIN DISEASE

## CUTANEOUS LUPUS ERYTHEMATOSUS

### Background (*NEJM* 2011;365:2110)

- Polygenic autoimmune disease linked to various HLA subtypes, immune signaling, & environmental factors → autoantibody production & T-cell dysfunction
- Cutaneous lupus erythematosus is often assoc w/ SLE (see *"Systemic Lupus Erythematosus"*) & always accompanied by photosensitivity; divided into 3 main subtypes:
  1. Acute (ACLE) = pathognomonic for SLE
  2. Subacute (SCLE) = 50% overlap w/ SLE, ~25% risk of progression to SLE w/in 3 years of dx (*Br J Dermatol*

2011;164:1335)
3. Chronic (DLE); 18% risk of progression to SLE w/in 3 years of dx (*Br J Dermatol* 2011;164:1335)

- Can occur w/ or w/o systemic disease (see *"Systemic Lupus Erythematosus"* for SLE criteria)

## Manifestations (*Am J Clin Dermatol* 2009;10:365; *Br J Dermatol* 2011;164:1335)

- **Acute cutaneous lupus erythematosus:** Symmetric erythema of malar cheeks, nasal bridge + mild scaling, *sparing of the nasolabial folds* ("butterfly rash"), oral erosions, photosensitivity, discoid-like lesions; this presentation pathognomonic for SLE (see *"Systemic Lupus Erythematosus"*)
- **Subacute cutaneous lupus erythematosus:** Erythematous, symmetric **annular, or psoriasiform plaques** in sun-exposed areas (i.e., chest, shoulders, back); pts exquisitely photosensitive
- **Discoid lupus erythematosus:** Violaceous/erythematous scaly plaques, hypopigmented scarring, hyperpigmented borders on **scalp, face, ear**; follicular plugging; scarring alopecia in 50% of cases

## Management

- If suspect above, perform full hx/PE including rheumatologic ROS; **meds** to r/o drug-induced SLE (minocycline, penicillamine, TNF-α inhibitors) or drug-induced SCLE (HCTZ [#1], terbinafine, CCBs, NSAIDs) (*Br J Dermatol* 2012;167:296; 2011;164:465)
- **Studies:** Labs (see *"Rheumatologic Testing");* skin bx to confirm dx

## Treatment (*JAAD* 2011;65:179)

- **PCP Initial tx: Photoprotection** (broad spectrum UVA + UVB, protective clothing), **smoking cessation**, mid to ↑ potency topical steroids (class I–IV) (body), low-potency steroids for face (VI, VII) (see *"Topical Corticosteroids"*)
- **When to refer:** If e/o cutaneous lupus dx → **Derm referral** for mgmt as above & consideration of other topical tx (Tacrolimus, intralesional steroids for DLE) or systemic tx (antimalarials, MTX, thalidomide); if e/o SLE → Rheum referral (see *"Systemic Lupus Erythematosus"*)

# DERMATOMYOSITIS

## Background (*Arch Dermatol* 2010;146:26; *JAAD* 1998;39:899; *Arch Dermatol* 2002;138:885)

- Inflammatory myopathy characterized by proximal muscle weakness & characteristic cutaneous eruption; due to T-cell–mediated complement deposition in small vessels → vasculopathy; typically present w/ cutaneous & systemic manifestations
- Incidence ~1/100,000; ♀:♂ is 2:1; more common in African-Americans; 20–25% of cases assoc w/ malignancy, ovarian, & lung most common, also GI & lymphoma

## Manifestations (*JAAD* 1998;39:899; *Pediatr Dermatol* 2011;28:357; *Arch Dermatol* 2010;146:76)

- **Cutaneous: Poikiloderma** (hyperpigmentation, hypopigmentation, telangiectasias, atrophy), **pruritus & burning** (vs. CLE), & violaceous erythema; *Heliotrope sign:* Violaceous erythema & edema of the upper eyelids; *Gottron papules:* Red–purple flat-topped papules over dorsal hand joints; larger plaques on elbows, knees; *Mechanic's hands:* Fissured, scaly, hyperkeratotic plaques on hands & fingers; ragged cuticles, dilated capillaries of nail folds; *Shawl sign:* Erythema & poikiloderma on the upper back & shoulders
- **Systemic:** Fatigue, myalgia (80% w/ myopathy), arthralgias, dyspnea, dysphagia, cardiac

## Evaluation (*Arch Dermatol* 2002;138:885; 2010;146:729; 2010;146:780)

- Include medication hx to r/o drug-induced DM (hydroxyurea, penicillamine, statins, TNF-α inhibitors)
- **Labs:** CK, aldolase, CRP, LDH, LFTs, **serologies:** Anti Mi-2 (assoc w/ classic DM & good therapeutic response); Anti Jo-1 (histidyl-tRNA synthetase, assoc w/ ILD); Anti p155, 140 → assoc w/ malignancy; Anti CADM-140 → assoc w/ rapidly progressive ILD; skin and/or muscle biopsies to confirm dx
- **Age-appropriate malignancy screen**; consider CT of C/A/P, colon cancer screening; mammogram & gynecologic screen for ♀ done at the time of dx & annually for next 3–5 y
- **Further studies:** Consider: PFTs w/ DLCO to r/o ILD, barium swallow

to eval dysphagia, MRI to eval muscle disease

### Treatment (*JAAD* 2008;59:99)

- **PCP initial treatment: Photoprotection** (broad spectrum UVA + UVB, protective clothing), topical steroids
- Refer all pts to **rheumatology & dermatology** for consideration of systemic tx: Antimalarials (for cutaneous disease), prednisone, AZA, MTX, MMF, IVIg

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## Morphea and Systemic Sclerosis

### Background (*JAAD* 2011;64:217; *NEJM* 2009;360:1989)

- **Definition:** Fibrosing d/o localized to skin (morphea) or w/ systemic involvement (SSc)
- Morphea incidence ~2.7/100,000; ♀:♂ is 4:1; ↑ in Caucasians; SSc incidence ~2.3/100,000; ♀:♂ is 3:1 (onset in 30s–50s)

### Clinical Features

- **Morphea:** Violaceous erythematous → sclerotic, indurated plaques w/ assoc alopecia; no Raynaud/acral sclerosis/nail fold capillaries (if ⊕ consider SSc)
- **Systemic sclerosis:** 2 types: (1) **Limited disease (CREST)** → Calcinosis, Raynaud, Esophageal dysmotility, Sclerodactyly, Telangiectasias; (2) **Diffuse disease:** Sclerotic indurated plaques begin distally → proximally, beak-like nose, microstomia, ± telangiectasia, ± calcinosis, ± "salt & pepper" hypopigmentation → renal, GI, pulm involvement

### Evaluation (*Arch Derm* 2009;145:545; *JAAD* 2011;64:217; *Arthritis Rheum* 2003;49:399)

- **History:** GI (dysphagia, GERD, PUD), Cardiopulmonary (DOE, cough, ↓ exercise tolerance, pleuritic CP), Renal (usually acute/severe: Hematuria, edema, HA), Rheum (arthralgias/myalgias), Constitutional (fatigue, malaise)
- **Labs:** Scl-70, anticentromere (see *"Rheumatologic Testing"*)

## Treatment (*JAAD* 2011;64:217; *Rheumatol* 2009;48(S3):14)

- **Morphea:** Referral to **dermatology** for tx options (MTX, phototherapy, tacrolimus)
- **Systemic sclerosis:** Referral to **rheumatology & dermatology** for tx (MTX, MMF, imatinib, cyclophosphamide)

# ROSACEA

## Background (*J Invest Dermatol Symp Proc* 2011;15:2)

- Chronic relapsing and remitting d/o; 2.7–10% prevalence among those w/ N. European ancestry
- **Epidemiology:** Onset btw 30–50 y; ↑ in ♀ & fair-skinned individuals; often ⊕ FHx
- **Pathogenesis:** Uncertain, may involve dysregulated innate immunity, inflammatory reaction to cutaneous microbes, ↑ angiogenesis & VEGF expression in response to UV light

## Diagnosis (*NEJM* 2005;352:793)

- **Diagnosis: clinical:** 4 major subtypes, but features may overlap; skin bx used only to r/o other dx

**Rosacea Subtypes (*JAAD* 2002;46:584)**

| Subtype | Morphology/Characteristic |
|---|---|
| **Erythematotelangiectatic** (most common) | Persistent **centrofacial erythema, flushing, telangiectasias**, ↑ cutaneous Se |
| **Papulopustular** | Centrofacial erythema; small dome-shaped erythematous papules & pustules; variant: **Perioral dermatitis** (unlike acne, pruritic & no comedones) |
| **Phymatous** | **Rhinophyma** (sebaceous gland hypertrophy w/ dilated pores, tissue hypertrophy if severe) occurring predominantly in ♂ on nose; chin, forehead, ears, eyelids may also be involved |
| **Ocular** | May be seen w/ other subtypes; nonspecific ocular itching, gritty sensation, dryness, conjunctival injection, recurrent chalazion or hordeolum, blepharitis; keratitis, uveitis, scleritis, or episcleritis rare |

(Adapted from *NEJM* 2005;352:793)

- **Elicit triggers in medical history:** Sun exposure, temperature

extremes, EtOH, hot liquids, spicy foods, exercise, topical irritants & **distinguish between other causes of flushing** (e.g., menopause, anxiety, carcinoid, mastocytosis, pheo); **assess ocular sx**

- **Differential diagnosis** for erythematotelangiectatic & papulopustular subtypes: Dermatoheliosis (photoaging), **SLE** (sparing of nasolabial folds, no pustules); seb derm (can occur simultaneously but has greasy yellow scale & occurs on facial creases/eyebrows), acne vulgaris (no comedones or scarring w/ rosacea), steroid-induced dermatitis (can be periorificial), & *Demodex* mite folliculitis

## Treatment (*NEJM* 2005;352:793)

- **General approach:** Aimed at ↓ bacterial burden & inflammation, ↓ trigger exposure
- **Nonpharmacologic treatment:** Sunscreen w/ UVA/UVB protection via physical barriers (titanium dioxide or zinc oxide), moisturizers, avoid harsh cleansers w/ acetone & vasodilating drugs (e.g., CCBs or nicotinic acid), **trigger avoidance**
- **Medical/surgical treatment:** Inflammatory lesions generally responsive to medication; telangiectasias or phymatous changes require lasers or surgery
- **Erythematotelangiectatic:** Difficult to treat; focus on behavioral modification & trigger avoidance; topical tx used for papulopustular subtype may irritate sensitive skin, evidence limited for light-based therapies for destruction of vessels
- **Papulopustular** (*Cochrane Database Syst Rev* 2011;3:CD003262)
  *Topical tx:* **MNZ 0.75% gel or cream QD–BID** (1st-line); 10% Na sulfacetamide/ 5% sulfur BID crm or lotion; azelaic acid 15% gel BID (↑ effective but ↑ irritating); benzoyl peroxide 2.5–10% gel, crm, or lotion QD–TID
  *Systemic tx:* If mod/severe, **doxycycline 50–100 mg QD or BID** × 6–12 wks; minocycline 50–100 mg BID × 6–12 wks; or MNZ 200 mg QD or BID × 4–6 wks; may need topical maintenance Rx
- **Phymatous:** Surgical excision or laser ablation
- **Ocular:** Eyelid hygiene (flush lids w/ water BID), artificial tears for mild sx; **refer promptly to ophthalmology for serious or persistent sx**; CsA 0.5% ophthalmic emulsion may be more effective

than artificial tears, & systemic abx may be used if local Rx fails (*Cochrane Database Syst Rev* 2011;3:CD003262)

# SCABIES

## Background (*NEJM* 2010;362:717)

- Infestation by mite *Sarcoptes scabiei* affects ~300 million worldwide; more common in debilitated pts or hx neuro d/o (crusted scabes), impoverished communities, group/crowded housing facilities
- **Transmission:** Close personal contact (including sexual), contaminated clothing (rare)
- **Pathogenesis:** Fertilized ♀ mite burrows into the stratum corneum → lays eggs → adult mites; affected individual typically has 10–15 mites at any given time; mites can live 24–36 h away from human host; skin eruption corresponds to degree of type IV hypersensitivity to mite, which begins ~2–4 wks after initial infestation

## Clinical Manifestations and Diagnosis (*NEJM* 2006;354:1718; *BMJ* 2005;331:619)

- **History:** Risk factors as identified above; **itching ↑ at night**, nipples in ♀, genitalia in ♂, **pruritus out of proportion to exam**, ask if household contacts have itching
- **Exam findings:** Erythematous papules, **linear burrows** (thread-like 5 mm gray-white ridges, representing tunneling of the mite), vesicles & pustules, **penile & scrotal nodules**; *2° characteristics:* Excoriations, sanguineous crust, lichenification (chronic cases)
- **Distribution:** In adults, usually spares face & scalp; flexural: **finger webs**, volar wrists, axillae, inframammary; periareolar, periumbilical, **genital**
- **Differential diagnosis:** Tinea, AD, drug eruption, dyshidrotic eczema, bullous pemphigoid, seb derm, psoriasis, Langerhans cell histiocytosis
- **Ancillary studies: Mineral oil prep:** Most accurate on burrow on hands or wrists → no. 15 blade to scrape skin/stratum corneum → add a drop of mineral oil to slide → observe under microscope, dx made by identifying intact mite and/or eggs/feces; **skin bx:** Often

doesn't reveal mite, shows hypersensitivity reaction

## Treatment (*Lancet* 2006;367:1767; *Cochrane Database Syst Rev* 2007;CD000320)

- **First-line: Permethrin 5% cream**; most widely used & effective topical agent; apply to skin from neck down for 8–10 h (before bedtime → wash off in the AM); repeat in 1 wk
- **Alternatives: Ivermectin** (1st-line for crusted scabies [see below] & large outbreaks): Not FDA approved; 200 μg/kg (dispensed in 3 & 6 mg tablets) in single dose, repeat 2 wks later; similar efficacy to permethrin, but better compliance
  **Lindane 1% lotion:** 2nd-line; organochlorine pesticide, can → neurotoxicity (numbness of skin, tremor); should not be used in pts ≤110 lbs (*MMWR* 2005;54:533–535)
- **Decontamination:** Mites cannot survive outside of human host for more than 3 d; linens & clothing should be placed in sealed plastic bags for 3 d → machine-washed & dried in hot dryer (>50°C)
- **Prophylaxis in close contacts:** Single application of topical permethrin as above

## Complications (*Lancet* 2006;367:1767; *Lancet Infect Dis* 2006;6:769)

- **Crusted scabies:** Hyperinfection w/ hundreds of mites 2/2 host immunosuppression (i.e., AIDS, post transplant), also seen in trisomy 21 or neuro impairment; *S/sx:* Heavy hyperkeratotic scale & powdery crust due to high mite carriage; *Tx:* Oral ivermectin ± permethrin ± keratolytic agent (*NEJM* 1995;333:26; 1995;332:612; *JAAD* 2004;50:819)
- **Postscabetic hypersensitivity: Most common sequela**; eczematous & pruritic; may persist for 1–2 wks after successful tx; tx w/ topical corticosteroids and/or antihistamines
- **Secondary infection:** *S. aureus:* Impetigo, furunculosis; *S. pyogenes:* Soft tissue infections; can rarely → poststrep GN
- **Patient information:** http://cdc.gov/parasites/scabies

# NONMELANOMA SKIN CANCER

## Definition and Pathogenesis

- Includes BCC, SCC, MCC; precursors to SCC include AKs & SCC *in situ*
- Sun exposure is primary cause of melanoma & nonmelanoma skin cancer: Cumulative risk of BCC/SCC linked to cumulative sun exposure
- UVB excites DNA → pyrimidine dimers (esp TT dimers) which are carcinogenic, esp in the basal layer of the epidermis; p53 mutations → resistant to apoptosis

## Epidemiology and Risk Factors (*AFP* 2012;86:161; *Arch Dermatol* 2000;136:1524)

- Generally, highest incidence in older, fair-skinned pts w/ long-term sun exposure
- Other risk factors: **Tanning beds** (1.5× ↑ risk of BCC, 2.5× ↑ risk of SCC), **Prior nonmelanotic skin CA** (risk of 2nd nonmelanotic skin CA 35% at 3 y, 50% at 5 y), Solid organ tx (10× ↑ risk of BCC, 65× ↑ risk of SCC: Heart/lung > > kidney > > liver, esp those on AZA, CsA (*JAAD* 2011;64:981), chronic voriconazole, vemurafenib), hx ionizing radiation (esp as child)
- **SCC-specific associations:** CLL, burns (Marjolin ulcers), chronic wounds, HPV (subtypes 16, 18, 33), **smoking** (*Arch Dermatol* 2012;148:939)
- **Prevention: Photoprotection is key:** Daily sunscreen use for 4.5 y ↓ risk SCC by 35% (*Cancer Epi Bio Prev* 2006:2546); see Prevention section of *"Melanoma"*

## Actinic Keratoses (*Br J Dermatol* 2007;157:S18;*JAAD* 2013;68:S2)

- **Epidemiology:** Prevalence in US 16–25%; incidence ↑ w/ age
- In patients w/ 7–8 AKs, risk of developing invasive disease is 6.1–10.2% over 10 y
- **Diagnosis/morphology:** Skin-colored, pink, or erythematous macules **w/ gritty scale** (no papule); easier to feel than to see; cutaneous horns (15% w/ SCC at base); ↑ **head, neck, forearms**
- **Treatment:** Individual lesion destruction or field Rx (5-FU 0.5% or 5% crm, diclofenac 3% gel, imiquimod 5% crm, ingenol mebutate gel, photodynamic Rx); caution w/ cryotherapy unless confident of dx

(SCCs, SKs, melanomas can mimic AK)

## Basal Cell Carcinoma

- **Epidemiology:** Most common skin cancer; rarely metastasize but locally invasive & destructive; recurrence risk is 30% (*JAAD* 1990;22:413)
- **Morphology:** Pearly translucent papule or plaque w/ telangiectasias, often eroded; can have globules of pigment; rolled border
  *Superficial variant:* Poorly defined pink patches w/ scale (Ddx: SCC-IS, eczema)
- **Distribution:** Can occur anywhere (~33% in areas w/o direct sun exposure), but most often on head/neck (85%), 25% of all lesions occur on **nose** (*AFP* 2012;86:161)
- **Diagnosis:** Shave or punch bx
- **Treatment:** Excision or electrodessication and curettage (ED&C) if superficial; topicals if superficial (imiquimod 5% crm or 5-FU 5% crm) >> cryotherapy; XRT considered for poor surgical candidates, debulking, or ↑-risk subtypes

## Squamous Cell Carcinoma in situ (Bowen Disease)

- Risk of transformation to SCC is 3–5% (*Dermatol Surg* 2011;37:1394)
- **Morphology:** Ill-defined pink scaly patches in sun exposed areas (Ddx eczema)
- **Treatment:** ED&C, excision, topicals (imiquimod 5% crm or 5-FU 5% crm)

## Squamous Cell Carcinoma (*JAAD* 2013;1:S019)

- **Epidemiology:** >700,000 new cases/y in US; 0.3–16% risk of metastic disease; incidence est 32–270/100,000 annually (no nat'l cancer registry); most pts >50 y
- **Morphology:** Eroded, friable, hyperkeratotic papules, plaques, nodules; pain can = perineural invasion (↑ risk)
- **Distribution:** Usually photodistributed; forearms/dorsum of hands most common
- **High-risk lesions:** (1) Histopathology: tumor thickness >2 mm,

perineural invasion; (2) Clinical location: lips, genitals, ear; immunosuppression; recurrent tumors
- **Diagnosis:** Shave bx (must get lesion base) or punch bx
- **Treatment:** Low-risk lesions on the trunk, extremities → excision; lesions on head/neck over 2 cm → Mohs micrographic surgery (tissue preserving, margin-controlled, cutaneous surgery achieved using local anesthesia), XRT considered for poor surgical candidates or for debulking

### Merkel Cell Carcinoma (*JAAD* 2008;58:375)

- **Most lethal of all skin cancers** including melanoma; mortality is 33%
- Most lesions presumed benign at time of dx (can resemble BCCs, asx, nontender, red or pink violaceous papules & nodules)
- **Acronym:** AEIOU (Asx; Expanding rapidly, **Immunosuppressed**, Older than 50 y, UV exposed site on fair skin)
- Workup/treatment: Sentinel LN bx, surgery & radiation

### Red Flags

- Any lesion w/ rapid growth, ulceration, spontaneous bleeding, pain
- Any nonhealing or enlarging lesion in an immunosuppressed pt
- Persistent hyperkeratotic or eroded lesions on the lip, ear, or "H" zone of the face
- Any lesion >2 cm on the extremities or trunk

### When to Refer

- Clinically suspicious lesion for BCC, SCC, or MCC; red flags (above); thick (hypertrophic) AKs or many lesions that require field tx; bx shows atypical nevus or melanoma
- **High-risk individuals:** Prior skin CA, solid-organ transplant pts (should be seen q3–6mos), CLL

## TINEA

### Background (*BMJ* 2012;344:e4380)

- **Dermatophytes:** Fungi that only infect stratum corneum, hair, & nails → **"tinea"**; distinguished from deep mycoses, which have ↑ ability to disseminate
- **Microbiology:** 3 dermatophyte genera: *Trichophyton* (most common), *Microsporum*, & *Epidermophyton;* zoophilic organisms (e.g., *M. canis*) have animal reservoirs, tend to cause ↑ inflammation than those restricted to humans
- **Transmission:** Person–person, autoinoculation, or via fomite (floor, gym mat, shower stall)
- Dermatophytoses largely characterized by **site of infection**

## Epidemiology and Risk Factors (*Clin Dermatol* 2010;28:197)

- 20% of world's population is affected; *T. rubrum* most common
- **Risk factors:** Hot, humid climates; local immunosuppression of the skin (topical corticosteroids), systemic immunosuppression (AIDS, transplant pts), animal contact, use of communal bathing facilities & occlusive footwear (onychomycosis)
- Extensive disease in adults should raise question of immunosuppression (e.g., HIV)

## Clinical Presentation

**Superficial Mycoses**

| Dermatophytoses | |
|---|---|
| **Subtype** | **Presentation** |
| Tinea pedis ("athlete's foot") | Can be intensely pruritic or asx, usually **bilateral**; gradually progressive, duration = mos–y<br>*Interdigitary skin:* (Most common/initial site) **white maceration/ fissuring or dry scale**<br>*Soles/lateral feet:* Well-demarcated erythema w/ powdery or hyperkeratotic, occasionally peeling "moccasin scale"<br>Often w/ simultaneous tinea cruris or onychomycosis (check groin & buttocks if feet involved)<br>**Ddx: Psoriasis**, AD, pityriasis rosea, 2° syphilis |

| | |
|---|---|
| Tinea unguium (onychomycosis) | Common w/ ↑ age, DM, tinea pedis, occlusive footwear<br>Yellow, thickened nail plate, **subungual hyperkeratotic debris**, nail plate lifting off nail bed (**onycholysis**)<br>Types: Distal plate (most common), also white superficial (spots which coalesce at nail plate), proximal subungual (HIV)<br>Ddx: Candida, other yeast (esp in tropical climates & in pts w/ DM or immunosupp); psoriasis |
| Tinea corporis "ringworm" | Common in younger adults; ⊕ pruritus<br>Erythematous pinpoint papules initially → **annular** patches w/ **central clearing** & enhanced border; **trailing scale**<br>Ddx: ACD, AD, psoriasis |
| Tinea cruris ("jock itch") | More common w/ ♂ gender, obesity<br>Well-demarcated dull red/tan plaques w/ overlying scale on thighs, inguinal region (scrotal involvement rare)<br>Cruris Ddx: Candida, erythrasma (coral-red fluorescence w/ Wood lamp) (*Br J Dermatol* 2003;149:S65:1) |

- **Other tinea subtypes** (*BMJ* 2012;344:e4380)
  *Tinea barbae:* Unilateral, tender boggy papules & plaques over bearded area
  *Tinea manuum:* Dry, scaly erythematous, burning patches on hand, **often unilateral**
  *Tinea faciei:* Asymmetric annular plaques often w/ trailing scale on face; Ddx seb derm
  *Tinea capitis:* Typically immunocompromised; "black dots" (broken-off hairs) in round patches of alopecia; Ddx: Seb derm, trichotillomania, cutaneous lupus (scarring)
- **Dermatophyte-related eruptions**
  *Dermatophytids:* "Id reaction"; widespread hypersensitivity most common w/ inflammatory tinea capitis; pinpoint monomorphic pruritic papules on palms/soles
  *Tinea incognito:* Tinea where scale is obliterated by use of emollients (usually topical steroids); key to dx is annular morphology, leading edge
  *Majocchi granuloma:* Fungal folliculitis: Tinea invades dermis/follicle; *T. rubrum* most common; erythematous to violaceous papules → annular boggy plaque; shins of women is classic (often due to shaving); ↑ risk w/ topical corticosteroid

## Diagnostic Tools

- **Microscopy:** Use in **all pts** in whom tinea is suspected; 15 blade used to scrape scale onto slide; apply coverslip & 1–2 drops of 10–20%

KOH w/ DMSO or Swartz Lamkins; view on low & high power to confirm septate hyphae

- **Culture:** Scale or nail clipping sent in saline or w/o medium (depending on lab); only definitive means of fungal speciation
- **Nail clippings:** Used to dx onychomycosis, most often to confirm infection before starting PO Rx; send for culture or in formalin for PAS stain
- **Wood lamp (365 nm):** Useful to identify certain subtypes of tinea capitis that fluoresce blue-green (most commonly *M. canis*) or dx erythrasma (coral-red)

## Treatment

- **General approach:** Esp important to Rx tinea pedis in all immunocompromised or DM pts due to ↑ risk of SSTI (from breakdown of skin barrier); if tinea pedis occurs in presence of onychomycosis, it can recur unless onychomycosis is treated; Nystatin **not** effective against tinea
- **Counseling:** Use ventilated shoes if possible; wear socks (cotton) w/ shoes; completing full tx course important for effectiveness; in recurrent diseases, assess for pet exposure; wash contaminated clothes, towels, socks, footwear
- **Topical:** Indicated for initial tx of tinea pedis, corporis, cruris; avoid combination antifungal/steroid products as can worsen tinea and → fungal folliculitis (above)
- **Systemic:** Consider in severe/refractory cases or immunocompromised pts, also for **onychomycosis** (or tinea pedis in presence of onychomycosis), tinea capitis, or Majocchi granuloma (fungal folliculitis)

**Tinea Treatment by Location**

| Type | Treatment |
|---|---|
| Tinea pedis | **Topical azole** (e.g., econazole 1% crm) daily × 4–6 wks<br>**Terbinafine** 1% crm topical daily × 4–6 wks (OTC)<br>**Ciclopirox** gel/crm 0.77% BID × 1–4 wks<br>(*BMJ* 1999;319:79) |
| Tinea unguium | **Terbinafine** 250 mg PO daily × 6 wks for fingernails, 12 wks for toenails—**most effective** (about 80%) (*Br J Dermatol* 2004;150:537)<br>**Itraconazole** 200 mg daily × 3 mos; or 400 mg/d for 1 wk, monthly for 3–4 mos (latter regimen is not FDA approved)<br>Nail avulsion (podiatry, dermatology) |
| Tinea corporis<br>Tinea cruris | **Topical azole** (e.g., econazole 1% crm) daily × 4–6 wks<br>**Terbinafine** 1% crm topical daily × 4–6 wks (OTC)<br>**Ciclopirox** gel/crm 0.77% BID × 1–4 wks (*BMJ* 1999;319:79) |

(*BMJ* 2012;344:e4380)

- **When to refer:** Consider derm referral if skin infections fail to improve w/in 1 mo, nail infections fail to improve w/in 3 mos, or either clinically *worsens* with tx

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## NONDERMATOPHYTIC CUTANEOUS FUNGAL INFECTIONS

### Selected Nondermatophytoses

| Organism | Presentation | Treatment |
|---|---|---|
| Tinea versicolor (*Malassezia furfur*) | **Salmon-colored**, hypopigmented, or hyperpigmented patches w/ **brawny scale** on V-chest, shoulders, upper back<br>**"Spaghetti & meatballs"**—hyphal & round yeast forms on KOH | Selenium sulfide lotion QD × 1 wk (leave on for 10 mins); **ketoconazole** crm or shampoo used as body wash QD × 2 wks (*JAAD* 1986;15:500) |
| Cutaneous candidiasis (*C. albicans*) | Intertrigo: Macerated, **erythematous** ("beefy red"), fissured, **eroded** plaques, w/ **satellite papules** or pustules in folds; ⊕ **burning or skin pain**<br>Risk factors: Warmth, moisture, oral abx | Topical azole, nystatin crm/ powder; consider fluconazole 150 mg PO × 1 |

# TOPICAL CORTICOSTEROIDS

### Selected Topical Corticosteroids (*AFP* 2009;79:135) (*www.aad.org*)

| Class/Potency | Name & Concentration | Formulation |
|---|---|---|
| I (ultra-high) | Betamethasone dipropionate 0.05% | O |
| | **Clobetasol propionate 0.05%** | C, G, O, L, So, F |
| II (high) | **Fluocinonide 0.05%** | C, G, O |
| III (high) | Fluticasone propionate 0.005% | O |
| IV (mid) | **Triamcinolone acetonide 0.1%** | C, O |
| V (low-mid) | Fluocinolone acetonide 0.025% | C |
| VI (low) | **Desonide 0.05%** | C |
| | Fluocinolone acetonide 0.01% | So |
| VII (least potent) | **Hydrocortisone 2.5%**<br>Hydrocortisone 1% (OTC) | C, L |

*C, cream; F, foam; G, gel; L, lotion; O, ointment; So, solution*

## General Approach (*www.aad.org*)

- **Steps in prescribing topical corticosteroids**
  1. Determine an appropriate vehicle
  2. Determine potency required
  3. Determine appropriate amount to dispense
  4. Select appropriate Rx given above; note certain topical steroids can be very expensive/not covered by insurance; above table includes only generics
  5. Counsel pts on appropriate use: amount, duration, & s/e (see below)

## Vehicle (*www.aad.org*)

- Choice should be determined by location & patient preference
  **Vehicle also dictates potency (oint [most potent] > crm > lotion)**
- **Ointment:** Lipophilic base (often petrolatum); occludes epidermis, "traps" Rx next to skin, most hydrating; best for hyperkeratotic lesions & nonhair bearing skin (palms/soles, trunk ok); avoid in intertriginous areas (too potent & can → maceration)
- **Cream:** Base includes water, less "greasy" & nonocclusive; often preferred by pts, good on trunk, face, neck
- **Lotion:** Includes water & ± EtOH; more drying, good for hair-bearing areas (e.g., genitalia); can sting when applied
- **Solution, foam:** Preferred for scalp
- **Gel:** Jelly-like, consider use for exudative lesions (i.e., acute contact dermatitis)

## Potency

- Use class to determine potency; cannot compare strengths of concentration across different molecules (e.g., hydrocortisone 2.5% *not* more potent than desonide 0.05%)
- Consider **location** of lesion, **etiology** of lesion, & its **severity**
- **Location:** Thicker skin (palms, soles) require ↑ potency; thinner skin (face, genitalia) require ↓ potency
- **Etiology:** Certain dermatoses require higher potency (psoriasis); some more responsive & respond to lower potency agents (seb derm)
- **Severity:** Not all lesions are created equal; trial of lower potency appropriate for milder disease; can up titrate as necessary
- Reserve high-potency steroids for areas of thick skin (e.g., acral skin, lichenified lesions) or in lesions refractory to lower potency steroids; avoid use in intertriginous regions (e.g., axilla, groin)

**Vehicle and Potency by Site**

| Site | Suggested Steroid Class |
|---|---|
| Scalp | Consider starting w/ Class IV → okay to escalate |
| Palms/soles | Class I or II |
| Periorbital | Class VII |
| Face/neck, Intertriginous areas | Class VI or VII |
| Trunk/extremities | Moderate inflammation: Class III–V |
| | Severe inflammation or thick plaques on extensor surfaces: Class I—II |
| Genitalia | Class V–VII |

(Adapted from: Schalock, eds., Primary Care Dermatology, 2010)

## Application (*AFP* 2009;79:135; *www.aad.org*)

- **Common causes of treatment failure:** Nonadherence, underapplication, tachyphylaxis (↓ response to one steroid over time), messiness/dislike of vehicle
- **Quantity:** Consider % body surface area involved; inadequate amount Rx'ed → underapplication; excessive amount Rx'ed can → extended duration of use w/o follow-up (e.g., avoid Rx'ing >15 g for facial lesion)
  *Single application:* 2% BSA (2 palms) requires 0.5 g; covering avg adult body requires 30 g

*1 month's worth of BID application:* Face → 30 g; extensor surfaces of both arms → 120–150 g; widespread on trunk, legs, arms: → 1–2 lb (454 g = 1 lb)

- May consider occlusion on acral surfaces (e.g., plastic wrap) to ↑↑ potency, but → ↑ risk of s/e

## Counseling

- **Duration:** ≤2 mos of consecutive use, stop tx when condition resolves (taper by ↓ freq and/or potency q2wks to avoid rebound); for face, intertriginous areas, **or** class I (ultra-high potency): ≤3 wks of consecutive use **or** if recurrent, use for 1–2 wk intervals to avoid s/e
- **Side effects: ≠ Potency & duration Æ ≠ risk**; should be discussed w/ all pts; write on all higher potency Rx: "Not for face, armpit, or groin"; s/e include **atrophy** (striae, telangiectasias, ↑ fragility); much of this damage can be **permanent; infection** (can worsen/mask); **hypopigmentation; systemic s/e** (if ↑ potency/duration/BSA; see *"Cushing Syndrome"*); **glaucoma/cataracts** in chronic periocular use

## When to Refer

- Patients who are not responsive despite above recommendations → **refer to dermatology**, regardless of etiology; consider referral in pregnant/breastfeeding pts

# URTICARIA

## Definitions and Epidemiology (*Allergy* 2009;64:1427; 2011;66:317)

- Type 1 (IgE-mediated) hypersensitivity reaction w/ numerous causes, characterized by the appearance of **wheals**; lifetime prevalence 20% (*AFP* 2011;83:1078)
- **Acute:** Duration <6 wks; accompanied by angioedema in 40% of pts (*NEJM* 2002;346:175)
- **Chronic:** Duration >6 wks, lifetime prevalence 1%, peak age 20–40 y, ♀ > ♂; majority of cases will resolve w/in 1 y

## Etiology (*Allergy* 2009;64:1417; 2011;66:317; *Br J Dermatol* 2010;163:275)

- **Pathophysiology:** IgE → mast cell degranulation → histamine release → plasma leakage into skin → wheals
- **Acute:** #1 cause is infection: **URIs** (esp streptococcal, viral); **medications** (PCN #1, ASA, NSAIDs); **food** (strawberries, peanuts, shellfish, tomatoes, eggs, milk, in pts w/ latex allergy: Chestnuts, banana, passion fruit, kiwi, avocados), ~**50% idiopathic**
- **Chronic: Idiopathic most common** (*J Allergy Clin Immunol* 2012;129:1307); may also be 2/2
  *Autoimmune:* SLE, Sjögrens, RA, anti-IgE receptor IgG antibodies, thyroid disease
  *Food additives:* Yeast, azo dyes, benzoic acid, sulfites, nickel
  *Infections:* HBV, HCV, *H. pylori*, parasitosis (in developing countries)
  *Hematologic malignancy* (rare) (*Arch Dermatol* 2012;148:103)
  *Physical:* Exercise, cold weather, dermatographism ("skin writing")

## Clinical Findings (*NEJM* 2002;346:175)

- Pink/erythematous edematous plaques, can be **arcuate or polycyclic** w/ central clearing, no scale; pruritic; ± soft tissue edema of lips, upper airway, eyelids, genitalia (angioedema)
- By definition, each **individual** lesion **must resolve in 24 h** → migratory appearance (circled lesion "disappears")

## Evaluation (*Allergy* 2009;64:1417; 2009;64:1427; 2011;66:317; *NEJM* 2002;346:175)

- **History:** Provoking features (medications, physical factors, infections), duration of individual lesions, freq of attacks; ask about SOB, angioedema (signs of anaphylaxis)
- **Labs:** *Acute:* none; *chronic:* CBC w/ diff, ESR, consider TSH, anti-TPO, ANA, *H. pylori*, hep panel
- **Differential diagnosis:** Urticarial vasculitis (**painful**), bullous pemphigoid (esp in elderly; lesions **not** migratory), Sweet's syndrome, mastocytosis, erythema multiforme (targetoid, not migratory), serum sickness; hereditary or ACEI-induced angioedema (no wheals)

## Treatment (*Allergy* 2009;64:1427; 2011;66:317; *NEJM* 2002;346:175)

- **General approach:** Treat underlying cause 1st whenever possible; topical agents typically have no role in mgmt; anyone w/ s/sx suspicious for anaphylaxis needs IM epinephrine (0.3 mL of 1:1000 dilution) & → to ED

**Management of Urticaria**

| Types | Interventions |
|---|---|
| Acute | 1st line: Nonsedating H1 antihistamines<br>2nd line: Consider oral corticosteroids (for 3–5 d, if no response to antihistamines; rebound may occur) |
| Chronic | 1st line: Around-the-clock nonsedating H1 antihistamines ± sedating H1 antihistamines; if no response in 2 wks → consider ↑ nonsedating antihistamines up to 4× standard dose (*Allergy* 2011;66:317; 2002;346:175)<br>2nd line: Change nonsedating H1 antihistamine; other agents per consensus recs (*Allergy* 2009;64:1427); omalizumab (anti-IgE) shows some relief for pts w/ mod–severe disease; SC injection; expensive (*NEJM* 2013;368:2527)<br>Avoid NSAIDs, ASA, salicylates<br>Trial of food additive-free diet |

(*Cochrane Database Syst Rev* 2012;14:CD008596; *AFP* 2011;83:1078)

## When to Refer

- **Dermatology:** Individual lesions persist for >24 h, assoc w/ postinflammatory purpura or pigmentation, bullae, skin pain; chronic urticarial for further mgmt
- **Allergy:** If ↑ suspicion for environmental, food, or med hypersensitivity → serologic (RAST) or prick testing; for consideration of newer generation antihistamines or omalizumab

# WOUND CARE

## Definitions

- Epidermal injury → **"erosion"** → wound regeneration, **no scar**
- Dermal injury → **"ulcer"** → wound repair, **scar**, & contraction; final strength ≤80% of original
- Primary intention: Wound edges are surgically approximated
- Secondary intention: Wound left to heal w/o approximation

## Stages of Wound Healing (*JAAD* 2008;58:185)

- **Stage 1: Inflammatory:** Platelets → PMNs → macrophages and fibroblasts
- **Stage 2: Proliferative:** First week, angiogenesis, collagen production
- **Stage 3: Remodeling w/ contraction:** Second week; contraction via myofibroblasts; at 3 wks, at 20% of final tensile strength

## Factors Adversely Affecting Wound Healing (*JAAD* 2008;58:185)

- Advanced age, DM, PAD/PVD, hypercoagulability, anemia, transfusions, malnutrition, hep, drugs (chemotherapies, **systemic glucocorticoids** (*Curr Probl Surg* 2007;44:691), Raynaud, **smoking**, HIV, **bacterial colonization** or **allergic reaction** (i.e., adhesives, latex, neomycin, bacitracin), necrotic tissue on wound base

## Evaluation of Wounds (*JAAD* 2008;58:185; *Clin Microbiol Rev* 2001;14:244)

- **History:** Etiology, past wound hx/tx/responses, pain characteristics, foreign bodies/prostheses/devices, resources/support system, **pathergy** (worsening w/ trauma), **factors affecting wound healing** (as above)
- **Physical exam:** Pulses, temperature, capillary refill, (consider ABI/TBI; see *"Peripheral Vascular Disease"*), edema, sensation, LAN, wound description (location size, shape, borders, texture: Consider including **photograph** in medical record), examine chronic wounds (esp burn scars) for signs of SCC (see *"Nonmelanoma Skin Cancer")* (*Plast Reconstr Surg* 2009;123:184)
- **Labs:** Routine labs not recommended; all wounds colonized so routine

culture unhelpful: Consider wound culture if new erythema, pain, purulence malodor, or obvious infection (see "*Skin and Soft Tissue Infections*")

## Acute Wound Management (*NEJM* 2008;359:1037; *JAMA* 1996;276:972)

- **Irrigation:** Clean w/ normal saline, high pressure if significant contamination
- **Tetanus vaccination:** http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5517a1.htm
- **Moisture:** Petrolatum preferred over topical abx— ↓ infection rate & ↓ contact allergy
- **Topical antimicrobial agents:** Consider on traumatic lacerations; avoid on surgical wounds given ↑ bacterial resistance, contact allergy (*Ann Emerg Med* 2013;61:86)

## Chronic Wound Management (*JAAD* 2008;58:185)

- **Emollients and occlusion:** Mod humidity important for wound healing
- **Infection/colonization management:** ↑ Bacterial burden impedes healing; topical antiseptics (e.g., Ag/silver agents, Dakin soln) & abx (e.g., mupirocin → Gram ⊕ coverage including MRSA; topical MNZ → Anaerobic); assess for honey-colored crusting (impetigo)
- **Debridement:** Removing fibrinous (yellow to gray) or necrotic adherent debris at ulcer base improves healing; *Physical:* Apply topical lidocaine 2.5% or prilocaine 2.5% → occlude w/ plastic wrap or Tegaderm for 30 mins → sharply curette debris; consider saline-soaked gauze for gentle debridement; *Enzymatic:* Collagenase to wound base QD–BID
- **Wound dressings** (*Arch Dermatol* 2007;143:1297)

**Common Wound Dressings**

| Dressing | Property | Wound |
|---|---|---|
| Low adherence (Telfa) | Cotton/viscose rayon backing covered by nonadherent coating | Superficial, dry |
| Paraffin gauze | Gauze w/ petrolatum | Superficial, dry |
| Semipermeable adhesive films (Tegaderm) | Porous to gas & water but not exudates → allow drying | Light exudates |
| Hydrogels (Vigilon) | Starch allows for fluid absorption w/o changing dressing | Mod exudates |
| Hydrocolloid (DuoDerm) | Gelatin ⊕ pectin dissolved by exudates → space occupying | Mod exudate, deep |
| Alginate (Sorbsan) | Forms fibrous gel w/ wound | Heavy exudate, deep |

(Data from: *Derm Clin* 1993;11:207, *Drug Ther Bull* 1991;29:97; Alguire PC, et al. Medical mgmt of lower-extremity chronic venous disease. uptodate.com)

- **Venous stasis ulcers** (see *"Lower Extremity Edema"*)

## When to Refer

- Failure of wound healing, complex wound mgmt, consideration of topical growth factors, vacuum-assisted closure devices

# NOTES

# ADRENAL NODULES

## Background (*Eur J Endocrinol* 2003;149:273; *AFP* 2010;81:1361)

- **Definition:** Mass lesion >1 cm visualized by imaging, usually incidentally during evaluation of unrelated process ("incidentaloma")
- **Epidemiology:** Incidence 8.7% in autopsy series (*Br J Surg* 1993;80:422); 4.4% in those undergoing unrelated abdominal CT (*J Endocrinol Invest* 2006;29:298); prevalence ↑ w/ age, obesity, DM, HTN; 10–15% of nodules are bilateral
- **Risk factors for malignancy:** ⊕ Personal hx of malignancy; lesion >4 cm in size, radiographic density >10 Hounsfield units, delayed contrast washout

### Adrenal Mass Classification (*Eur J Endocrinol* 2009;161:513; *Endocr Pract* 2009;15:S1)

| | |
|---|---|
| **Benign, nonfunctional** | **Adenoma** (~80% of all lesions), ganglioneuroma, myelolipoma, benign cyst |
| **Benign, hormonally active** | 5–15% of all lesions: Pheo (~3–5% of all lesions), cortisol-secreting ("Subclinical Cushing" ~5–6%), aldosteronoma (0.5–1%) |
| **Malignant** | 1° adrenal cortical carcinoma (ACC: 2–5% of all lesions), metastatic disease (0.7–2.5%) |

## Evaluation (*Endocr Pract* 2009;15:S1; *NEJM* 2007;356:601)

- **General approach:** (1) Is the nodule hormonally active?; (2) Does it have imaging characteristics concerning for malignancy?; (3) Does the pt have prior hx of malignancy?
- **History/Exam:** Eval for personal hx malignancy; examine for e/o adrenal hyperfunction, e.g., HTN, paroxysmal panic-like episodes (pheo), edema, hyperglycemia, striae (Cushing, see *"Cushing disease"*), hypokalemia, hyperandrogenism
- **Lab:** *All* pts w/ adrenal nodule merit testing for cortisol excess ± pheo

### Lab Testing (*Endocr Pract* 2009;15:S1)

| | |
|---|---|
| **Cortisol excess** | All pts w/ potential adenoma: Dexamethasone suppression test (DST) 1st-line (see *"Cushing"*) |
| **Pheochromocytoma** | Consider in all pts: Plasma-free metanephrines (if ↓ suspicion) or 24 h urine catecholamines/metanephrines (if ↑ suspicion) |
| **Aldosterone:renin ratio** | If HTN: Levels drawn at 8 AM; ⊕ if >20; spironolactone or eplerenone can → false ⊖ by ↑ renin |
| **Androgen testing** | If e/o hyperandrogenism: T, SHBG, DHEA-S |

- **Imaging:** For lesions <4 cm, adrenal-protocol CT or MRI indicated to delineate benign vs. malignant characteristics (as per radiology & noted above under "Risk factors")

## Management (*J Am Coll Radiol* 2010;7:754; *Endocr Pract* 2009;15:S1)

- All lesions >4 cm, those w/ malignant characteristics, pt w/ hx malignancy, or hormonally active lesions → surgical referral for likely resection vs. bx; pts w/ hormonally active lesions also → endocrine referral; pts w/ hx malignancy → referral back to oncology
- If no hx CA, nonfunctioning, imaging consistent with myelipoma or simple cyst → no further monitoring
- All other lesions (nonfunctioning, radiographically benign, no hx CA) → serial monitoring; details vary by professional society but principle of continual monitoring consistent; discuss planned algorithm with pt; American Association of Clinical Endocrinologist recs below:
  *Hormonal:* Annual reassessment × 5 y; if becomes active → referral for resection
  *Radiographic:* Repeat imaging at 3–6 mos, then annually for 1 y; if grows by >1 cm → referral for biopsy vs. resection
- **Primary hyperaldosteronism:** Can consider med mgmt for pts who decline or are poor surgical candidates: Na restriction, EtOH avoidance, healthy body wt, & either:
  *Spironolactone:* Nonselective mineralocorticoid receptor antagonist; monitor BP, K, & Cr when initiating; s/e: Gynecomastia, impotence, menstrual irregularities; caution w/ digoxin, NSAIDS
  *Eplerenone:* Selective antagonist; more expensive, consider if s/e with spironolactone (*J Clin Endocrinol Metab* 2008;93:3266)
- **Endocrine referral:** If dx uncertain, lab results difficult to interpret, or homonally active

## Patient Information

- http://www.urologyhealth.org/urology/index.cfm?article=89

# CALCIUM DISORDERS

## Background (*NEJM* 2011;365:2389)

- **Definition:** Determined by elevated *ionized* (free) Ca, which is physiologically active; *total Ca* (mg/dL) also measures Ca bound to albumin → value affected by ↓ ↑ albumin; to adjust for this, must calculate:
  Albumin-corrected total Ca = [measured Ca] + 0.8 × (4 − [albumin])
- **Physiology:** Serum Ca homeostasis normally tightly regulated; Ca in blood derived from diet, bone turnover, & reabsorption by kidneys; hypocalcemia → ↑ PTH → ↑ Ca (also ↓ phosphate) via ↑ bone release & ↑ renal reabsorption; ↑ production in 1,25OH Vit D → ↑ Ca by ↑ GI absorption (& ↑ bone release)

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## HYPERCALCEMIA

- **Etiology:** In outpt setting, most commonly 2/2 **primary hyperparathyroidism (1∞ HPT):** ↑ PTH despite ↑ or ↑ nl Ca, due to benign adenoma (80%) > 4-gland hyperplasia (15–20%) > carcinoma (~1%)
- **Epidemiology:** Incidence peaks age 70–79, ♂ > ♀ ~3:1 (♂ = ♀ at younger ages); ~5% hereditary (e.g., MEN-1, MEN-2a, FHH, hyperparathyroidism-jaw tumor syndrome)

**Etiologies of Hypercalcemia** (*JCEM* 2005;90:6316)

| Cause | Examples/Mechanisms |
|---|---|
| 1° Hyperparathyroidism | See above |
| Meds (usually mild) | Lithium (via ↑ PTH), excess of Vit D, Ca, Vit A, thiazides |
| Malignancy | Solid organ tumors (PTH-rP production &/or local osteolysis >> ectopic PTH); MM (cytokines); lymphoma ($1,25(OH)_2D$-production) |
| Granulomatous disease | Sarcoid, TB (25OH Vit D → $1,25(OH)_2$ Vit D w/in granuloma) |
| Renal disease | *Early:* ↓ Conversion 1,25 D by kidneys → ↑ PTH ("secondary hyperparathyroidism," often p/w **low** Ca)<br>*Late:* Over time, stimulated parathyroid gland → autonomous PTH production ("tertiary hyperparathyroidism", rare) |
| Other | Thyrotoxicosis, immobilization (esp w/ Paget), milk-alkali syndrome; Addison disease; familial hypocalciuric hypercalcemia (FHH, inactivating mutation of CaSR) |

## Evaluation (*AFP* 2003;67:1959)

- **General approach:** Determine if pt currently symptomatic (dictated by magnitude & rate of ↑ Ca); if so, consider admission; otherwise continue outpt w/u; if suspect medication-induced (usually mild), d/c med if possible, then recheck Ca
- **Signs and symptoms:** Dehydration (↑ urinary Ca excretion → polyuria), hx nephrolithiasis, CKD (also consider MM), constipation, bone pain, weakness, nausea, can also → fatigue, mood, or cognitive changes; severe disease can p/w somnolence, large peaked T waves on ECG
- **Labs: PTH values guide Ddx:**
  *Suppressed PTH:* Excess Vit D ingestion/production or malignancy (unregulated Ca release from bone by lytic lesions or PTH-rP production)
  *Normal/Increased PTH:* 1° or 3° HPT (distinguished by ⊕ hx longstanding CKD in 3° disease) or familial hypocalciuric hypercalcemia (FHH)
  *25OH Vit D;* ↑↑ in excess intake
  *1,25OH Vit D:* ↑ if increased conversion (granulomatous disease, lymphoma)
  *24 h Urine Ca/Cr:* Check if PTH nl/increased → if Ca/Cr low, suggests FHH
  *Other labs:* Consider SPEP, PTH-rP, TSH, LFTs per hx/PE & lab findings above

## Management (*NEJM* 2005;352:373; *JCEM* 2009;94:335)

- Severe disease (e.g., Ca > 14 or significant sx) → IV fluids and ED referral, regardless of etiology
- **1° HPT:** Parathyroidectomy by experienced surgeon definitive tx; indicated if sx **or:** Age < 50, Ca > 1 mg/dL above ULN, T-score < −2.5, hx of nephrolithiasis; pre-op U/S + sestamibi scan often be helpful;
  *If medical mgmt:* Serial monitoring of Ca (at least q12mos), avoid over-repleting Vit D, thiazides; avoid dehydration; bisphosphonates if ↓ BMD; consider cinacalcet (no improvement in bone health when used in 1° disease)
- **3° HPT** (see *"Chronic Kidney Disease"*)
- **Hypercalcemia of malignancy:** Typically managed by oncology; tx often includes bisphosphonates (e.g., zoledronate); nadir 4–7 d after infusion, response lasts 1–3 wks
- **Exogenous Vit D or ≠ conversion:** Treat underlying cause; low-Ca diet; glucocorticoids can ↓ conversion to 1,25OH Vit D, consider endocrine referral
- **Endocrine referral:** If dx uncertain, ↑ Ca persists despite tx of presumed cause

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# HYPOCALCEMIA

## Etiologies (*NEJM* 2008;359:391)

- **Hypoparathyroidism:** *Acquired:* most common, s/p thyroidectomy or other neck surgery; *infiltrative* (hemochromatosis, Wilson, metastases); *genetic:* DiGeorge, 22q11.2 microdeletion, autosomal dominant hypocalcemia; *severe Mg deficiency* (↓ PTH secretion & ↑ resistance)
- **Inadequate Vitamin D:** Severe **Vit D deficiency, CKD** (2° HPT), ESLD, INH, ketoconazole (see *"Vitamin D Deficiency"*)
- **Other:** Bisphosphonates or denosumab (**if** Vit D deficient & CKD), s/p parathyroidectomy, resistance to PTH (pseudohypoparathyroidism, ↓ Ca despite ↑ PTH) or Vit D

## Evaluation (*Curr Opin Endocrinol Diabetes Obes* 2012;19:435; *NEJM* 2012;367:e15)

- **Signs and symptoms:** Muscle cramping, numbness, paresthesias; ⊕ *Chvostek sign:* Tap cheek over facial nerve; ⊕ if → ipsilateral twitching of upper lip (90/66% Se/Sp); ⊕ *Trousseau sign:* Inflate BP cuff >SBP × 3 mins; ⊕ if → carpal spasm (94/99% Se/Sp); severe disease can p/w seizures, CHF, stridor/laryngospasm
- **Diagnostic studies:** iCa (or Ca & albumin), Phos, Mg, BUN/Cr, PTH, Vit D, consider 24 h urine Ca

**Expected Labs by Etiology**

| Diagnosis | Lab Studies |
|---|---|
| Hypoparathyroidism | ↓ Ca, ↑ Phos, ↓ PTH |
| Vitamin D deficiency | ↓ Ca, ↓ Phos, ↑ PTH |
| Pseudohypoparathyroidism | ↓ Ca, ↑ Phos, ↑↑ PTH |

## Treatment

- Severe disease or symptoms → ED for IV Ca bolus followed by drip
- Correct Vitamin D deficiency (see "*Vitamin D*"); for CKD, see "*Chronic Kidney Disease*"
- **Primary hypoparathyroid patients:** Goal is sx relief, w/ total Ca in low–nl range (i.e., 7.5–8.5 mg/dL) to avoid hypercalciuria; treat with oral Ca (if on PPI, citrate is preferred, e.g., 500 mg elemental Ca TID) & 1,25OH Vit D (e.g., calcitriol 0.25 μg BID) significant variability in dosing requirements; pts w/ 1° hypoparathyroidism should have medical alert bracelets; PTH replacement under study
- If hypercalciuria (>300 mg Ca/d), consider thiazide

# CUSHING SYNDROME

## Background (*NEJM* 2010;362:156; *BMJ* 2013;346:f945; *BMJ* 2012;345:e4928)

- **Definitions:** *Cushing syndrome* is the manifestation of prolonged/excessive exposure to glucocorticoids, *regardless of etiology*; *Cushing disease* is endogenous cortisol excess 2/2 *pituitary hypersecretion of ACTH*
- Cushing syndrome is assoc w/ significant ↑ morbidity & mortality (CVD > infection)

- **Etiologies:** *Iatrogenic* (exogenous): most common 2/2 chronic glucocorticoid use (usually PO, but can occur w/ topical, inhaled, intranasal, or injected forms); 1% of population uses chronic corticosteroids; of these 70% will experience s/e & 10% will develop overt Cushing syndrome; providers should be alert to any s/sx of systemic cortisol excess
  *Endogenous:* Rare (annual incidence <3/million); Cushing disease (70%), adrenal tumors (15%; adenoma > hyperplasia > carcinoma) or ectopic production (15%; can be ACTH or CRH: SCLC, carcinoid, islet cell, medullary thyroid, pheo)
- Hypercortisolism should be considered as a potential dx in pts with: (1) Specific findings (below); (2) unusual presentation of nonspecific features (e.g., osteoporosis in the young); (3) imaging compatible w/ adrenal adenoma (see *"Adrenal Nodules"* ); (4) growth delay (childhood or adolescence)

## Evaluation (*JCEM* 2008;93:1526; *JCEM* 2007;92:4123)

- **General approach:** Complete hx/PE if suspected, as s/sx can be subtle & diffuse; if e/o hypercortisolism on exam or eval indicated (above) → lab eval
- **Specific features:** Highly suggestive of ↑ cortisol: Easy bruising, facial plethora (review old photograph, e.g., driver's license), violaceous striae, proximal weakness, osteonecrosis of femoral/humeral head
- **Sensitive features:** Less specific but more common: *Endocrine:* Hyperglycemia (new onset/worsening DM2), obesity, menstrual irregularities, PCOS, vertebral osteoporosis; *Derm:* Acne, poor skin healing, hirsutism, hyperpigmentation (if ↑ ACTH); *Neuropsychiatric:* Depression, insomnia, irritability, ↓ libido; *Other:* Dorsocervical ("buffalo hump") & supraclavicular fat pad, HTN (new/worsening), renal calculi, new/unusual infections, peripheral edema, facial fullness, hypokalemic metabolic alkalosis
- **Diagnostics: For exogenous Cushing, dx primarily clinical; if endogenous disease suspected Æ** screening test (3 choices, below); sources of false ⊕ screening include **OCPs:** Estrogen → ↑ [cortisol-binding globulin] → ↑ total [cortisol]; hold for 6 wks prior to testing; also EtOH, uncontrolled DM, pregnancy, depression, eating d/o,

intense regular exercise, physical stress (injury, surgery, hospitalization, acute illness)

**Lab Testing for Cushing Syndrome** (*JCEM* 2008;93:1526)

| Screening Test | Mechanics/Interpretation |
|---|---|
| 24 h urine-free cortisol (UFC) | Starts *after* 1st urine of the day, *includes* 1st urine of the next day; collected in plain urine bottle (coordinate w/ lab); lesser elevations less specific; useful if clinical suspicion high (Sp > 90%); pathognomonic if greater than 4× > ULN; cumbersome for pts; avoid if CKD |
| Dexamethasone suppression test (DST) | 1 mg PO at 11 PM, then check serum cortisol at 8 AM: ⊕ If >1.8 µg/dL (50 nmol/L); avoid for adrenal incidentaloma or pts on drugs which ↑ dex metabolism (e.g., phenytoin); useful if clinical suspicion low (Se > 95%) |
| Late night salivary cortisol | Requires specific collecting swab; chew or rub on inner cheek at 11 PM: ⊕ If level >145 ng/dL (4 nmol/L); avoid in pts w/ irregular schedule (e.g., 3rd-shift workers); Se/Sp 92/93% (*BMJ* 2013;346:f495) |

- **If screening negative:** Continue to monitor clinical s/sx: Consider repeat testing at 6 mos
- **If screening positive:** Perform add'l screening test (repeat original vs. new test), ✔ ACTH, & refer to endocrinology for further mgmt; tx options depend on source
- **Iatrogenic/exogenous Cushing:** Reduce dose/duration of corticosteroids as possible, consider use of corticosteroid-sparing agents; consider pneumocystis Ppx & BMD screening/tx (see *"Pneumocystis (PCP) Prophylaxis"* & *"Osteoporosis"*)
- **Refer to endocrinology:** If testing ⊕ or interpretation uncertain, clinical suspicion high, or ⊕ FHx MEN syndromes

# DIABETES MELLITUS

## Background (*cdc.gov/diabetes*)

- **Definition:** Diabetes is a metabolic disorder characterized by hyperglycemia due to problems with insulin secretion and/or response to insulin in target tissues
- **Epidemiology:** Diabetes affects 11.3% of all US adults, 27% of people > 65 y; 95% of cases are DM2; 3× ↑ in DM2 prevalence over past 30 y, primarily due to lifestyle changes: diet (↑ CHO, ↑ calories),

physical inactivity, & obesity; DM1 also ↑ in all ages

- **Complications:** Microvascular disease (nephropathy, peripheral & autonomic neuropathy, retinopathy), macrovascular disease (CAD, stroke, PVD), impaired wound healing, & immunodeficiency; DM is the leading US cause of ESRD, nontraumatic lower-limb amputations, & blindness
- **Mortality:** Pts w/ DM have 2–4 × ↑ risk of MI, stroke, & death compared to otherwise similar pt of same age; CV events responsible for majority of deaths in pts w/ DM; aggressive mgmt of CV risk factors in diabetes pts (lipids, BP, smoking cessation) can ↓ risk (*BMJ* 1998;317:703; *Lancet* 2008;371:116; *Chest* 2007;131:446)

## Classification (*Diabetes Care* 2004;24:s5; *Lancet* 2009;373:1773)

**Selected Glycemic Disorders** (*Diabetes Care* 2013;36:S67)

| Disorder | Notes |
|---|---|
| DM1 (5–10%) | Autoimmune d/o against pancreatic β cells → *insulin deficiency;* typically presents prior to puberty, but can occur in adulthood: Suspect in thin, ⊕ FHx of other autoimmune disease, ⊖ DM2 FHx; ⊕ pancreatic autoantibodies (ICA, insulin or GAD), extreme hyperglycemia despite tx w/ oral agents shortly after dx |
| DM2 (90–95%) | Assoc w/ *insulin resistance* in target organs & *relative insulin deficiency;* tx targets resistance and/or deficiency |
| Other syndromes | **Ketosis-prone** "Flatbush" **DM:** Characterized by severe, **reversible** β-cell dysfunction: Demographics ≈ DM2 but p/w DKA; with aggressive control, some β-cell function restored & insulin/med needs ↓↓ (*Diabetes Care* 2006;29:2755)<br>**MODY** (Mature Onset DM of the Young); rare, presents in young, *autosomal dominant inheritance* (*Diabetes Care* 2011;34:1878) |
| Prediabetes | On spectrum with DM2; **affects 35% of US adults**; equivalent to "impaired fasting glucose" or "impaired glucose tolerance" (reflect test used to dx prediabetes); defined as FBG 100–125 mg/dL, HbA1c = 5.7–6.4%; **5 y risk of progression to DM2 ~15–30%** (cdc.gov/diabetes; *Diabetes Care* 2004;27:S47) |
| 2° DM | Etiologies incl hemochromatosis, CF, pancreatic CA, surgical resection |
| Medications | Can ↓ glucose tolerance or impair insulin secretion: Corticosteroids, protease inhibitors, atypical antipsychotics, HCTZ, tacrolimus |

# Type 2 Diabetes

## Prevention

- **Risk factors:** Assoc w/ obesity, inactivity, ⊕ FHx, PCOS, HTN, HLD, hx

GDM; ↑ prevalence in African-American, Latino, Native American, Pacific Islander

- **Lifestyle:** In pts with prediabetes, wt loss (5–10% of total body weight), diet, & exercise (150 mins/wk mod exercise, e.g., **walking**) ↓ risk of developing DM2 by 58% over 3 y period (DPP, *NEJM* 2002;346:393)
- **Metformin:** In same study, metformin (850 mg PO BID) reduced risk of DM2 by 31%; ADA recommends for those at "very high risk" for developing DM *in addition to* lifestyle tx
- **Surgery:** For obese pts (BMI >34 in ♂, >38 in ♀) bariatric surgery ↓ incidence of DM2 (*NEJM* 2012;367:695); not considered a 1° indication for surgery

## Diagnosis (*Diabetes Care* 2010;33:101; *Diabetes Care* 2013;36:S67)

- **Hemoglobin A1c >6.5% (preferred),** random glucose >200 mg/dL, fasting glucose ≥126 mg/dL, or OGTT (glucose >200 mg/dL after 75 g glucose challenge); initial ⊕ tests should be repeated to confirm unless pt p/w sx of hyperglycemia (e.g., polydipsia, polyuria, unexplained wt loss)
- **Screening:** USPSTF: >35 y with HTN; ADA: For people <45 y, screen if BMI >25 and "add'l risk factors"; for >45 yo, universal screening (*see "Disease Screening"*)

## Monitoring

- **Hemoglobin A1c** (% of Hb molecules which are glycosylated) preferred; estimates mean glucose over preceding 90 d, weighted toward the last 30 d can be affected by states which alter RBC turnover, e.g., hemoglobinopathies, hemolysis, pregnancy
  Hemoglobin A1c 7% ≈ mean glucose 154 mg/dL; for every 1% HbA1c ↑ mean glucose ↑ ~30 mg/dL; e.g., HbA1c 8% ≈ 180 mg/dL
- **Home glucose monitoring:** Indicated for pts on insulin or at risk of hypoglycemia
  *Nonhypoglycemic regimens:* Not shown to improve outcomes (*BMJ* 2008;336:1174)
  *Hypoglycemic PO regimens:* Can be used PRN to monitor for hypoglycemia

*Single-dose insulin:* AM fasting & after biggest meal of the d and/or before bed

*Multiple-dose insulin:* Prior to meals/snacks, at bedtime, prior to exercise or critical tasks, if suspect hypoglycemia, ± postprandial

- **Monitoring supplies:** Rx for glucometer, test strips, & lancets

## Evaluation (*Diabetes Care* 2013;36:S67)

- **History:** Assess for *behaviors:* Physical activity, tobacco, EtOH use; *macrovascular disease:* Angina, ↓ exercise tolerance, CV risk factors; *microvascular disease:* Visual changes, sensory neuropathy (see *"Peripheral Neuropathy"*) or *autonomic neuropathy:* ED, orthostatic HoTN, GI dysmotility; autonomic neuropathy strongly assoc w/ CAD; *diabetes regimen:* Adherence, s/e, hypoglycemia/hyperglycemia (review log)
- **Exam:** BMI, BP; check for carotid bruits, distal pulses, foot exam (including pulses, inspecting, & monofilament testing, (if tinea pedis present, Rx to ↓ DFI risk, see *"Tinea"*), acanthosis nigricans
- **Labs:** Yearly urine microalb/Cr ratio; baseline Cr, baseline ECG (no further cardiac testing warranted if asx & nl ECG, although may consider if starting vigorous exercise regimen; see *"CP & Noninvasive Testing"*), annual lipids (or q2y if low-risk values)
- **Medications: ASA 81 mg** (Men >50, women >60 with 1 other CV risk factor unless ↑ bleeding risk); **Statin** (indicated for any DM pt w/ CAD or if >40 y with either HTN, ⊕ tob, ⊕ FHx CVD, or albuminuria, *regardless of lipid levels*); **ACEI or ARB:** 1st-line for HTN or microalbuminuria; **immunizations:** Pneumococcal, influenza (annual), hep B series (recommended for pts <60, consider in pts ≥60); peripheral neuropathy tx options: see *"Peripheral Neuropathy"*
- **Referral:** Nutritionist, diabetes educator at baseline & PRN, podiatry PRN, optho annually (can → q2–3y if >1 nl exam), renal if CKD >stage III (see *"Chronic Kidney Disease"*)
- **Endocrine referral if** pt requiring >80 units of basal insulin w/o adequate control of fasting glucose; persistent, frequent episodes of hypoglycemia; suspect late-onset DM1

## Treatment (*NEJM* 2012;366:1319; *Ann Intern Med* 2011;154:554)

- **Cardiovascular risk reduction:** Exercise, wt loss, lipid & BP control, smoking cessation of special importance; however, 28–48% of pts not at target for BP, 43% not at target LDL, & 22% continue to smoke (*NEJM* 2013;368:1613)
- **Blood pressure:** Goal area of some controversy; <130/80 mmHg recommended by JNC7, although no better than <140/90 in absence of nephropathy/CKD (*NEJM* 2010;362:1575)
  ADA 2013 recs <140/80, consider ↓ systolic target in younger pts/on individual basis (*Diabetes Care* 2013;36:S4); ACEI or ARB 1st-line tx due to microvasc benefits, but BP control more important than Rx choice
- **Lipids:** Generally, goal LDL <100 mg/dL, HDL >40 mg/dL, TG <150 mg/dL
- **Goal of glycemic control:** Prevent sx hyperglycemia, & ↓ **microvasc** complications**;** intensive control not shown to ↓ risk of CV disease or mortality in DM2
- **Glycemic control:**
  *Purpose:* Primarily to ↓ microvascular complications; intensive control not shown to ↓ risk of CV disease or mortality in DM2 (ACCORD *NEJM* 2011;364:818)
  *Target HbA1c:* **<7%**; however, this must be adjusted for individual pts, both at presentation & over course of disease; less intensive goals (e.g., HbA1c <8, fasting glucose 100–150 mg/dL) should be considered in older pts or those w/ significant comorbidities, advanced complications, ↑ risk hypoglycemia, or ↓ life expectancy; discuss target w/ pts & incorporate their preferences into goal-setting (*Diabetes Care* 2012;35:1364)
  *Target fasting blood glucose:* 80–130 mg/dL; lower end of target may be 70–90 depending on individual pt's risk of hypoglycemia or per glycemic goal), postprandial <180 mg/dL (*Diabetes Care* 2013;36:S11); **have pts bring in glucometer or glucose log at each visit**

## Nonpharmacologic Therapy

- **Diet: Low-carbohydrate or Mediterranean**
  "Plate method" = ½ nonstarchy vegetables, ¼ lean meat/protein, ¼

whole grains; heart-healthy diet low in saturated fats, low in trans fats; monitoring & awareness of CHO intake

- **Weight loss:** 5–10% body wt loss good initial target in the obese
- **Exercise:** Improves glycemic control independent of wt loss, ↓ CV risk factors; goal is 30 mins, 5×/wk, at 50–70% max HR (max HR = 220 – age, e.g., for 60 yo, max HR = 160, target HR ≈ 115) should be strenuous enough, pt is "able to talk but not sing"
- **Education:** Self-mgmt education by trained professional (can be RN, PharmD, CDE) shown to help pts ↓ HbA1c, prevent/manage complications, address psychosocial aspects of DM2, & ↑ quality of life; cost-effective (*Diabetes Care* 2013;36:S11)
- **Surgery:** Bariatric surgery for obese pts can improve glycemic control, ↓ number of DM agents, increase wt loss & induce remission as c/w medical/lifestyle tx alone (*NEJM* 2012;366:1567; *NEJM* 2012;366:1577); however, long-term effects unknown; surgery has perioperative risk & possible complications; appropriate/interested pts may be referred to a comprehensive bariatric surgery ctr for eval (see "*Obesity*")

## Pharmacologic Therapy

- **Metformin:** *1st-line Rx* for DM2 unless contraindicated → 1–2% avg ↓ in HbA1c, wt loss common, hypoglycemia rare; *Mechanism:* Biguanide (↑ insulin Se & ↓ gluconeogenesis); *S/e:* GI upset common, minimize by starting at lower dose, taking with food, & titrate ↑; lactic acidosis (type B, rare), should *not* generally cause hypoglycemia, esp as monotherapy; *Contraindications:* Caution in CHF, ESLD; contraindicated if CrCl <60 mL/min/1.73 $m^2$ or acute ↓ in GFR (2/2 risk of lactic acidosis, although some debate re: magnitude of risk); *Dosing:* Start at 500 mg QD w/ meal, can → 1 g BID

**Other Pharmacologic Agents (each Ø HbA1c by 0.5–1.5%)** (*NEJM* 2012;366(14):1319)

| Class (e.g.) | Mechanism | Notes |
|---|---|---|
| Sulfonylureas (glipizide—shorter $t_{1/2}$, cleared by liver; also: Glyburide, glimepiride) | ↑ β cell sensitivity to glucose, ↑ insulin release | High failure rate over time due to ↓ β cell function; long $t_{1/2}$, elderly/CKD at ↑ risk of hypoglycemia, esp w/ glyburide; s/e: Hypoglycemia, wt gain; caution in liver & renal dz; contraindicated if sulfa allergy |
| GLP-1 analogs (exenatide, liraglutide) | ⊕ Insulin secretion & delays gastric emptying | Injectable, expensive<br>Assoc w/ wt loss, hypoglycemia rare; can → N/V, pancreatitis; adjust dose in CKD |
| Thiazolidinediones (pioglitazone) | ↑ Insulin sensitivity | Assoc w/ wt gain, CHF exacerbation, ↑ fractures, hepatotoxicity; monitor LFTs |
| Acarbose | Inhibits GI tract CHO metabolism | GI intolerance common |
| Meglitinides (repaglinide, nateglinide) | ↑ β cell insulin secretion | Can → wt gain & hypoglycemia<br>Expensive |
| DPP-4 inhibitor (sitagliptin) | Blocks inactivation of incretins, e.g., GLP-1 | Dose adjustment in CKD<br>Wt neutral, assoc w/ pancreatitis, expensive |
| Amylin analogue (pramlintide) | ↓ CHO absorption & GI motility | Injectable; expensive; assoc w/ wt loss; use w/ insulin can → severe hypoglycemia; avoid in pts w/ gastroparesis, osteopenia |

## Insulin

- **Indications:** Pts with DM2 on 2 medications with HbA1c >8 (or 8.5% in elderly) on 2 occasions, 3 mos apart, performing self-testing with a glucometer
- **Advantages:** Inexpensive relative to brand-name newer agents, no dose limit
- **Disadvantages:** Wt gain, hypoglycemia, requires regular BG monitoring
- **Administration:** SC in adipose areas (abdomen, thighs); site of injection should be rotated to avoid lipoatrophy

**Pharmacokinetics of Selected Insulin Analogs** (*JAMA* 2003;289:2254)

| Preparation | Onset | Peak | Duration |
|---|---|---|---|
| Aspart, Lispro | 5–15 mins | 30–90 mins | 5 h |
| Regular | 30–60 mins | 2–3 h | 5–8 h |
| NPH | 2–4 h | 4–10 h | 10–16 h |
| Glargine | 2–4 h (to steady-state) | Min | 20–24 h |

**Insulin Troubleshooting**

| Problem | Strategy |
|---|---|
| AM glucose ↑↑ | ↑ Glargine or evening NPH; consider ✓ 2 AM BG to r/o overnight hypoglycemia |
| Prelunch glucose ↑↑ | Add/↑ breakfast insulin |
| Predinner glucose ↑↑ | Add/↑ AM NPH or add/↑ lunchtime insulin |

## Insulin Delivery Method: Choose one (below)

| |
|---|
| **Pens/Cartridges:** Carry insulin in self-contained cartridge, "dial in" desired dose; more convenient but less often covered by insurance, should only be used for self-administration (↑ risk of needle stick); disposable pens come w/ single cartridge but still need to change needle, more $$; 1 cartridge = 300 units, 1 box = 5 pens = 1500 units<br>*Sample Rx:* Lantus SoloSTAR or Novolin N Pen—2 boxes for 1 mo/5 boxes for 3 mos; pen needles are a **separate** Rx (# injections/mo) |
| **Vials/Syringes:** Require pt to withdraw insulin from vial for each injection; allows mixing of insulin types, generally less expensive; 1 vial = 1000 units, 1 box = 100 needles<br>*Sample Rx:* Glargine (Lantus) 3 vials for 1 mo/8 vials for 3 mos<br>*Syringes:* 0.5 cc size for <60 units, 1 cc for doses > 60units, all w/ 31 g needle; Rx: 1 box |

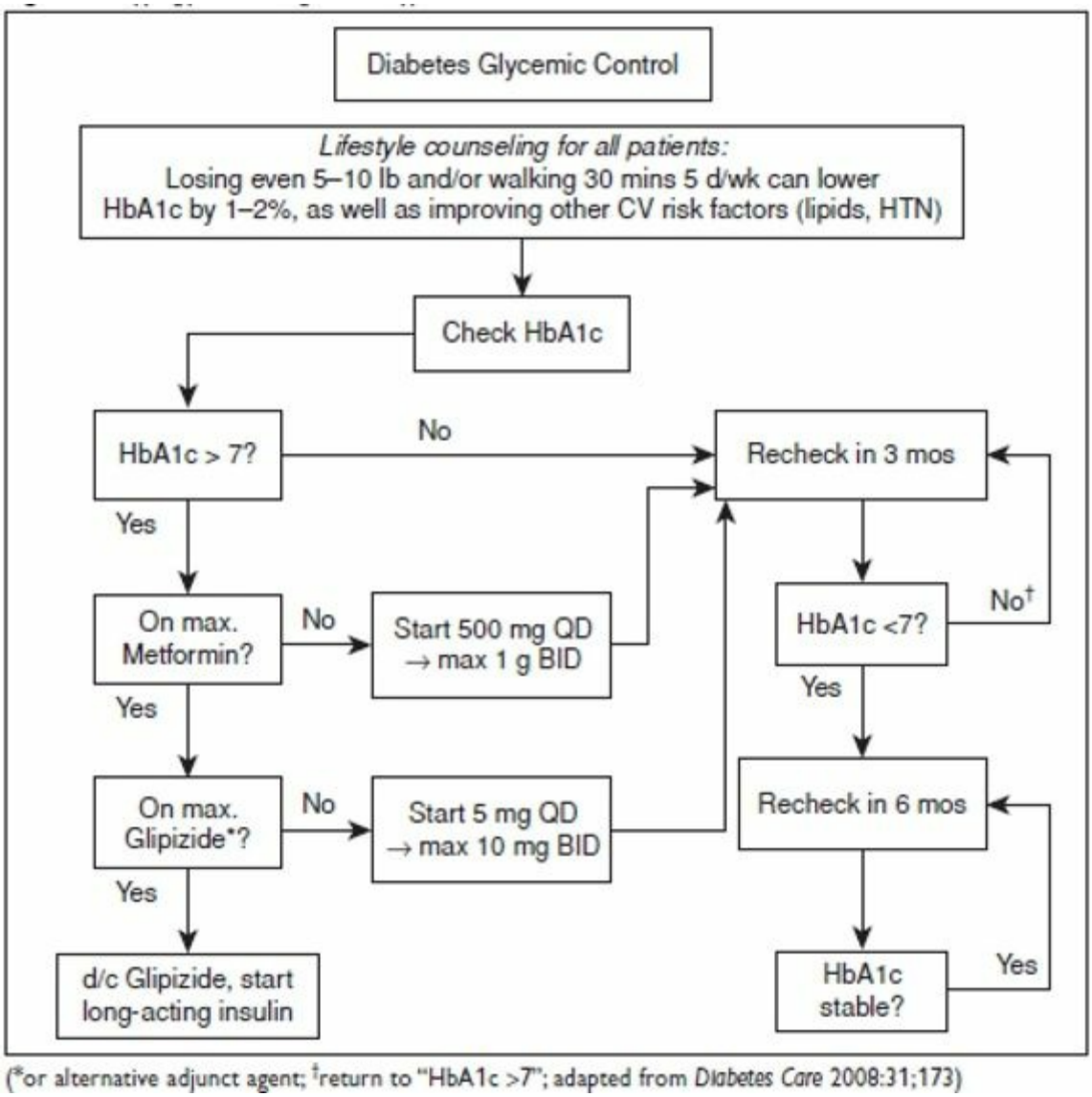


Figure 4-**1** Hyperglycemia management in type 2 diabetes

- **Step 1:** Initiate Rx (lifestyle ± metformin); for pts w/ severe hyperglycemia or HbA1c >9%, consider → direct to step 3 as oral/lifestyle tx alone unlikely to be sufficient
- **Step 2:** If HbA1c above target, add sulfonylurea or GLP-1 analog
- **Step 3:** If HbA1c above target, add insulin (required in ~27% of DM2 pts)
- **Step 3:** Add **basal** insulin (0.1 mg/kg/d); usually safe to start glargine 10 units QHS, increase by 2 units every 3rd night until FSBG <130; can usually start w/ 20 units if BMI >30 & all blood sugars are ≥200; instruct pt to take the same time each evening, within 1 h; d/c all DM2 agents other than metformin (can ↓ insulin requirements)

- **Step 4:** Add **prandial** insulin: Indicated when HbA1c remains above goal & postprandial sugars elevated *despite fasting sugars at goal;* usually safe to start with 4 units/meal, increase by 2 units every 3rd day until postprandial BG <180; consider carb counting (nutritionist referral)
  **Typical regimen:** NPH/regular or glargine/aspart, 2/3 LA, 1/3 prandial; NPH/regular can be given in 70/30 prepared combo (admin before breakfast & dinner)

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## HYPOGLYCEMIA

### Background (*Diabetes Care* 2005;28:1245)

- **Definition:** Serum glucose <70 mg/dL; may be sx or asx, considered **severe if** ⊕ **CNS sx** (confusion, seizure, coma) necessitating tx from another person (i.e., unable to self-tx); **relative hypoglycemia:** Sx of hypoglycemia in pt w/ chronic hyperglycemia as glucose approaches 70; likely not dangerous but can be distressing to pt; **hypoglycemia unawareness:** Inability to sense ↓ glucose at safe threshold, screen all pts on insulin
- **Overview:** Hypoglycemia frequent, anticipated complication of diabetic tx: Serum glucose affected by food intake, **exercise**, drug interactions, **EtOH use**, insulin absorption, clearance; improved glycemic control often → ↑ episodes of hypoglycemia; occurs in pts on insulin or insulin-secreting agents (e.g., sulfonylureas); should not occur in pts on insulin-sensitizing agents (e.g., metformin)
- **Morbidity:** Severe hypoglycemia assoc w/ ↑ risk of macrovascular, microvascular events, & 3.3× ↑ risk death (*NEJM* 2010;363:1410)
- **Pathophysiology:** In diabetes pts, physiologic response to hypoglycemia impaired: Insulin levels do not ↓, glucagon does not ↑, & attenuated ↑ in epinephrine; DM pts with prior hypoglycemic episodes less likely to register hypoglycemic sx; some of this likely reversible
- **Risk factors:** ↑ Age, ↑ duration of DM, ↑ Cr, ↓ cognitive function, insulin or >2 oral hypoglycemic agents, DM1, hx of chronic pancreatitis or pancreatectomy (glucagon def), ⊕ tobacco, PMHx microvascular disease, intensive glucose control; episodes may occur

at any HbA1c in pts on hypoglycemic agents (*NEJM* 2010;363:1410; *BMJ* 2010;340:b5444)

- **Clinical manifestations:** Sx may be diverse but are often individually consistent; pts can learn to recognize which sx indicate hypoglycemia for them at a given glucose threshold; *autonomic:* Palpitations, sweating, tremor, hunger; *neuroglycopenic:* Primarily altered mental status, can → to sz, coma, even death (*Diabetes Care* 2005;28:1245)

## Treatment

- **Counseling:** All pts should be counseled re: precipitants of hypoglycemia & potential consequences (incl driving), & should have plan in place if develop sx; screen for hypoglycemia unawareness by determining the threshold at which sx are sensed; if level is <60 mg/dL, relax glycemic targets & recommend checking BG before driving or other dangerous activity
- **Prevention:** Modify glycemic target/pharmacologic regimen in pts where risk of hypoglycemia > benefit of regimen
- **Episode management:** At onset of suspected hypoglycemic episode, advise pt to **check serum glucose** (if feasible) & **ingest ~15 g carbohydrate** ≈ $^1/^2$ cup fruit juice/sugar soda (not diet) ≈ 4 glucose tabs ≈ 1 tbs sugar/honey; **recheck glucose in 15 mins; if still <70, repeat glucose load;** counsel pts to **call provider** if recurrent episodes/unclear precipitant

# DIABETES INSIPIDUS

## Background (*JCEM* 2012;97:3426; *Ann Intern Med* 2006;144:186)

- **Definitions:** Diabetes insipidus is the result of either ADH deficiency ("central DI," most common) or ADH resistance ("nephrogenic DI"); can be inherited or acquired, & results in polyuria & compensatory polydipsia
- **Physiology: Serum osmolality** & **arterial blood volume normally tightly regulated;** Antidiuretic hormone (ADH, also known as vasopressin or AVP) is synthesized in hypothalamus → stored in, then secreted from the posterior pituitary → activates vasopressin renal

receptors → aquaporin water channels inserted into collecting duct → free water reabsorption

- **Pathophysiology:** Functional ↓ ADH → ↓ free water reabsorption → ↑ serum osmolality (i.e., ↑ Na) & ↓ arterial blood volume → thirst mechanism → polydipsia as compensation → nl or near-nl Na & blood volume
- **Etiologies:** *Central* (most common); either due to structural damage/disruption to hypothalamus or posterior pituitary (**trauma, surgery, neoplasm,** granuloma, stroke, infection; 25% idiopathic); rarely, hypothalamic lesions can → impaired osmoreceptor function, which → impaired ADH secretion & impaired thirst (↑↑ Na, ↓↓ volume)
  *Nephrogenic:* Medication-induced (DI develops in 10–20% of pts on long-term **lithium**), demeclocycline, cisplatin; **infiltrative** (sarcoid, amyloid, MM, Sjögren), sickle cell disease; nephrogenic DI usually milder as kidney can use other mechanisms to concentrate urine
- **Differential diagnosis:** 1° **polydipsia** (disruption in thirst mechanism; here, polydipsia → polyuria); psychogenic polydipsia, can be ⊕ by oral dryness

## Evaluation

- **General approach:** Attempt to determine most likely etiology based on hx/exam, confirm hypotonic polyuria, & refer → endocrinology
- **History:** Ψ disease, "neurotic" personality, fluctuating sx (1° polydipsia); head trauma, surgery, sudden onset, consistent need for overnight fluids, preference for cold fluids (central DI); lithium, cisplatin use (nephrogenic DI), gradual onset (nephrogenic or 1° polydipsia)
- **Lab evaluation:** First, confirm hypotonic polyuria; check urine & serum osms (↓ serum osm suggestive of 1° polydipsia, ↑ serum osm suggestive of DI)
- **Further workup** includes water restriction test (can help distinguish 1° polydipsia & central DI) ± administration of exogenous ADH (i.e., DDAVP) ± brain MRI; best performed by endocrinologist
- **Patient information:**

www.nlm.nih.gov/medlineplus/diabetesinsipidus.html

# HYPERPROLACTINEMIA

## Background (*AFP* 2010;81:617; *J Clin Endocrinol Metab* 2011;96:273)

- **Definition:** A single measurement of serum prolactin (PRL) > ULN; can be physiologic or pathologic; symptomatic or asymptomatic
- **Physiology:** PRL is a hormone secreted by lactotrophs of anterior pituitary; its function is to induce lactation in prepared breast; secretion is tonically inhibited by hypothalamic DA & stimulated by estrogen & TRH
- **Etiology:** Can be due to disruption of hypothalamic inhibition (e.g., meds such as DA receptor antagonists, structural lesions, including metastases, craniopharyngiomas) **or** autonomous PRL secretion (prolactinoma: Benign tumor; microadenoma <10 mm, macroadenoma ≥10 mm, PRL levels usually proportionate to tumor size)

**Selected Causes of Elevated Prolactin Other Than Prolactinoma**

| | | |
|---|---|---|
| **Meds** | Typical antipsychotics (40–90% of pts)<br>Risperidone (50–100% users)<br>Olanzapine (35% of pts)<br>Verapamil (8% of users)<br>Metoclopramide, opiates | Slow onset after initiation; takes 3 d to "wash out"<br>Effect usually mild (25–100 μg/L) but rarely can be >200 μg/L, esp w/ risperidone |
| **Physiologic** | Sleep, stress, pregnancy, exercise, oral carbohydrate loads | Elevation usually mild/borderline |
| **Intracranial** | Cranial XRT, trauma, surgery, epilepsy, tumors, granulomatous disease | |
| **Systemic** | 1° hypothyroidism, ESLD, ESRD (PRL renally cleared), pregnancy, lactation, ↑↑ nipple stimulation, chest wall disease (trauma, VZV, surgery) | |

- **Epidemiology:** Treated prolactinoma lifetime prevalence <0.1% in US; ↑ serum PRL common (sx or asx) in pts on 1st-gen antipsychotics & some atypical antipsychotics (e.g., risperidone →↑ PRL in 40–60% of pts)

## Evaluation (*NEJM* 2010;362:1219; *JCEM* 2011;96:273)

- **General approach:** Assess for sx of ↑ PRL; for symptomatic pts or those w/ significant elevation, exclude pregnancy, meds, ESRD, hypothyroidism, & parasellar tumor, then → diagnostics (below)
- **History and exam:**

*Clues to etiology*: Meds, recent pregnancy (normalizes after few wks in non-nursing women or ~6 mos in nursing mothers), CNS disease, chest wall trauma, stress assoc w/ lab draw (can → modest elevation), causes listed above

*S/sx:* Gynecomastia, galactorrhea, oligomenorrhea or amenorrhea, acne, hirsutism, infertility; low libido, ED, small testes; HA, bitemporal visual field defect (compression of optic chiasm 2/2 mass effect), osteopenia (2/2 hypogonadism)

- **Diagnostics:** For asx pts w/ borderline elevation, consider repeating test to r/o transient physiologic elevation; for all others check TSH, Cr, LFTs, β-hCG (reproductive-aged women), T/LH/SHBG (men) & **pituitary** MRI; if all nl then ✓ macroprolactinemia (PRL molecules aggregate into polymer w/ ↓ clearance → ↑ serum [PRL]; accounts for 10% of ↑ PRL (*JCEM* 2005;90:3927) usually asx & no tx required)
- For patients w/ suspected medication-induced ↑ PRL, if possible, d/c or use alt Rx for 1 wk, then repeat test → if PRL normalized, suggests medication responsible; if unable to d/c Rx or PRL remains elevated → MRI
- Visual complaints or visual field defect on exam → formal neuro-ophtho testing
- Women with amenorrhea 2/2 to ↑ PRL: Consider further eval (see *"Amenorrhea"*)

## Treatment (*JCEM* 2011;96:273; *Clin Endocrinol* 2006;65:265)

- **Med-induced hyperprolactinemia:** If symptomatic, consider alt Rx (e.g., for antipsychotics, aripiprazole in consultation with pt's psychiatrist); in pts w/o alt Rx → endocrine referral, consider testosterone tx for hypogonadal sx or to prevent ↓ BMD

  *Asx:* No tx required; consider periodic monitoring, monitor for ↓ BMD
- **Microadenoma:** Indications for DA agonist tx: symptomatic or enlarging, ♀ who desire pregnancy, clinically significant galactorrhea

  *Amenorrhea:* DA agonist or OCP; for other indications, DA agonist (below)

  *Monitoring:* For asx pts who are not treated, PRL & MRI annually × 3 y, then q2y
- **Macroadenoma:** Tx to ↓ tumor burden/intracranial sx; DA agonist

(cabergoline 1st-line); if PRL only mildly elevated, obtain serial dilutions to r/o "hook effect" (spuriously low PRL levels 2/2 assay limitations); assessment of other pituitary axes

- **Dopamine agonists:** ↓ PRL, restore reproductive function, reverse galactorrhea, & ↓ tumor size; s/e include orthostasis & GI upset; cabergoline ↑ efficacy but possible assoc w/ valvular disease (data conflicting (*Pituitary* 2009;12:153); consider baseline & 12 m T TE); bromocriptine better for ♀ who desire pregnancy (these pts should be referred to endocrine; d/c DA agonist if pt becomes pregnant)
- **Endocrine referral:** If etiology uncertain, persistent ↑ PRL; consider for initiation of DA agonist or other therapies (e.g., hormonal Rx for persistent hypogonadism), ♀ w/ PRL who desire pregnancy (require closer monitoring)

# MALE HYPOGONADISM

## Background (*J Clin Endocrinol Metab* 2010;95:2536; *JCEM* 2007;92:4241)

- **Definition:** Clinical syndrome resulting from failure of the testes to produce physiologic levels of testosterone (T) and/or a normal sperm count; due to disruption of the hypothalamic–pituitary–gonadal (HPG) axis
- **Epidemiology:** Hypogonadism affects 2–4 million men in US; serum testosterone levels typically decline 1–2%/y; 50% of men >80 y have levels below the reference range for healthy young men (*NEJM* 2004;350:482; *JCEM* 2001;86:724)
- **Physiology:** Testosterone levels regulated by HPG axis; hypothalamus releases pulsatile GnRH → ⊕ anterior pituitary, which releases LH + FSH → ⊕ testes, which synthesize sperm & release testosterone; Testosterone (& metabolite DHT) required for spermatogenesis, involved in libido, potency, muscle mass, & BMD (also prostate hypertrophy & ♂ pattern baldness)
- **Pathophysiology:** Leydig cell failure ("1° hypogonadism") or inadequate LH/FSH due to hypothalamic or pituitary lesions ("2° hypogonadism," more common); can → infertility & s/sx of low T (below)

**Selected Causes of Hypogonadism**

| Cause | Example/Notes |
|---|---|
| Congenital | *1°*: **Klinefelter syndrome;** 46,XY/XO; 47,XXY (common, 1 in 500 ♂), cryptorchidism, d/o of androgen biosynthesis; *2°*: LH, FSH, or GnRH receptor mutations; Kallmann, Prader–Willi |
| 1° acquired | Autoimmune; chemotherapy; medications (ketoconazole); infection (HIV, mumps); bilateral orchiectomy; radiation; torsion; trauma |
| 2° acquired | **DM; obesity;** medications (**GnRH agonists, opioids**); critical illness; ↑ PRL; CNS tumors; pituitary apoplexy; TB; CNS XRT; trauma |
| Combined | Chronic systemic disease (**cirrhosis, CKD**), infiltrative disease (hemochromatosis, sarcoidosis), sickle cell disease, thalassemia, alcoholism, meds (**glucocorticoids**), *DAX1* mutations, **older age** |

## Evaluation (*JCEM* 2010;95:2536; *NEJM* 2010;363:123)

- **General approach:** Hypogonadism should be considered as a potential dx in men with specific or multiple findings (below); if sx present, assess for potential etiology via hx/PE & lab testing; both hx & labs can be nonspecific → **symptoms** *and* **lab abnormalities required to make a diagnosis**
- **Specific features:** Highly suggestive of ↓ hypogonadism: *Sexual:* Incomplete or delayed sexual development, ↓ **am erections**, ↓ ejaculate volume, ↓ testicular size or volume, infertility; *Chest:* ↓ Body hair or shaving requirement; *Endocrine:* ↓ BMD, hot flashes
- **Sensitive features:** More common, less specific: *Cognitive/Ψ ;* ↓ **energy, depression,** concentration/memory; sleep disturbances; *Sexual:* ↓ **Libido,** ED; *MSK:* ↓ Muscle bulk/strength, ↑ body fat, ↓ **physical stamina;** *Heme:* Mild normocytic/normochromic anemia
- **History:** Also attempt to assess age of onset, fertility, & etiological clues: Medications, **EtOH**, PMHx of obesity, DM, OSA, or chemo/XRT hx (*CCJM* 2012;79:717)
- **Physical:** BMI, 2° sex characteristics (facial & body hair); testicular volume
- **Lab:** If suspect hypogonadism based on hx/PE, total AM testosterone is 1st-line; any ⊕ test should be confirmed as 30% of repeats will be nl; with repeat AM testosterone level, send LH/FSH, PRL, ± estradiol, and SHBG
- **Testosterone measurement:** 98% of serum testosterone bound to SHBG or albumin; 2% of serum T is "free," however, amount loosely

bound to albumin also considered "bioavailable"; significant alterations in [SHBG] → total T being a less reliable marker → use free T values in these cases; sources of false ⊕ screening (low T) include acute illness; glucocorticoid use, hypothyroidism, obesity, DM

- **Other studies:** Semen fluid analysis if c/o infertility, see *"Infertility";* PRL, iron studies if 2° hypogonadism & no clear etiology (DM, obesity); pituitary MRI indicated if 2° hypogonadism & severe ↓ T or CNS sx; DXA (see *"Osteoporosis"*); further studies as per sx & in consultation w/ endocrinology

**Lab Testing for Hypoandrogenism** (*JCEM* 2011;96:38)

| Screening Test | Mechanics/Interpretation |
|---|---|
| Total testosterone (1st-line) | Measured at 8–10 AM (values fluctuate during the d, AM values best standardized)<br>*Advantages:* Standardized values, reflects free & "bioavailable" levels<br>*Disadvantages:* More difficult to interpret in conditions which alter [SHBG], e.g., obesity, DM, aging, cirrhosis, ESLD, hypothyroidism, AEDs, HIV; if level low-nl → ✓ free T |
| Free testosterone | This should be *calculated* (requires simultaneous measurement of total T, SHBG, albumin); free T direct measurement often unstandardized/ unreliable |
| Bioavailable testosterone | Measures free + albumin-bound T; similar to free T, measured if suspect altered [SHBG]; many assays unstandardized/unreliable |

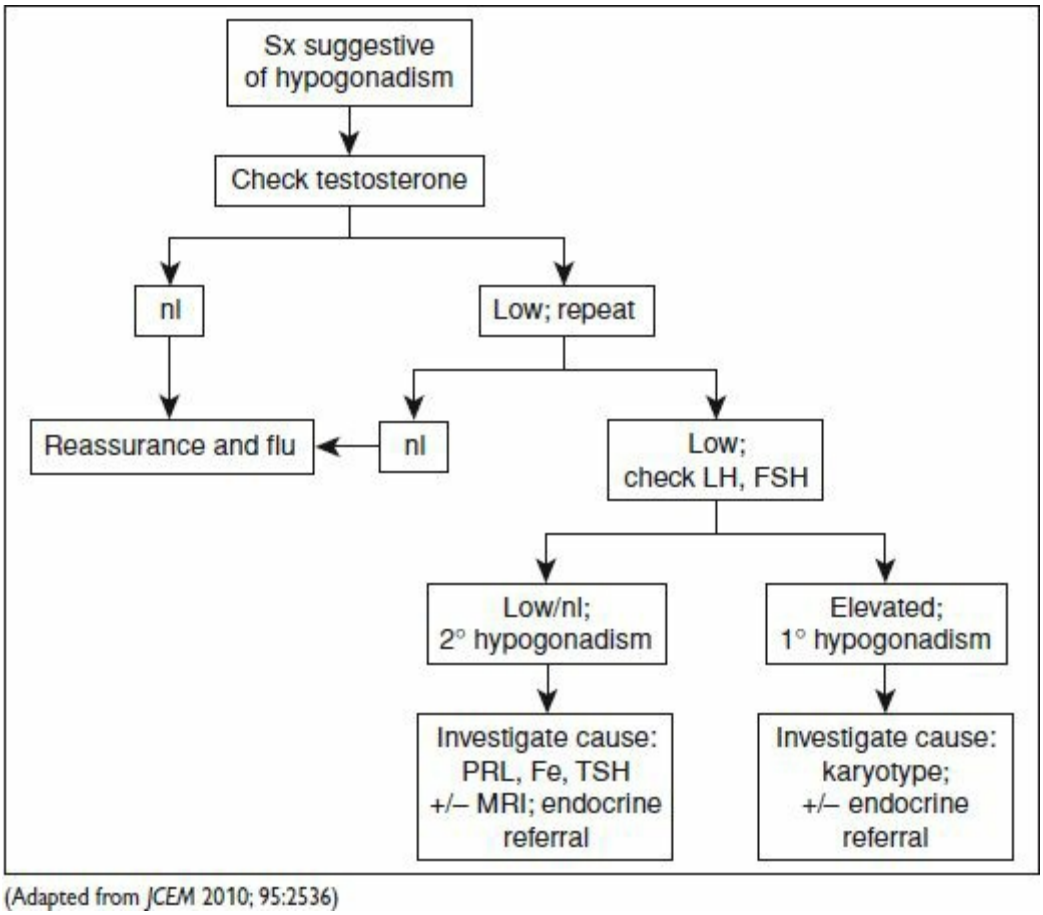


Figure 4-2 Testing algorithm

## Management (*NEJM* 2004;350:482)

- **Comorbidities:** In pts w/ diseases known to → low testosterone (obesity, DM), should also treat underlying condition which may be contributing (*CCJM* 2012;79:717)
- **Testosterone replacement therapy:** Indicated for pts w/ sx hypogonadism; contraindicated in pts w/ breast or prostate CA; use w/ caution in pts w/ ↑ risk of prostate CA (↑ PSA, prostate nodule on exam, ⊕ FHx, IPSS >19, poorly controlled BPH/LUTS–see *"BPH & LUTS"*), CHF, OSA, HCT >50; *S/e:* Acne, ↑ HCT, ↑ OSA, ↓ sperm count, ± gynecomastia, ♂ pattern baldness (*JCEM* 2011;96:38)

  **Preparations**

  *Gel (Testim, AndroGel; Axiron):* 5 g TOP QD typical starting dose; apply to shoulder, upper arm or abdomen; *S/e:* transfer to others; skin irritation; odor

  *IM (testosterone enanthate/cypionate):* 100–300 mg q2–3wks; *S/e:* fluctuating levels → fluctuating sx; injection site pain

*Patch (Androderm):* 5 mg TD QD to back, abdomen, upper arm, thigh; dose 2.5–10 mg

**Serum testosterone levels:** Target is mid-nl range

*Injection:* Check level between injections (goal 500–600 ng/dL) or check through before next dose (goal 200–400 ng/dL)

*Transdermal:* Check level any time (goal 400–700 ng/dL; 300–400 ng/dL acceptable for men >60 y)

**Monitoring:** At 1–2 mos, then q3mos × 4, then yearly: Assess response to tx, perform DRE; *Labs:* check Hct q6mos then annually, PSA; if baseline >0.6 ng/mL, check at 3 & 6 mos, then annually; BMD at baseline and if low, then 1–2 y after initiating tx (*NEJM* 2004;350:482)

- **When to refer:** Dx uncertain, labs difficult to interpret; suspect pituitary pathology; fertility desired (↑ chance of success if 2° hypogonadism; → hCG injections) → endocrinology

# OSTEOPOROSIS

## Background (cdc.gov; *Annals Int Med* 2011;155:ITC1-1)

- **Osteoporosis** is characterized by ↑ bone fragility which predisposes to fracture; can be mild (**osteopenia**) or severe; can be prevented, diagnosed, & treated *prior to fracture* → importance of early detection & mgmt to ↓ risk
  - **1∞ osteoporosis:** Occurs w/ declining gonadal function with advanced age
  - **2∞ osteoporosis:** Due to medications, endocrinopathy, toxins, or systemic disease
- **Fragility fracture:** Bone fracture caused by low-trauma activity (e.g., fall from ≤standing height) which presumably would not occur w/o underlying bone weakness = **pathognomonic for osteoporosis, regardless of measured (or unmeasured) BMD**
- **Physiology:** Multiple determinants of bone strength: size/shape of bone, BMD, mineralization, bone turnover, & microarchitecture
- **Epidemiology:** Osteoporosis affects 2% of men & 10% of US women >50 y; 49% of adults over 50 y have e/o osteopenia by DXA (at femoral neck and/or lumbar spine); ethnic variation in prevalence

(Asian, Hispanic > Caucasian > African-Americans); 50% of Caucasian women & 20% of Caucasian men will have osteoporotic fracture in their lifetime; highest RR if osteoporosis, but most fractures occur in pts w/ osteopenia

## Diagnosis (*Ann Intern Med* 2011;154:356; *JCEM* 2012;97:1802)

- **General approach:** All pts should be assessed for presence of risk factors (below); if present → FRAX ± BMD testing
- **Screening: Important as disease clinically silent until fracture;** all adult pts should be assessed for risk factors for osteoporosis; BMD assessment via DXA is recommended in all women >65 (USPSTF), men >70 (ACP, Nat'l Osteoporosis Foundation, Endocrine Society), & younger adults at equivalently ↑ risk of fracture (~9.3% over 10 y); NNS >1000 to prevent 1 hip fracture in women <65 y of avg risk (see *"Disease Screening"*)
- **Determining fracture risk:** Myriad risk factors play a role in bone density & risk of fracture (below); FRAX (available at http://www.shef.ac.uk/FRAX/) estimates 10 y risk of major osteoporotic fracture *if pt untreated;* can be used w/ or w/o BMD info; does not account for nonmeasured RF (e.g., fall risk, # of fractures) (*Osteoporos Int* 2008;19:385)

**Selected Risk Factors for Osteoporosis & Fractures**

| Group | Screening Recommendation |
|---|---|
| Personal characteristics | ↑ Age, ↓ wt <59 kg (women) |
| Medications (*Am J Med* 2010;0123:877) | **Glucocorticoids** (>5 mg prednisone QD or equivalent for >3 mos), GnRH agonists, medication-induced hypogonadism (aromatase inhibitors, androgen-deprivation tx), PPI, HAART, high-dose thyroxine |
| Medical history | RA, IBD, **prior fracture** (as adult), celiac disease, s/p gastric bypass, HIV, ESRD, ESLD, COPD, CHF |
| Lifestyle/activity | ↓ Ca intake, inadequate Vit D, lack of wt-bearing activity, heavy EtOH use, tobacco |
| Genetics | ⊕ **FHx,** CF, hemochromatosis |
| Endocrinopathy | Hypogonadism (e.g., anorexia, ↑ PRL, POI, early menopause) ↓ or ↑ cortisol, acromegaly, ↑ thyroid |

(Adapted from Nat'l Osteoporosis Foundation, 2011 Clinician's guide)

- **Bone mineral density assessment:** Via Dual-energy X-ray Absorbitometry (DXA, aka DEXA)

**Skeletal site***:* Best assesses risk of fracture *at that site:* Density of femoral neck is standard; vertebral assessment recommended in pts at higher risk, age, if prior fracture, height loss >1.5 cm (can be difficult to interpret if prior compression fracture, osteophytes, or scoliosis)

**Indications:** Those who benefit from screening (above); adults with a fracture at age >50 y; anyone being considered for or being treated for osteoporosis

**Scoring:** Density of skeletal area compared & reported as standard deviations

**T-score:** Bone density as compared to *average 30 yo adult:* Should not be used to diagnose osteoporosis in premenopausal women or men <50 y

**Z-score:** Bone density as compared to *average person of* pt*'s age & gender;* useful in eval of premenopausal women or men <50 y; low Z-score for any pt raises suspicion of 2° etiology

- **DXA Interpretation:** When multiple sites measured, category typically determined by lowest ("worst") T-score; *Normal:* T-score $\geq -1$; *Osteopenia: T-score between* $-1$ *&* $-2.5$*; Osteoporosis:* T-score $\leq -2.5$ (WHO 2004; who.int/chp/topics/Osteoporosis.pdf)

## Evaluation (*Annals Int Med* 2011;155:ITC1-1)

- For pts with new dx of osteoporosis, important to assess for underlying etiology (if 2° osteoporosis suspected) or potential contributing factors (if 1° osteoporosis)
- **History/Physical exam:** Obtain ht & wt, assess for osteoporosis risk factors (e.g., review meds, hypogonadism s/sx, PMHx), presence of complications (kyphosis, focal back pain suggestive of compression fx), & fall risk (evaluate gait & balance)
- **Diagnostics:** CBC, Ca, phos, Cr, Aφ, LFTs, 25OH Vit D, PTH, TSH, spot urine Ca/Cr; further/specific studies as dictated by findings (see *"Anemia," "Hyperprolactinemia," "Celiac Disease," "Cushing Disease," & "Male Hypogonadism"*)

## Treatment (*NEJM* 2010;363:2027)

- **Nonpharmacologic therapy: Indicated for all pts w/ Ø BMD or**

**fragility fracture**

**Calcium:** Carbonate or citrate available; citrate can be taken w/ or w/o food & w/ PPI; goal is 1200 mg total daily intake

**Vit D:** Replete to goal serum >20 ng/mL; typical dose 800 IU daily (*JCEM* 2011;96:53)

**Exercise** (e.g., walking; even 1 h walking/wk → 20% reduction in risk of hip fx compared with no activity; ↑ benefit w/ ↑ activity) (*JAMA* 2002;288:2300)

**Smoking cessation:** Can → improved BMD (*J Womens Health* 2006;15:1141)

**Limit EtOH:** ↓ BMD & ↑ fall risk; >3 drinks/d → 38%↑ fx risk (*Osteoporos Int* 2005;16:737)

**Fall prevention:** In those at ↑ risk (see *"Fall Prevention"*)

- **Pharmacologic therapy:** Indicated in postmenopausal women or men >50 with osteoporosis (incl hx of fragility fracture) **or** osteopenia **and** (10 y risk of hip fx ≥3% or 10 y risk of major osteoporotic fractures ≥20% per FRAX algorithm) (*Osteoporos Int* 2010;21:41); premenopausal women or men under 50 merit endocrinology referral
- **Oral bisphosphonates: 1st-line tx for most patients;** documented ↓ incidence of hip & vertebral fractures w/ alendronate (generic) & risedronate (patent expires 2014)

**PO Bisphosphonate Properties** (*NEJM* 2010;363:2027)

| | |
|---|---|
| **Sample Rx** | Alendronate 10 mg/d or **70 mg/wk** (↓ esophagitis risk)<br>Risedronate 35 mg/wk or 150 mg/mo |
| **Pt instructions** | Should be taken in AM 30 mins prior to meds or food; take w/ 8 oz water & remain upright for 30 mins to ↓ esophagitis |
| **Contraindications** | CrCl <35 (consider dose adjustment if stage III CKD), pts w/ dysphagia or gastric motility d/o, Vit D deficiency or hypocalcemia |
| **Side effects** | Esophagitis, ONJ (0.01–0.1% annual incidence, 95% of cases occur in CA pts on 10× ↑ doses), atypical femur fx (absolute risk vs. low, likely ↑ w/ Rx duration >5 y) hypocalcemia (↑ risk if Vit D deficient; ensure replete prior to initiating tx) (*J Bone Miner Res* 2010;25:2267; 2007;22:1479) |
| **Duration of Rx** | Bisphosphonates have a prolonged duration of action (continue to work after Rx d/c'ed); consider drug holiday after 5 y if T-score >−2.5, no prior fx, or relatively low risk for future fx; after 10 y if ↑ risk of fx; consider alt tx (*JAMA* 2006;296:2927; *JCEM* 2010;95:1555) |

- **Intravenous bisphosphonate:** Consider if pt has esophagitis/GERD

with PO tx or otherwise unable to tolerate PO; Zoledronic acid 5 mg is *annual* dose; s/e similar to PO + myalgias w/ infusion

- **Raloxifene:** SERM; less effective than bisphosphonates but can be considered in *postmenopausal* women who cannot use bisphosphonates (e.g., CKD) or who have ⊕ FHx breast CA (raloxifene ↓ risk of ED + breast CA) (*JAMA* 1999;281:2189); *s/e:* DVT/PE, peripheral edema, hot flushes, muscle cramps
- **Monitoring response to treatment:** No clear consensus; reasonable to repeat DXA 2 y after initiation of tx; expectation is that BMD stable or improved → less frequent checks; if worsened BMD, warrants further eval
- **Refer to endocrinology:** If nl BMD + fragility fx; recurrent fx or worsening BMD despite tx; when osteoporosis unexpectedly severe or unusual features; when pt has condition that complicates mgmt options or warrants consideration of other therapies (including rPTH, SERM raloxifene, RANKL Ab denosumab)

# POLYCYSTIC OVARY SYNDROME

## Background (*NEJM* 2005;352:1223)

- **Definition:** Polycystic ovary syndrome (PCOS) is a clinical syndrome characterized by menstrual dysfunction, hyperandrogenism, and/or polycystic ovary morphology on U/S
- Polycystic ovary syndrome carries ↑ risk of infertility, pregnancy complications, & endometrial CA; PCOS is assoc w/ DM, obesity, HTN, HLD, NAFLD, OSA, & depression/anxiety
- **Epidemiology:** Affects 5–10% of reproductive-age women; the most common endocrine disorder in this population (*Endocr Pract* 2001;7:0121)
- **Etiology:** Incompletely understood; genetic predisposition & obesity ↑ risk

## Evaluation (*Am J Med* 2007;120:128; *NEJM* 2005;352:1223; *NEJM* 2005;353:2578)

- **General approach:** Assess for s/sx of PCOS, clinical features of Ddx (see below), & metabolic diseases assoc w/ PCOS (obesity, CAD, DM)

- **History:** Obtain detailed OB/GYN hx, including menses frequency & onset (~95% of PCOS pts have amenorrhea or oligomenorrhea), infertility & pregnancy complications, presence/duration of hyperandrogenism sx (hirsutism, acne, androgenetic alopecia (>50% of hirsute pts have PCOS; 70% of PCOS pts have hirsutism) (*Fertil Steril* 2012;97:28)
- **Exam:** Measure BP, BMI, waist circumference; note signs of hyperandrogenism (hirsutism, ♂ pattern baldness, seborrhea, acne, clitoromegaly) & hyperinsulinemia (acanthosis nigricans, skin tags); pelvic exam for size & contour of ovaries; thyroid exam, presence of galactorrhea
- **Lab evaluation:** Not required if classic presentation; can obtain total testosterone & DHEAS (will be nl/↑ in PCOS pts) & LH/FSH (↑ ratio in PCOS) but not diagnostic
- **Imaging:** U/S findings operator-dependent & classic finding "string of pearls" has low Sp → U/S recommended only in women w/ *regular* menses & hyperandrogenism or in women w/ ↑ suspicion for ovarian tumor (i.e., virilization or T >200 ng/dL)

## Diagnosis (*JCEM* 2006;91:781)

- Varying diagnostic criteria exist (NIH 1990, Androgen Excess Society 2006; 2012 NIH expert panel; prevention.nih.gov/workshops/2012/pcos); suggest use of Rotterdam criteria w/ documentation of which criteria on which the dx is based (e.g., "PCOS: Androgen excess & ovulatory dysfunction")
- **Rotterdam criteria:** 2 out of 3 of the following
  1. **Oligo- &/or anovulation** (in absence of other causes)
  2. **Hyperandrogenism** (clinical or biochemical, in absence of other causes)
  3. **Polycystic ovaries** (by U/S)

**Differential Diagnosis** (*NEJM* 2005;352:1223)

| Etiology | Distinguishing Features |
|---|---|
| Pregnancy | Breast tenderness, abdominal cramps, N/V → check β-hCG |
| POI | Hot flashes, other autoimmune dx, chemotherapy/XRT, ⊕ FHx → check FSH & secreting estradiol |
| Endocrinopathies | Hypothyroidism, ↑ PRL, Cushing (see respective chapters)<br>Androgen-secreting tumor (rapid onset of hyperandrogenism, virilization on exam; ✔ DHEAS, total T, & SHBG)<br>Nonclassic CAH (⊕ FHx, Ashkenazi Jewish or Mediterranean descent; ✔ follicular phase 17-hydroxyprogesterone<br>Acromegaly (frontal bossing, coarse features, prognathism; ✔ IGF1) |
| Medications | Androgens, VPA, CsA, exogenous glucocorticoids |
| Nonfunctional pituitary tumor | ↑ Risk HA, focal neurologic sx → neuroimaging |

## Treatment (*Am J Med* 2007;120:128; *NEJM* 2005;352:1223)

- **Screening for metabolic complications:** Clinical screening for HTN, OSA, & depression, labs for DM, HLD, NAFLD; ± endometrial hyperplasia assessment if longstanding PCOS & anovulation
- **Lifestyle modification:** Exercise, diet, & wt loss ↑ ovulation rate, ↓ insulin resistance & ↓ progression from prediabetes → diabetes
- **Oral contraceptive pill:** If pregnancy is not desired, combination estrogen/progestin pill ↓ hyperandrogenism & ↓ risk for endometrial hyperplasia; for pts w/ contraindication to estrogen, progestin-only pill ↓ risk for endometrial hyperplasia (see *"Contraception"*)
- **Spironolactone:** ↓ Hyperandrogenism; 50—100 mg BID can be used as adjunct to OCP; *should not be used w/o OCPs* due to teratogenicity
- **Metformin:** Indicated for DM ± prediabetes; can ↑ ovulation rate, ↓ hyperandrogenism (although OCPs better for endometrial protection & cosmetic sx); not recommended during pregnancy
- **When to refer:** If infertility & pregnancy desired → specialist for consideration of tx such as clomiphene citrate (↑ ovulation rate)
- **Patient information:** http://womenshealth.gov/publications/our-publications/fact-sheet/polycystic-ovary-syndrome.cfm

# THYROID DISORDERS

## Background (*JCEM* 2002;87:489; *Lancet* 2004;363:793; *AFP* 2012;86:244)

- Thyroid hormone is responsible for calorigenesis, potentiating sympathetic nervous system tone, & turnover/clearance of multiple

body components (lipids, CHO, vitamins) & tissues (muscles, bone); thyroid hormone receptors are found throughout the body
- Inappropriate levels of thyroid hormone can lead to myriad effects, often subtle or nonspecific but occasionally serious & even life-threatening; however, these effects are reversible with appropriate tx
- **Physiology:** In response to TSH (secreted from pituitary in response to hypothalamic TRH); the thyroid gland synthesizes, stores, & releases thyroid hormone (T4 & T3); >99% of T4 & T3 are bound in serum (most to TBG); T3 is more "active"; its availability also regulated by peripheral T4 → T3 conversion; free T4 (fT4) best represents the amount of hormone available to tissues
- Most thyroid diseases are 2/2 thyroid gland d/o (1°) rather than central (2°) process

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# HYPOTHYROIDISM

## Background (*JCEM* 2009;94:1853)

- **Classification:** Hypothyroidism is diagnosed by lab abnormalities (below):
  *1° (most common):* ↑ TSH & ↓ fT4
  *Subclinical* (variant of 1°): ↑ TSH with nl fT4 levels (must have stable thyroid, no recent/ongoing illness, & nl hypothalamus–pituitary–thyroid axis); some assoc w/ ↑ CAD incidence & mortality (*JCEM* 2010;95:1734) & CHF (*Lancet* 2012;379:1142)
  *Central* (due to pituitary or hypothalamic dysfunction): ↓ /nl TSH & ↓ fT4; accounts for <1% of hypothyroidism (*JCEM* 2012;97:3068)
- **Epidemiology:** 3–8% of the population in US has hypothyroidism; ↑ incidence in elderly, ♀ > ♂, Caucasian/Hispanic prevalence > African-Americans; ↑ risk if postpartum, hx autoimmune disease, ⊕ FHx thyroid disease, chest/neck XRT (*Thyroid* 2007;17:1211)

**Etiology of Hypothyroidism** (*Endocr Practice* 2012;18:988)

| Etiology | Distinguishing Features |
|---|---|
| Autoimmune | Chronic autoimmune thyroiditis (Hashimoto); also assoc w/ multiple autoimmune endocrinopathies |
| Iatrogenic | S/p tx for hyperthyroidism or thyroid CA; (RAIU, surgery) neck XRT |
| Central | CNS tumor, inflammatory, infiltrative disease, Sheehan, surgery, or XRT |
| Transient | Postpartum thyroiditis, subacute granulomatous thyroiditis |
| Medications | Lithium, amiodarone, sunitinib (tyrosine kinase inhibitor), PPI |
| Other | Iodine deficiency (Rare in US 2/2 iodized salt; most common cause worldwide), congenital (all US newborns screened) |

- **Manifestations:** Highly variable & diffuse; can include: *Constitutional:* wt gain, **fatigue, cold intolerance;** *HEENT:* Voice changes, goiter; *CV:* Diastolic HTN; *Pulm:* Sleep apnea; *GI:* **Constipation,** *Ext:* Nonpitting edema; *MSK/Neuro:* Carpal tunnel syndrome, myalgias, **delayed DTR relaxation** (↑ Se/Sp); *Endo:* Dyslipidemia; *GU:* Decreased libido, menstrual irregularities; *Derm:* Brittle hair/nails, **dry skin,** lateral eyebrow hair loss
- Extreme/prolonged hypothyroidism can → myxedema coma (hypothermia, HoTN, hypoventilation, AMS) esp in setting of another stressor (trauma, infection, drugs) = emergency → ED
- **Screening:** Sx often subtle or nonspecific, tx effective, & ↑ prevalence, so low threshold to screen; however, no evidence that screening asx (nonpregnant) people improves outcomes; differing clinical guidelines (AAFP, USPSTF, ACP, AACE) exist (see *"Disease Screening"*) but reasonable to test patients at ↑ risk, with disease which could be worsened by hypothyroidism, or with s/sx of disease
- **Lab:** TSH alone for screening purposes; if this is elevated (or ↓ /nl but suspicion high enough to consider central etiology) → free T4; if pt w/o goiter, clinically c/w general autoimmune hypothyroidism, no further testing required; anti-TPO Abs indicated in *subclinical* hypothyroidism: ⊕ Suggests ↑ risk of progression to overt hypothyroidism (anti-TPO often ↑ in Hashimoto but does not change mgmt); T3 measurements not helpful
- **Lab abnormalities associated with hypothyroidism:** ↑ LDL, ↓ HDL, anemia, ↑ CK, mild hyponatremia, & hypoglycemia; however, these should not be used in dx

## Treatment (*Endocr Practice* 2012;18:988)

- **General approach:** Uncomplicated 1° hypothyroidism can be managed

by PCP with synthetic T4; referral indications below

- **Subclinical hypothyroidism:** Consider tx if TSH >10, pt sx, or ⊕ Anti-TPO; initial dose 25–75 μg, monitor via TSH

### Prescribing Synthetic Thyroxine

| | |
|---|---|
| **Choice of Rx** | Some concerns re: different pharmacokinetics/bioavailability of different formulations; AACE recommends keeping patient on same formulation (or if must switch, recheck TSH 6–8 wks later) (*AFP* 2012;86:244) |
| **Initial dosing** | Empiric dosing 1.6 μg/kg/d (~110 μg for 70 kg person); for healthy younger adults, okay to start at full dose; for elderly or pts w/ CAD, start at 25–50 μg & slowly up titrate to avoid s/e |
| **Administration** | All patients should take in AM 1–2 h prior to food (missed pill can be taken later in day), 2–3 h apart from Ca or iron supplements; some pts prefer QHS dosing (but should be 4 h after last meal) |
| **Monitoring** | Recheck TSH in 6–8 wks & adjust accordingly; goal is TSH w/in nl range; once in range, recheck q6–12mos; if TSH in nl range but pt still symptomatic, consider ↑ dose with target TSH in low-nl range |
| **Tx interruptions** | Avoid if possible; if <6 wks, generally ok to resume prior dose (assuming no CV event or significant wt loss) (*Endocr Pract* 2012;18:988) |

- **Persistent/newly ↑ TSH in hypothyroid patient:** Assess adherence (most common) & timing of dose; review medications, assess if formulation changed
- **When to refer:** Pts in whom difficulty achieving euthyroid state, cardiac disease, women planning pregnancy or currently pregnant; thyroid structural abnormality, other endocrine d/o (adrenal, pituitary), labs difficult to interpret, unusual cause suspected → endocrine

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## HYPERTHYROIDISM

### Background (*JCEM* 2002;87:489; *Endocr Practice* 2011;17:e1; *AFP* 2005;72:623)

- **Epidemiology:** 1.2% of US population (0.5% overt & 0.7%) subclinical; ♀:♂, 5:1
- **Etiology: Graves disease** (autoimmune d/o with TSH-receptor stimulating Abs) 60–80%; thyroiditis (lymphocytic or granulomatous), toxic adenoma, toxic multinodular goiter (TMNG) 5%; pts often older, w/ longstanding goiter); medications (**amiodarone,** iodine, excess thyroxine use); rare causes incl TSH-secreting pituitary tumor, hCG-secreting tumors, struma ovarii,

widely metastatic follicular thyroid cancer

- **Manifestations:** Diffuse, range from mild–severe; *Constitutional:* Sweating, wt loss; *HEENT:* Stare, lid lag (Graves); *Derm:* Onycholysis, softening nails, hyperpigmentation (2/2 ↑ ACTH), pruritus, thinning hair; *CV:* Tachycardia, AF; *Endo:* ↓ BMD; *Ext:* Pretibial myxedema (Graves); *Neuro:* Tremor, anxiety, hyperreflexia

## Evaluation

- If hyperthyroidism suspected, full assessment should include *hx:* Onset/duration of s/sx, above, as well as full medication & supplement list, recent CT scans; *Exam:* VS: HR, BP, RR, wt; HEENT: Ocular exam (EOM, proptosis), thyroid (size, tenderness, nodules); CV, pulmonary function, presence of edema
- **Diagnostics:** TSH best initial test; if ↓, then obtain T3, fT4 (T3-predominance suggestive of Graves) & RAIU (best if no recent iodine exposure, as can → falsely low uptake); thyroglobulin if concern for exogenous T4 overdose (will be low); U/S if nodule noted on exam (see section below)

**Radioactive Iodine Uptake Results**

| Low uptake | High uptake |
|---|---|
| Thyroiditis | Graves disease (diffuse uptake) |
| Exogenous hormone | Toxic multinodular adenoma (multiple foci) |
| Iodine exposure (incl amiodarone) | Toxic adenoma (one focus) |

## Treatment (*JAMA* 2004;291:228)

- **Acute management:** Methimazole 1st-line (PTU 1st line in pregnant women); βB (e.g., propranolol 10–40 mg TID) indicated for pts w/ CAD & resting pulse >90 or elderly pts w/ sx thyrotoxicosis
- **Endocrine referral:** Indicated for all hyperthyroid patients; Graves disease tx choices include $^{131}$I tx, antithyroid medication, or surgery; glucocorticoids considered in mod-severe Graves ophthalmopathy
- **Subclinical hyperthyroidism:** ↓ TSH with nl fT4; often due to TMNG; *if asx*, recheck labs at 3–6 mos to document persistence vs. resolution; *If persistent & TSH <0.1*, consider tx & RAIU; *If TSH 0.1–0.5:* Consider tx in elderly, symptomatic, pts w/ CV disease

## THYROID NODULES

- **Background:** Nodule is discrete mass w/in thyroid gland visualized on imaging; may be palpable or clinically inapparent; 4–7% of adults have palpable nodule; 50% of pts >60 y have nodule evident on autopsy; ~5% of nodules are malignant (*NEJM* 2004;351:1764)
- Incidentally detected & palpable nodules have the same risk of CA → same eval
- **Evaluation:** Full hx & physical w/ special attention to thyroid exam & paracervical LN; asses for factors which suggest ↑ likelihood of malignancy (below)

### Features Associated with Increased Risk of Malignancy

| History | Physical/Radiographic |
|---|---|
| Hx childhood head & neck XRT | Vocal cord paralysis |
| Hx total body XRT | Lateral cervical LAD |
| ⊕ FHx thyroid Ca or Ca syndrome (e.g., MEN2) | Nodule fixation to surrounding tissues |
| Hx childhood radiation exposure | Microcalcifications |
| Rapid growth of mass/nodule | Hypoechoic or ↑ vascularity |
| Hoarseness | Infiltrative margins |
| | Taller than wide on transverse view |

- **All nodules:** Dedicated thyroid U/S & TSH; if TSH low → RAIU; if nodule suspected on exam not present on U/S → reassurance (ATA 2009 guidelines; thyroidguidelines.net)
- **Fine-needle aspiration indications:** Not indicated in simple cyst; always indicated if ⊕ cervical LAD; other general indications below by size:
  *5 mm nodule:* If risk hx
  *1 cm nodule:* If solid hypoechoic or nodular microcalcifications
  *1–1.5 cm nodule:* If solid iso- or hyperechoic
  *1.5–2 cm nodule:* If mixed–cystic w/ suspicious features
  *2 cm nodule:* If mixed–cystic w/o suspicious features or spongiform
- **Fine-needle aspiration interpretation**

### FNA results and management

| | |
|---|---|
| **Benign** | Follow (as below) |
| **Nondiagnostic** | Repeat; if nondiagnostic again → close f/u or surgery |
| **Indeterminate** | Hurthle cell → surgery<br>Follicular → RAIU: If hyperfunctioning → follow; o/w → surgery |
| **Suspicious** | Preop U/S → surgery |
| **Malignant** | Preop U/S → surgery |

- **Monitoring:** Nodules which do not require bx *or* have ⊖ cytology on FNA → serial monitoring (e.g., q6mos); if nodule stable, can space to q12mos or longer; many nodules grow over time; however, if ↑ diameter by 20% → repeat FNA
- **Endocrine referral:** Multiple nodules, ambiguous testing results, nodule + ↑ risk, abnl FNA

# VITAMIN D DEFICIENCY

## Background (*NEJM* 2007;357:266; 2011;364:248)

- **Definitions:** Vit D deficiency: serum 25OH Vit D < 20 ng/mL; insufficiency 20–29 ng/mL
- **Physiology:** Vit D is a hormone which ↑ GI absorption & ↓ renal excretion of Ca, ↓ PTH production, & contributes to nl bone growth/mineralization
- **Complications:** Inadequate Vit D causes 2° hyperparathyroidism & inadequate bone mineralization (> osteomalacia), can ↑ fracture risk & ↑ falls in elderly; has also been assoc w/ myriad extraskeletal disease, including DM, cancer, & MS, although these are controversial & RCTs demonstrating extraskeletal benefits of supplementation are lacking
- **Metabolism:** Dietary intake of Vit $D_2$ (ergocalciferol = from plants) or Vit $D_3$ (cholecalciferol = from animals) as well as synthesized $D_3$ (created in UV-exposed skin) converted to 25OH Vit D by the liver → converted to 1,25OH Vit D by the kidney; this final step is regulated by Ca, PTH, & phosphate levels
- Vitamin D deficiency can occur with ↓ intake (↓ dietary intake, GI absorption, or UV exposure), impaired hepatic conversion to 25OH Vit D (rare), impaired renal conversion to 1,25OH Vit D (common, seen in CKD)

- **Epidemiology:** 33% of US population have Vit D <20; 6–8% of adult men & 10–12% of adult women have Vit D <12 ng/mL (*cdc.gov; NCHS* 2011:59)
- **Groups at increased risk of insufficient vitamin D:** Elderly (↓ skin production), inhabitants of Northern climates, obese (Vit D sequestered in adipose tissue) homebound, institutionalized, or otherwise inadequate sun exposure, postmenopausal women, GI disease (↓ absorption: IBD, celiac, biliary disease) medications (e.g., phenytoin, glucocorticoids, rifampin, cholestyramine)

## Evaluation (*Mayo Clin Proc* 2011;86:50)

- **Screening:** Some debate about merits of screening asx individuals; however, many (including AACE) suggest clinically screening all pts to find those at ↑ risk, & then to test Vit D in this population
- **Labs:** Obtaining 25OH Vit D generally sufficient; in pts w/ ESRD, would also obtain PTH & 1,25OH Vit D (due to ↓ renal conversion, they may have insufficiency despite adequate 25OH Vit D)

## Treatment (*NEJM* 2007;357:266; *JCEM* 2011;96:53)

- **Vitamin D deficiency:** Ergocalciferol 50,000 IU weekly for 8 wks; may require longer course for repletion in obese patients or extreme deficiency
- **Vitamin D insufficiency:** 800–2000 IU QD will replete levels in an avg adult by 3 mos
- **Prevention:** The IOM recommends **600 IU of Vit D** & 1000 mg Ca daily intake for all adults, and 800 IU of Vit D & 1200 mg Ca for adults >70 y; upper level of Vit D intake (above which ↑ risk of harm) set at >4000 IU daily for all adults (www.nap.edu/catalog.php?record_id=13050)
  **Special populations:** *Osteoporosis:* (see *"Osteoporosis"*); *CKD:* Repletion based on GFR & PTH; refer to practice guidelines (www.kidney.org/professionals/kdoqi/guidelines.cfm)
- **Vit D2 vs Vit D3: D2** (ergocalciferol) available by Rx in high-dose formulations for weekly/monthly repletion, not animal-based for pts w/ objections; $\mathbf{D_3}$ (cholecalciferol) appears to ↑ serum Vit D levels higher at equivalent dose, although does not account for potential

differences in adherence (*JCEM* 2011;96:E447; 2011;96:981)

- **Calcitriol:** Use primarily restricted to CKD pts w/ hypocalcemia or parathyroid disease
- **Referral:** Consider referral if low Vit D is refractory to supplementation or if etiology unclear

# ABDOMINAL PAIN

## Background

- Abdominal pain is a common complaint in outpt medicine; one of the 20 most common reasons for office visits in US (*NAMCS* 2010, http://www.cdc.gov/nchs)
- Complaint reflects a wide array of potential etiologies & organ systems, which vary in severity; careful hx & consideration of demographics key to guiding differential & identifying pts who merit ED referral (acute pain) or GI referral (chronic pain)

## Evaluation (*AFP* 2008;77:971; *Emerg Med Clin N Am* 2011;29:159)

- **History:** *Pain hx:* Acute vs. chronic, onset, location, radiation, severity, quality (colic → gallstone, nephrolithiasis, SBO); is pain worsening, stable, or improving?
  *Assoc sx:* N/V, diarrhea, constipation, or lack of flatus (SBO), fever, abd distention, edema (CHF gut edema, cirrhosis), jaundice (hepatitis), rectal bleeding (IBD, infection), reflux (GERD), wt loss (↑ likelihood of organic disease)
  *Aggravating/alleviating factors:* Eating, defecation (IBS), movement or lying still, pleuritic (thoracic), ↑ w/ tensing abd wall (hernia, myofascial abd wall pain; *AFP* 2001;64:431)
  *PMHx:* Including cancer hx (tumor, ↑ Ca), prior abd surgery, immunosuppression, CAD/PAD (mesenteric ischemia), endocrinopathy (thyroid, adrenal disease); in women, LMP, new sexual partners (see *"Pelvic Pain"*)
  *Social hx:* EtOH (gastritis, pancreatitis, hepatitis), tobacco (AAA), travel hx (infection)
  *Medications:* NSAIDs (gastritis), abx (*C. diff*)
- **Physical exam:** VS (fever, HoTN/HTN), general appearance; skin exam (zoster on abd wall, stigmata of liver disease, jaundice), LN exam (HIV, lymphoma), gyn exam in women w/ lower abd pain (see *"Pelvic Pain"*), rectal exam (stool impaction, stool color, rectal mass/lesion)
  *Abdominal exam:* Distention, bowel sounds, bruits, palpation in each quadrant, assessing for tenderness, rebound, masses,

organomegaly, percussion (organomegaly, gas, ascites, stool)
*Murphy sign:* Inhalation cessation w/ RUQ pressure by examiner (acute cholecystitis)
*Psoas sign:* Pain if supine pt lifts thigh against resistance (peritonitis, appendicitis on R)

- **Diagnostics:** Guided by hx; may not be indicated in all pts (esp young, healthy pts w/o red flags & w/ nl-appearing exam)
  *Labs:* Acute → hCG, CBC, BMP, LFTs, lipase, U/A; chronic → CBC, BMP, LFTs, lipase, TSH, Fe studies, celiac testing
  *Imaging:* Radiograph (constipation, obstruction, perforated viscus); CT (↑ Se for structural abnormalities of alimentary tract, vascular disease, liver), U/S (biliary disease, organomegaly) (*Emerg Med Clin N Am* 2011;29:175)
- **Endoscopy:** Highest yield in the presence of alarm signs or overt GIB; diagnostic colonoscopy may be useful in chronic abd pain if concern for inflammatory or neoplastic process

## Acute Abdominal Pain

- **General approach:** May help to organize differential by pain location; Red flags → ED
- **Red flags:** Fever (esp in immunosuppressed), protracted vomiting, HoTN or e/o hypovolemia, jaundice, severe pain; e/o peritonitis (rigid abdomen, pain w/ minimal movement, incl flex hips, cough) → ED
- **Non-gastrointestinal causes:** Consider cardiac (MI, see *"Chest Pain"* ), pulm (PNA), vascular (dissection), endocrine (DKA, ↑ Ca, adrenal insufficiency), GU (renal colic, pyelonephritis, cystitis)
- **Diffuse:** Gastroenteritis (N/V/D, sick contacts, recent abx use → often supportive care, stool Cx if ? bacterial); peritonitis (peritoneal signs → ED ± CT), SBO (N/V, no BM/flatus, distention, ↑ bowel sounds, often hx CA or abd surgery → ED [KUB or CT])
- **Right upper quadrant:** *Acute cholecystitis* (⊕ Murphy sign, fever) → ED; *cholangitis* ( jaundice, fever) → ED, *sx cholelithiasis:* Recurrent, postprandial colicky RUQ pain, often nl bili & Aφ → RUQ U/S ± surgical referral
- **Central/Epigastric pain:** Gastritis (burning, can be assoc w/ reflux sx;

see *"GERD"* & "Peptic Ulcer Disease" [PUD]; pancreatitis (worse w/ food, ⊕ N/V, radiates to back); ↑ lipase (& amylase), see *"Pancreatitis"; mesenteric ischemia* (pain out of proportion to exam, ± N/V, bloody diarrhea ↑ lactate, often ↑ WBC → ED)

- **Right lower quadrant:** Appendicitis (N/V, ± peritoneal signs, persistent pain) → ED
- **Left lower quadrant:** Diverticulitis (fever, ↑ WBC, distention, ± BRBPR; see *"Diverticular disease"* )
- **Pelvic pain:** Ectopic pregnancy, ovarian cyst or torsion, PID (see *"Pelvic Pain"* & *"PID"* ), testicular pain (see *"Scrotal and testicular lesions"* )
- **Left upper quadrant:** Splenic infarct (embolic) or splenic rupture (trauma, EBV assoc), or colonic disease (mesenteric ischemia, colitis)

## Chronic Abdominal Pain

- **General approach:** Red flags → urgent eval (imaging ± endoscopy); other than GERD/dyspepsia, may be helpful to organize differential by types of pathology
- **Red flags:** Wt loss, hemoccult ⊕ stools or microcytic anemia, malnutrition, new pain in pt >50, new ascites, splenomegaly, hepatomegaly → urgent outpt w/u
- **Epigastric** (*Gastroenterology* 2005;129:1756)
  *Dyspepsia*: Epigastric pain, bloating, gas; EGD if alarm sx (see *"Dyspepsia"* subsection)
  *GERD:* Recurrent postprandial burning discomfort in epigastrium/chest ± sx of reflux (see *"GERD"* )
- **Inflammatory** (*AFP* 2011;84:1365, *AFP* 2007;76:1795, *NEJM* 1995;332:1482)
  *IBD:* Diarrhea, hemoccult ⊕ stools, anemia, ⊕ fever, ⊕ extraintestinal sx, wt loss → lower endoscopy w/ bx (*see "IBD"* )
  *Celiac disease:* Variable sx: Diarrhea, fatigue, wt loss, abd distention; Fe deficiency, transaminitis (see *"Celiac disease"* )
  *Chronic pancreatitis:* Recurrent episodes of upper abd pain, ± malabsorption, usually hx ↑ EtOH intake (see *"Pancreatitis"* )
- **Motility** (*Gastroenterology* 2013;144:218; *Gut* 2010;59:1716)
  *Constipation:* Per pt report; hx straining, lumpy/hard stools, sense of

incomplete evacuation, anorectal obstruction/blockade, <3 defecations/wk (see *"Constipation"*)

*Gastroparesis:* Often assoc w/ autonomic neuropathy in DM, ♀ > ♂; c/o postmeal N/V, bloating, early satiety → gastric emptying studies

- **Vascular:** *Chronic mesenteric ischemia:* PAD/CAD hx, postprandial pain & "food fear," wt loss → duplex U/S, mesenteric angiography (*JACC* 2006;47:944)
- **Neoplastic:**

  *CRC:* **Typically asymptomic unless advanced or rectal disease;** often p/w Fe-deficiency anemia → colonoscopy

  *HCC:* LFT abnormalities, s/sx of biliary obstruction → CT, RUQ U/S

  *Gastric:* Dyspepsia, bleeding → CT or endoscopy

  *Pancreatobiliary:* S/sx of cholestasis (jaundice, ↑ Aφ, bili) → CT, RUQ U/S → MRCP/ERCP

  *Ovarian:* Often nonspecific bloating, fullness sensation → CT
- **Functional** (*NEJM* 2008;358:1692)

  *IBS:* Pain relieved w/ BM; pain onset assoc w/ change in stool freq/appearance; sx ↑ w/ stress; see *"IBS"*

  *Functional abd pain syndrome:* Chronic pain, not related to physiologic events; impact on daily functioning, does not meets criteria for another d/o (e.g., IBS); must meet all criteria for 3 mos w/ sx for >6 mos; tx similar to IBS (*Gastroenterology* 2006;130:1377)
- **Gynecology/Gastric ulcer:** See *"Pelvic Pain"* & *"Peptic Ulcer Disease"*

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## DYSPEPSIA

- **Definition:** Chronic or recurrent pain in upper abdomen, not assoc w/ bowel habits, & without e/o organic disease (*Gastroenterology* 2005;129:1756)
- **Evaluation: EGD** indicated for all pts >55 y w/ new onset dyspepsia **or** alarm features

### Dyspepsia Alarm Features

| | |
|---|---|
| Age of sx onset >55 y | GI bleed/Fe-deficiency anemia |
| ⊕ FHx upper GI cancer | Persistent Vomiting |
| Unintended wt loss | Palpable mass/lymphadenopathy |
| Dysphagia/odynophagia | Jaundice |

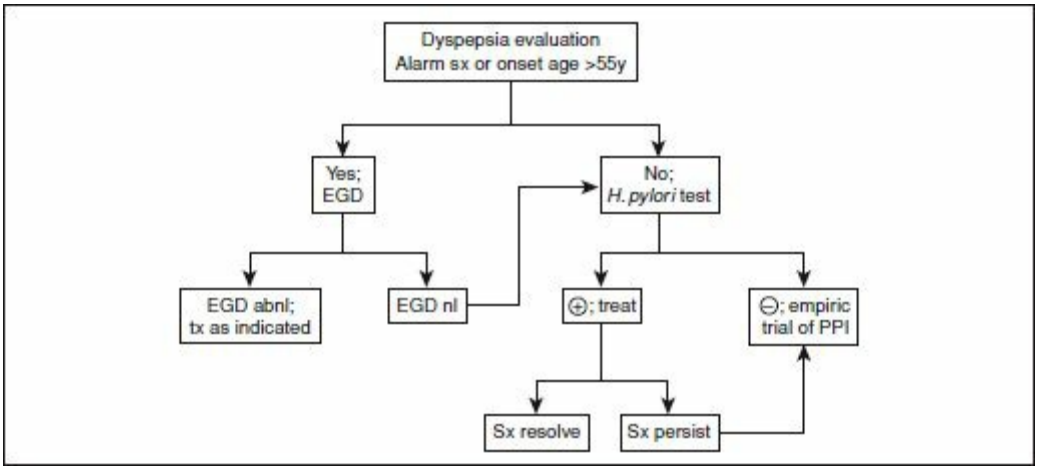


Figure 5-**1** Dyspepsia Evaluation (*Am J Gastroenterol* 2005;100:2324)

# ABNORMAL LIVER FUNCTION TESTS

## Background

- Liver biochemical tests ("LFTs") are obtained under a variety of circumstances, ranging from severe illness to drug monitoring; correct interpretation requires considering clinical presentation w/ pattern of abnormalities

**Tests Used in Assessing Liver Function** (*Clin Liver Dis* 2009;13:167)

| | |
|---|---|
| **Aminotransferases (AST, ALT)** | Intracellular enzymes released in hepatocyte damage; ALT more specific to liver than AST; also found in cardiac, skeletal muscle (↑ in rhabdo); levels do not always correlate w/ liver damage |
| **Alkaline Phosphatase (Aϕ)** | Enzyme bound to hepatic canalicular membrane, also found in bone (mets, turnover), intestines, kidney, & placenta; ↑ enzyme synthesis in biliary obstruction, delayed peak/clearance after obstruction resolves |
| **Gamma Glutamyl-Transpeptidase (GGT)** | Enzyme on the surface of hepatocytes & biliary epithelia, also in kidney, pancreas, heart, lung, brain, but NOT bone; used to confirm hepatic origin of Aϕ; ↑ w/ EtOH, warfarin, phenytoin |
| **Bilirubin (Bili)** | Product of heme metabolism, conjugated in liver, excreted in bile; direct (conjugated) + indirect (unconjugated) = total bili |
| **Albumin** | Marker of liver synthetic function, delayed response to liver injury ($t_{1/2}$ = 20 d); ↓ w/ losses (nephrotic syndrome), turnover (glucocorticoids) or ↓ intake (malnutrition) |
| **Prothrombin Time (PT & INR)** | Marker of liver synthetic function (clotting factors except VIII made in liver); early marker of injury; correlates poorly w/ bleeding risk |

## Evaluation (*NEJM* 2000;342:1266)

- **General approach:** Confirm persistence/severity, Ddx guided by pattern of elevation; full eval should include PMHx, meds, EtOH use, & careful exam
- **Is it severe or is patient symptomatic?** If asx & $<2\times$ ULN, recheck → LFTs will normalize in 30% of pts upon retesting (*Ann Int Med* 2008;148:348)
- **What is pattern of elevation?**
  **Hepatocellular:** ↑↑ Aminotransferases, ± ↑ bili or Aφ
  **Cholestatic:** ↑↑ Aφ, ± ↑ aminotransferases, ↑ bili
  **Infiltrative:** ↑↑ Aφ, ± ↑ bili or aminotransferases
  **Isolated Hyperbilirubinemia:** ↑↑ bili

## Differential Diagnosis

- **Hepatocellular pattern:** Prevalence in US is 9%, likely driven by NAFLD (*Am J Gastroenterol* 2006;101:76); if AST: ALT >2:1: consider EtOH, cirrhosis, rhabdo; if ALT <5× ULN, work through table below; if these ⊖ or dx indicates → hepatology referral

**Hepatocellular Injury Ddx When ALT <5¥ ULN**

| | |
|---|---|
| **Meds, Toxins** | EtOH most common cause; see medication table below |
| **Viral Hepatitis** | ✔ HBsAg, HBsAb, HBcAb, HCV Ab; see *"HBV" & "HCV"* |
| **Hemochromatosis** (see *"Hemochromatosis"*) | Common in pts of Northern European descent<br>✔ Fe/TIBC ratio: If >45%, ✔ ferritin → if ferritin >400 ng/mL (♂) or >300 ng/mL (♀), ✔ *HFE* gene mutations<br>Consider bx: Age >40, hepatosplenomegaly, abnl LFTs or ferritin >1000 |
| **NAFLD** | Assoc w/ metabolic syndrome & insulin resistance; includes spectrum from steatosis to steatohepatitis (NASH) to cirrhosis; ✔ RUQ U/S, consider liver bx if age >50 y and BMI ≥30 or DM or any e/o liver synthetic dysfunction |
| **Autoimmune Hepatitis** | ♀ > ♂ (4:1), bimodal age distribution; ✔ SPEP (80% have ↑ IgG), consider ANA, anti-SMA, soluble liver antigen (SLA); refer for liver bx |
| **Celiac Disease** | Chronic diarrhea, wt loss, fatigue (see *"Celiac Disease"*) |
| **Other** | α-1 Antitrypsin deficiency: Assoc w/ panacinar emphysema; ✔ α1AT level (<80 mg/dL suggestive), SPEP;<br>Wilson disease: Usually age <40 y; ✔ceruloplasmin |

- **Cholestatic/Infiltrative pattern:** Usually from intra/extrahepatic obstruction or infiltrative disease; if confirmed w/ ↑ GGT, obtain RUQ U/S
- If no ductal dilatation on ultrasound, consider:
  **Medications:** See chart, below: D/c potential offenders & monitor for response (recall delayed peak after injury)
  **PBC:** ♀ > ♂, onset 40–50s; fatigue, pruritus; ✔AMA (Se/Sp 95/98%) & SPEP (↑ IgM); if ⊕, refer for liver bx (*NEJM* 2005;353:1261; *Clin Liver Dis* 2008;12:261)
  **Other:** Biliary epithelial damage from hepatitis (↑ ALT) or cirrhosis (↑ PT, ↓ albumin); infiltrative process incl liver abscess, amyloidosis, fungal infection, HCC (check AFP), lymphoma, metastatic CA, sarcoidosis, TB; consider MRI or CT, hepatology referral
- If ductal dilatation present, consider:

**Choledocholithiasis:** Referral for MRCP or EUS (intermediate probability) vs. ERCP (if ↑ probability) (*Gastrointest Endosc* 2010;71:1)

**Cholangiocarcinoma or pancreatic CA:** MRI or CT → referral for bx vs. ERCP

**Primary sclerosing cholangitis:** ♂ > ♀, age 30–40, assoc w/ IBD, always involves common bile duct; MRCP & hepatology referral

- **Isolated hyperbilirubinemia** (see *"Jaundice"*)

**Common Medications Causing Liver Injury** (*NEJM* 2006;354:731)

| Hepatocellular Pattern | | Mixed Pattern | Cholestatic Pattern |
|---|---|---|---|
| Acarbose | **Losartan** | Amitriptyline | Amoxicillin–clavulanate |
| **APAP** | MTX | **AZA** | Anabolic steroids |
| Allopurinol | **NSAIDs** | Captopril | Chlorpromazine |
| **Amiodarone** | Omeprazole | Carbamazepine | Clopidogrel |
| Baclofen | Paroxetine | Clindamycin | Oral contraceptives |
| Bupropion | PZA | Cyproheptadine | Erythromycins |
| Fluoxetine | Rifampin | Enalapril | Estrogens |
| **HAART Rx** | Risperidone | Flutamide | Irbesartan |
| Herbals: Kava kava, germander | Sertraline | Nitrofurantoin | Mirtazapine |
| | **Statins** | Phenobarbital | Phenothiazines |
| INH | Tetracyclines | Phenytoin | Terbinafine |
| Ketoconazole | Trazodone | Sulfonamides | Tricyclics |
| **Lisinopril** | Trovafloxacin | Trazodone | |
| | VPA | **TMP–SMX** | |
| | | Verapamil | |

# CELIAC DISEASE

## Background (*Gastroenterology* 2006;131:1977)

- **Definition:** Celiac disease ("celiac sprue") is a systemic immune-mediated disorder, precipitated by exposure to dietary gluten (protein found in wheat, rye, & barley) in genetically predisposed individuals, characterized by malabsorptive enteropathy (*NEJM* 2012;367:2419; *Gut* 2013;62:43)
- **Epidemiology:** Frequently undiagnosed; US prevalence ~0.7% (*Am J Gastroenterol* 2012;107:1538); incidence ↑ in women (♀:♂ ~1.5:1); occurs in people of all races/ethnicities, but less common in pts of Asian, sub-Saharan African, Inuit descent (*JAMA* 2011;306:1582)
- **Risk factors:** ⊕ FHx (10–15% if 1st-degree relative), DM1 (2–16%),

Hashimoto thyroiditis (5%), other autoimmune disease, Down syndrome (5%), Turner syndrome (3%), IgA deficiency (9%)

- **Pathophysiology:** Gluten exposure, change in intestinal permeability → transglutaminase- modified gluten → HLA recognition → Ab against transglutaminase/gluten complex → celiac enteropathy (*Gastroenterology* 2009;137:1912)

## Evaluation (*NEJM* 2012;367:2419)

- **General approach:** Celiac disease should be considered in pts w/ malabsorption, chronic abd pain; testing for celiac is part of a complete eval for these sx, & celiac diagnosis often delayed due to nonspecific presentation
- **Presentation:** *Typical:* Diarrhea, steatorrhea, wt loss, abd pain/bloating, poor appetite; *Common:* Recurrent abd pain, aphthous ulcers, fatigue, Fe deficiency (± anemia), ↓ BMD ↑ ALT/AST; *Rare:* Dermatitis herpetiformis (vesicular rash on extensor surfaces, diagnosed by biopsy)

### Whom to Test for Celiac Disease

| Pretest probability | Presenting features |
|---|---|
| **High (>10%):** Test; consider bx even if serology ⊖ | (Autoimmune disease, IgA deficiency, or ⊕ FHx celiac) **and** abd pain/bloating; chronic diarrhea; dermatitis herpetiformis (rare); Fe-deficiency anemia not responsive to oral supplementation |
| **Mod (4–10%)** Test; ⊖ serology adequate to r/o disease | IBS, ↑ LFTs, Fe-deficiency anemia (unclear etiology), chronic GI sx, fatigue/lethargy, chronic abd pain/bloating, peripheral neuropathy, recurrent aphthous ulcers, microscopic colitis, infertility/recurrent miscarriage, Down syndrome, Turner syndrome, IgA deficiency |
| **Low (<4%)** Consider testing only if more likely causes r/o | ↓ BMD, fibromyalgia, chronic fatigue, GERD, pancreatitis, alopecia, myalgias/arthralgias, autoimmune liver disease, personal hx, other skin rashes, HA, mood d/o, ADHD, dementia, epilepsy, restless leg syndrome |

- **Complications:** Can include osteoporosis, ↓ splenic function, neuropathy, ataxia (rare), infertility/recurrent miscarriage, ulcerative jejunoileitis, & small bowel lymphoma (rare)
- **Diagnosis:** Generally made by serologic screening, followed by confirmatory bx; avoid starting gluten-free diet prior to testing (↓ Se); additionally, trial of gluten-free diet not sensitive or specific as test

for celiac disease, so should be avoided ( *JAMA* 2011;306:1582)

- **Gluten disease differential diagnosis:** Gluten *allergy* (IgE-mediated food, contact, or asthmatic reactions) & gluten *sensitivity* (nonimmune idiopathic response to gluten, improves on GFD)
- **Serology:** Celiac antibodies include anti-tissue transglutaminase (anti-TTG), anti-endomysial antibody (EMA), and anti-deamidatedgliadinpeptide (DGP)
  **1st-line: ✔ Anti-TTG IgA** (Se/Sp 95/95%) ± **total IgA;** pts w/ IgA deficiency are at risk of false ⊖ & should have **IgG**-based DGP or TTG testing
  **If initial testing ⊖ but ↑ suspicion,** refer for bx
  **False ⊕ :** Autoimmune disease → if concern, ✔ IgA EMA
  **Borderline results:** ✔ IgA EMA
- **Biopsy:** If screening ⊕ → for confirmatory small bowel bx (villous atrophy, ↑ intraepithelial lymphocytes, crypt elongation); may also obtain if screening ⊖ but ↑ suspicion

## Treatment (*Gastroenterology* 2006;131:1977; *Am J Gastroenterol* 2013;108:656)

- **Diet:** Lifelong gluten-free diet mainstay of therapy; no wheat, barley, or rye; pure oats may be introduced w/ caution; pts should be referred to experienced dietician when available
- **Counseling:** Gluten-free diet helps improve sx & ↓ risk of complications; typically lifelong requirement or damage recurs; many substitutes available; even a crust of bread/day can → intestinal damage over time; sx begin to improve in 2–4 wks & intestines heal by 6–24 mos
- **Treat complications:** Treat nutritional deficiencies (✔ Fe, folate, Vit D, Vit $B1_2$); consider DXA (see *"Osteoporosis"* )
- **When to refer:** May refer if screening ⊖ but still ↑ suspicion; after dx confirmed, pts often followed by PCP but may need re-referral to GI if sx refractory *despite* confirmed adherence to gluten-free diet

# CIRRHOSIS

## Background (*Am J Gastroenterol* 2009;104:1802)

- **Definition: Cirrhosis:** End stage of chronic liver disease from any cause; histologic diagnosis of liver fibrosis & nodular regeneration from hepatocellular injury; *clinically* classified as compensated or decompensated
- **Decompensated cirrhosis:** Cirrhosis which is complicated by **portal HTN** (ascites, variceal bleeding) and/or **hepatic insufficiency** ( jaundice, encephalopathy)
- **Epidemiology:** Compensated cirrhosis often clinically silent & thus underdiagnosed; estimated at 1% prevalence, but may ↑ in US in next decade 2/2 progression of chronic HCV acquired during peak of1970/80s (*Gastroenterology* 2010;138:513)
- **Etiology:** EtOH (60%), HCV (10–20%), NAFLD (10–15%) (*Curr Opin Gastroenterol* 2011;27:204)
- **Natural history:** 58% of pts w/ compensated cirrhosis → decompensation over a 10 y period; clinical risk factors for decompensation: Obesity, EtOH use, smoking, new viral hepatitis infection, undertreatment of underlying cause; *biochemical:* MELD >10, albumin <4 g/dL, HVSG >10 mmHg (*Hepatology* 2011;54:555; 2012;56:1983; *Gastroenterology* 2007;133:481)
- Median survival w/ compensated cirrhosis ~9 y, median survival w/ decompensated cirrhosis 1.6 y (*Hepatology* 1987;7:122)

## Evaluation ( *JAMA* 2012;307:832)

- All pts w/ chronic liver disease should be evaluated for cirrhosis; this includes history, exam, & diagnostic testing; pts w/ known cirrhosis should be routinely assessed for e/o or risk factors for progression
- **History:** Assess for risk factors of liver injury: PMHx (HCV, HBV, obesity, HLD, DM); soc hx (EtOH use, lifetime hx of IVDU), Meds (APAP, NSAIDs; see *"Abnormal LFTs"* )
- **Physical exam:** Examine for e/o portal HTN & hepatic insufficiency *HEENT:* Scleral icterus; *Chest:* Gynecomastia; *GI:* Firm, nodular liver, hepatomegaly, splenomegaly, **ascites** (⊕ LR 7.2), caput medusa (⊕ LR 10, dilated veins flow *away* from umbilicus); *GU:* Testicular atrophy, *Derm:* Jaundice, ↓ body hair, **spider angiomata** (⊕ LR 4.3), palmar erythema; *Ext:* Clubbing, edema, **Terry nails** (⊕ LR 16), silver-white discoloration of proximal nail bed; *Neuro:*

**Asterixis** (⊕ LR 10)

- **Labs:** CBC: Neutropenia, anemia, ↓ **PLT** (⊕ LR 6.8 if PLT <160 K); ↓ Na, ↑ TB (conjugated hyperbilirubinemia; ⊕ LR 2.7 if TB >1.2), ↑ Aφ /GGT, AST/ALT (often ↑ but degree correlates poorly w/ disease severity), ↓ Alb (⊕ LR 3.5 in Alb <3.5 g/dL), ↑ INR (⊕ LR 5 if abnl)

| MELD Score | 3 Mos Mortality |
|---|---|
| >40 | >70% |
| 30–39 | 50% |
| 20–29 | 20% |
| 10–19 | 6% |
| <9 | 2% |

- **Diagnosis:** If cirrhosis suspected → liver bx (transjugular > percutaneous if ascites/coagulopathy) or biomarkers (FibroSURE, validated in HCC), **hepatology referral**
- **Prognosis:** MELD score:(Model for End-Stage Liver Disease), TBili, Cr, INR → predicts survival & stratifies transplant list (*Gastroenterology* 2003;124:91); www.mayoclinic.org/meld/mayomodel6.html

## Treatment (*Am J Gastroenterol* 2009;104:1802)

- **General approach:** Cirrhosis often co-managed by hepatologist & PCP, with routine visits to screen for decompensation & encourage appropriate tx of underlying cause; some cases of compensated cirrhosis may stabilize/reverse w/ appropriate tx
- **Treatment underlying/contributing cause:** HBV tx, HCV tx, EtOH cessation, wt loss
- **Immunizations:** HAV, HBV, influenza, pneumococcus
- **Counseling**
  - **Lifestyle:** EtOH abstinence, tobacco cessation; limited data suggests coffee linked to *improved* outcomes (i.e., okay to continue); obesity/DM assoc w/ worse outcomes but limited data re: wt loss, glycemic control
  - **Medications:** Limit APAP to <2 g/d, avoid NSAIDs, BZDs, & opioids; discuss herbal supplements w/ provider, avoid PPI in pts w/ ascites if possible (↑ risk SBP) (*Hepatology* 2013;57:1651)
  - **Diet:** 50–90% of cirrhotic pts are malnourished, which predicts morbidity/mortality; protein requirement ↑ c/w healthy adults (1–

1.5 g/kg/d vs. 0.8 g/kg/d); supplement Vits A, D, E, & K, selenium, zinc; no CHO restriction (*Clin Gastroenterol Hepatol* 2012:10:117)

- **Screening**

**Screening in Compensated Cirrhosis**

| Complication | Screening modality |
|---|---|
| HCC | RUQ U/S ± AFP q6–12mos → ↓ mortality (*Clin Gastroenterol Hepatol* 2007;5:508) |
| Varices | EGD at time of dx, then q3y if no varices or at decompensation |
| Decompensation | Hx/PE at routine visits, CBC, BMP, LFTs, INR q3–6mos |

- **Referral for Transplant:** After 1st episode of decompensation, HCC, MELD ≥14

## Decompensated Cirrhosis

- Acute complications typically managed as inpt or by hepatologists; given ↑ morbidity/mortality in this group; all decompensated pts should be evaluated for transplant; discussion of goals of care appropriate
- Any new decompensation → inpt eval, e.g., new ascites → ED for dx para, further w/u

**Decompensated Cirrhosis Management**

| Complication | Indications & Rx |
|---|---|
| **Variceal bleed** | *Ppx:* Nonselective βB (e.g., nadolol, goal HR 60)<br>*1° prevention:* Pts w/ varices<br>*2° prevention:* βB as above + endoscopic band ligation (↓ mortality > EBL alone) (*Hepatology* 2000;32:461)<br>*Refractory/recurrent:* Consider TIPS |
| **SBP** | *Concern for current SBP:* Refer to ED<br>*Ppx:* Norfloxacin 400 mg QD or TMP–SMX<br>*1° prevention:* Pts w/ ascitic TP <1.5 g/dL & (altered renal function **or** liver failure)<br>*2° prevention:* Pts w/ hx SBP |
| **Ascites** | *New/worsening ascites:* Refer to ED<br>*Stable:* Restrict Na <2 g/d; if Cr stable, spironolactone 50–100 mg QD (max 400 mg); add furosemide 20–40 mg (max 160 mg) if ↑ K or wt loss <2 lb/wk; monitor BUN/Cr, K, Na; reduce/hold diuretics if Cr ↑<br>*Refractory:* Serial LVP + albumin, TIPS |
| **Encephalopathy** | *New/worsening encephalopathy:* Refer to ED<br>*Stable:* Diet: 1–1.5 g/kg/d protein; lactulose 30 mL titrated to 2–3 BMs/d; consider adding rifaximin 400 mg TID or 550 mg BID, can ↓ hospitalizations (*NEJM* 2010;362:1071)<br>*Refractory:* Add rifaximin |
| **Hepatorenal syndrome** | Typically in pts w/ refractory ascites—HRS1 rapidly progressive ↑ Cr (median survival 2 wks), HRS2 gradual (med survival 6 mos)<br>**Hold diuretics** in any pt w/ ↑ Cr to >1.5 mg/dL or ↑ 1.5× baseline & discuss w/ hepatology (*Transp* 1995;59:361)<br>Acute ↑ Cr → ED for albumin & r/o other causes |
| **Transplant eval** | 1st episode of decompensation, HCC, or MELD ≥ 14 |

# CONSTIPATION

## Background (*NEJM* 2003;349:1360; *Gastroenterology* 2013;144:211)

- **Definition:** Constipation characterized by a history of straining, lumpy/hard stools, sense of incomplete evacuation, anorectal obstruction/blockade, <3 defecations/wk
- **Epidemiology:** Chronic constipation affects ~16% of adults; 33% of pts >60 y; risk ↑ in women, non-Caucasian ethnicity, lower SES, depression, ↓ physical activity
- **Etiology:** Majority of cases are functional (2/2 colonic and/or pelvic floor/anorectal dysfunction); however, can also be due to structural disease (stricture, CA, fissure, proctitis), systemic disease (hypothyroid, DM, ↑ Ca, neuro disease such as PD, spinal cord injury)

## Evaluation (*AFP* 2011;84:299)

- **General approach:** Consideration of dangerous or correctable causes w/ appropriate eval, & then emphasis on treating sx
- **History:** Ask about onset, diet, fiber intake, bowel habits, rectal bleeding, alternation w/ diarrhea, abd pain; ask about current & past tx or medications
  *PMHx:* Thyroid, depression DM, IBS, anorectal disease (fissures), neuro (Parkinson, MS, stroke, spinal cord injury), electrolyte abnormalities
  *Meds:* Antacids, iron, opioids, CCBs, TCAs, antihistamines, anticholinergics, anti-parkinsonian meds, Ca supplements, antipsychotics, NSAIDs all can → constipation
- **Exam:** General appearance, BMI; abdominal exam (masses, tenderness)
  **Perineal/rectal exam:** Often most revealing part of evaluation
  *Inspection:* Look for hemorrhoids, scars, fissures; nl perineum should descend 1–3.5 cm w/ pt bearing down (abnl descent may be reduced or excessive)
  *Digital Exam:* R/o impaction, anal stenosis, rectal Ca; tight sphincter suggests anismus, pain may indicate fissure; patulous anal sphincter may suggest trauma or neuro d/o
- **Diagnostics:** FOBT, CBC; consider glucose, Ca, TSH as guided by hx
- **Red flags:** Hematochezia, unintended wt loss, ⊕ FHx colon cancer, anemia, ⊕ FOBT, acute-onset constipation in older pt, or no prev colonoscopy in pt >50 y/o → colonoscopy (may consider flex sig, CT colonography, barium enema as alt depending on circumstances)
- **Assess mechanism of 1° constipation** (pts may have >1 process)

**Types of Primary Constipation** (*NEJM* 2003;349:14)

| Type | Presenting Features |
|---|---|
| Normal Transit Constipation (NTC) | Most common, nl BM freq but subjective sensation of constipation |
| Slow Transit Constipation (STC) | Often in young women, onset at puberty, infrequent urge to defecate, BMs 1×/wk or less |
| Defecatory disorder | Hx of need for manual disimpaction, abnl perineal descent or anismus (↑ anal resting pressure) on exam |

## Treatment (*NEJM* 2003;349:14; *Gastroenterology* 2013;144:218)

- Tx approach varies by subtype:

**Defecatory d/o:** Often requires biofeedback-aided pelvic floor retraining (efficacy well documented in RCTs as >60% respond w/ 5–6 sessions, 30–60 mins each) (*Gastroenterology* 2005;129:86)

**Slow or normal transit:** Managed as below; STC may be ↓ responsive to osmotics, ↑ responsive to stimulants

- **Initial treatment:** Should be initiated as maintenance tx

  **Lifestyle:** ↑ Physical activity may correlate w/ ↓ constipation; ↑ fluid intake does not improve chronic constipation unless concurrent dehydration; d/c offending meds as feasible

  **Fiber:** 1st-line tx, particularly for NTC**:** Data limited but safe, inexpensive, & may have other health benefits; ↑ stool bulk, ↓ colonic transit time → ↑ GI motility; often takes a few wks for desired effect

  *Mechanism:* ↑ Stool bulk, ↓ colonic transit time → ↑ GI motility

  *Administration:* 2 doses w/ fluids and/or meals; may ↑ dose after 1 wk period, up to 20 g/d

  *S/e:* Bloating, gas/flatulence, ↓ after a few d of tx; can be worse w/ natural fibers (psyllium, bran) which undergo bacterial digestion

- **Additional therapy:** If sx persistent, osmotic laxative next choice; well-tolerated, effective (NNT = 3), but may take a few d to take effect; stimulants typically used as "rescue" medication

**Selected Pharmacotherapy in Constipation**

| Class | Medication | Notes |
|---|---|---|
| **Osmotic** | **Polyethylene glycol 17 g QD–BID**<br>Mg hydroxide, Mg citrate<br>lactulose | PEG preferred due to ↑ efficacy & ↓ bloating vs. lactulose (*Cochrane Data Syst Rev* 2010;7:CD007570)<br>S/e: Gas, bloating; caution w/ Mg-containing compounds in CKD (can ↑ serum Mg) |
| **Stimulant** | **Senna** (8.6 mg tabs)<br>2 tabs QD–4 tabs BID PO<br>Bisacodyl 10 mg PR or 5–10 mg PO up to TIW | Preferred as PRN, effects of long-term use unknown<br>S/e: Malabsorption, abd cramps, senna can → reversible staining of colonic wall "melanosis coli" |
| **Secretory** | Lubiprostone<br>(typically Rx by GI) | Chloride channel activator<br>S/e: N/V, teratogen |
| | Linaclotide<br>(typically Rx by GI) | New, well tolerated; activates CFTR to stimulate intestinal chloride & fluid secretion (*NEJM* 2011;365:527) |
| **Other** | Enemas<br>(Tap water, mineral oil, soap suds) | May be stool softener (mineral oil), mechanical lavage (tap water, soap suds), avoid phosphate enema in CKD<br>S/e: Mechanical trauma |
| | Mineral oil (PO or enema) | Lubricant; s/e: Incontinence, can → malabsorption over time |
| | Stool softener (colace) | Well tolerated, limited data re: efficacy |

- **When to refer:** If severe/refractory disease, suspected neurologic or structural component → referral to GI for additional testing; may include anorectal manometry, defecography, & colonic transit testing (Sitz marker study); surgery may be considered for pts w/ STC or defecatory d/o only in severe disease refractory to medical management

# DIARRHEA

## Background (*NEJM* 2009;361:1560)

- **Definition:** Increase in stool frequency, volume (>200 g/d), urgency and decrease in stool consistency; *acute:* Occurring for <4 wks; *chronic:* Occurring for >4 wks
- **Pathophysiology:** Mechanisms of diarrhea include ↑ mucosal secretion, ↓ epithelial absorption, altered motility and/or ↑ in intraluminal osmolarity
- **Epidemiology:** 2.4–5.9% of adults experienced an episode of acute diarrhea in the past month (avg ~0.6 episodes/y); chronic diarrhea affects 3–5% of US adults (*Epidemiol Infect* 2007;135:293; *Gastroenterology* 1999;116:1464)
- Distinct evaluation, differential, & management for acute vs. chronic diarrhea

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## ACUTE DIARRHEA

## Evaluation (*Clin Infect Dis* 2001;32:331; *Am J Gastroenterol* 1997;92:1962)

- **General approach:** Assess for inflammatory features (below), hypovolemia, or historical features (immunosuppression, travel) which may alter Ddx & mgmt
- **History:** Onset, stool features (watery, presence of blood, pus, mucus), freq/volume of BMs, ability to maintain PO intake, sick contacts, daycare or SNF exposure
  *Assoc sx:* Inflammatory sx (fever, N/V, abd pain, tenesmus, blood, pus in stool) hypovolemia sx (thirst, ↓ UOP, orthostasis), myalgias
  *Exposures:* Recent hospitalization, travel (see *"Travel Medicine"*), camping, anal receptive intercourse, exposure to infants in daycare
  *PMHx:* Immunosuppression, meds, recent abx (antibiotic-assoc diarrhea, *C. diff*)
- **Physical exam:** *VS:* fever, HoTN, tachycardia, general appearance, *HEENT:* Mucous membranes, JVP; *GI:* Severe pain (mesenteric ischemia), distention; *Derm:* Jaundice, rash, skin turgor
- **Labs:** Dictated by hx/PE; noninflammatory generally self-limited &

does not indicate additional testing unless persistent (>10–14 d)

### Laboratory Testing

| Test | Indications |
|---|---|
| *C. diff* | Recent abx, hospitalization, or chemotherapy |
| Fecal WBC | Mod-severe diarrhea, inflammatory sx |
| FOBT | Mod-severe diarrhea, inflammatory sx |
| Stool culture | Should not be ordered routinely (<2% of tests yield ⊕ result); definite fever, fecal WBC/FOBT ⊕, persistent diarrhea not already tx w/ abx |
| Stool ova + parasites | Should not be ordered routinely; MSM, HIV⊕, sx for >14 d, bloody diarrhea but fecal WBC ⊖, travel (Russia, Nepal, mountainous regions), infant daycare exposure |
| Specific organisms | Enterohemorrhagic *E. coli* (EHEC, O157:H7): Foodborne dysentery<br>Vibrio if assoc w/ raw or undercooked seafood<br>Consider microsporidia, MAC if >7 d & HIV ⊕ |
| Other | CBC, BMP, U/A, blood Cx: May be indicated by hx/PE or ↑ severity |

- **Imaging:** Generally not indicated; consider CT/KUB if concern for toxic megacolon or severe abdominal pain (see *"Abdominal Pain"* )

## Treatment (*Clin Infect Dis* 2001;32:331; *Am J Gastroenterol* 1997;92:1962)

- **Differential diagnosis:** Infectious (viral, bacterial, parasitic), medications, IBD, ischemia
- **Noninflammatory:** Often self-limited; supportive tx (oral rehydration, loperamide, bismuth subsalicylate; probiotics can ↓ stool freq & duration of sx × 24 h (*Cochrane Database* 2010;11:CD003048)
- **Traveler's diarrhea** (see *"Travel medicine"* )
- **Inflammatory:** Supportive Rx as above
  *Empiric abx:* (E.g., ciprofloxacin 500 mg BID × 3–5 d) if: >50 y or immunocompromised, fever >102°F, severe dysentery, sx >1 wk, severe dehydration
  *Selective abx:* Shigella (TMP–SMX), Campylobacter (erythromycin), Giardia (MNZ); Salmonella (TMP-SMX, tx if disease severe, pt >50 y or CAD (aortitis risk)
  *C. diff:* D/c other abx if possible, MNZ for 10–14 d (or through 14 d past last dose of other abx); **if appears ill** (↑ WBC, abnl VS, sig abd pain) → **ED**
  *EHEC:* Suspect if bloody diarrhea, no fever, WBC >10 K, abd tenderness; avoid abx due to ↑ risk HUS & unclear benefit (*Ann Int*

*Med* 1997;126:505)

- **Emergency department referral/admission:** If concerned for mod–severe *C. diff*, elderly, immunocompromised, chronically ill & severe dehydration or unable to maintain PO intake

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## CHRONIC DIARRHEA

### Evaluation (*Gastroenterology* 1999;116:731; 2004;127:287; *NEJM* 1995;332:725)

- **General approach:** May be due to variety of causes, attempt to narrow Ddx by determining if sx are predominantly "*watery*" (secretory, motility, or osmotic), "*fatty*" (malabsorptive), or *inflammatory*
- **History:** Onset (postinfectious), stool characteristics, frequency, exacerbating factors (e.g., fatty meals), intermittent constipation ("pseudodiarrhea" 2/2 fecal impaction, IBS)
  *Effect of fasting:* Osmotic, malabsorptive sx improve, but inflammatory, secretory do not
  *PMHx:* Prior XRT, surgery (CCY, bowel resection), pancreatitis, thyroid disease
  *Meds/Toxins:* Metformin, colchicine, motility agents/laxatives, digoxin, PPI, Mg-containing antacids, abx, acarbose, orlistat
  *Assoc Sx:* Abd pain, wt loss, incontinence (sometimes reported as "diarrhea"), hyperthyroid sx (see *"Thyroid disease"*)
  *Exposures:* Travel, hospitalization, abx use
- **Physical exam:** BMI, volume status, lymph nodes, abd exam (distention, hyperactive bowel sounds, masses) rectal exam (anal fistula, ↓ sphincter tone, impacted stool)
- **Initial diagnostics:** Baseline testing
  **Labs:** CBC, BMP, albumin, anti-tTG (see *"Celiac Disease"*) ESR, LFTs, TSH
  **Stool studies:** FOBT, fecal leukocyte testing (⊕ suggests infectious/inflammatory), fecal pH (<5.3 suggests CHO malabsorption such as lactose intolerance)
- **Red flags:** Sx <3 mos duration, >5 kg wt loss, nocturnal predominance, continual (rather than intermittent) sx, ↑ ESR, anemia, ↓ albumin all suggest organic, not functional etiology

- If above tests all nl & no red flags, consider IBS (see *"IBS"*) or functional diarrhea
- **Further diagnostics:** As dictated by phenotype

### Additional Diagnostics in Chronic Diarrhea

| Phenotype | Further Testing |
|---|---|
| **Watery** | **Stool osmolar gap:** Osmolar gap = 290 – 2($Na_{stool}$ + $K_{stool}$)<br>Best to calculate rather than measure directly as measured may be artificially ↑ w/ delayed sample processing<br>**Gap >125 (osmotic):** Osmotically active substance "drawing" water into intestinal lumen → consider lactose intolerance, ↑ sorbitol ingestion (in "sugar-free" items), laxative testing<br>**Gap 50–125 (nl/mixed):** Consider IBS, celiac<br>**Gap <50 (secretory):** Infection (Aeromonas, Giardia), anatomic abnl, endocrinopathy (hyperthyroid, Cushing), malignancy (pheo, VIPoma, carcinoid); bile acid malabsorption |
| **Inflammatory** | Fecal calprotectin, **colonoscopy,** stool culture, Giardia Ag testing |
| **Malabsorptive** | **Fecal fat,** stool O+P, consider stool chymotrypsin testing for pancreatic insufficiency |

- **Imaging:** May be indicated in secretory or inflammatory d/o as guided by hx
- **Colonoscopy:** Frequently indicated in setting of abnl studies or clinical features & ongoing diarrhea of unclear etiology

## Management (*AFP* 2011;84:1119)

### Selected Causes of Chronic Diarrhea

| Phenotype | Differential Diagnosis |
|---|---|
| **Watery** | *IBS:* Alt. constipation & diarrhea, ♀ > ♂; see *"IBS"*<br>*Lactose intolerance:* Can be postinfectious, improves w/ lactose-free diet<br>*Other:* Medication or diet-induced: Mg ingestion, endocrinopathy, CA, bile acid malabsorption (may trial empiric cholestyramine) |
| **Inflammatory** | *CD:* Recurrent abd pain, fever, ± perianal fistulae, ⊕ FOBT<br>*UC:* Recurrent abd pain, fever, ± perianal fistulae, ⊕ FOBT; see *"IBD"*<br>*Microscopic colitis:* Elderly, nocturnal diarrhea, ?NSAID assoc<br>*C. diff:* Subacute, recent abx use or hospitalization, fever<br>*Other Infections:* Aeromonas, cryptosporidium, cyclospora, entamoeba, Giardia, microsporida, strongyloides |
| **Malabsorptive** | *Celiac disease:* Fatigue, bloating, anemia; see *"Celiac"*<br>*Giardia:* Gas, "frothy" stool, foul odor, camping/daycare/travel hx<br>*Pancreatic insufficiency:* hx pancreatitis, CF, steatorrhea, wt loss |

(*Gastroenterology* 1999;116:731; *AFP* 2011;84:1119)

- Tx of underlying cause as appropriate/feasible; **indications for empiric tx:** (1) Sx mgmt during eval, (2) idiopathic diarrhea, or (3) tx of underlying cause not feasible or can be used as temporizing measure; consider trial of abx for infectious causes; tx as per "Acute Diarrhea," above
- **When to refer:** Suspected inflammatory disease, dx unclear despite lab abnorm, endoscopy indicated, or persistent/severe sx → **gastroenterology**
- **Patient information:** http://patients.gi.org/topics/diarrhea-acute-&-chronic/

# DIVERTICULAR DISEASE

## Background (*NEJM* 2007;357:2057; *J Clin Gastroenterol* 1999;94:3110)

- **Definitions: Diverticula:** Fingerlike external protrusions of the colonic wall, predominantly found in the sigmoid & descending colon; **diverticulosis:** Phenomenon of having diverticula; **diverticulitis:** Clinical syndrome resulting from inflammation of diverticula
- **Pathophysiology:** *Diverticulosis* thought to arise 2/2 ↑ intraluminal pressure & herniation of the colonic mucosa through weakened areas of the bowel wall (adjacent to vasa recta); *diverticulitis* thought to be 2/2 stasis/obstruction at neck of diverticulum → local infection/ischemia
- **Natural history:** Most pts w/ diverticulosis are asx, but some develop diverticular disease: (~3–5% develop hemorrhage, ~10–25% develop diverticulitis (& 10–33% of them will have recurrent episode)
- **Epidemiology:** Prevalence ↑ w/ age; found in <10% of pts <40 y, ~70% of pts >80 y (*Gastroenterology* 2009;136:1134); initial presentation of diverticular disease is typically after age 50
- **Risk factors: For diverticular disease:** Low-fiber diet (thought that this → ↑ colonic transit time & ↑ colonic pressure), ⊕ FHx (2.9× ↑ risk), obesity (~1.5× ↑ risk), smoking, NSAIDs, constipation; **for diverticular bleeding:** ASA/NSAID use (*Gastroenterology* 2013;144:736; 2011;140:1427; 2009;136:115)
- **Bleeding:** Diverticular disease responsible for ~23% of LGIB cases (see

*"GI Bleeding"*)

### Treatment (*Dig Dis* 2012;30:35)

- **Diet:** Fiber data somewhat conflicting, but fiber intake may improve sx & ↓ diverticulitis risk; red meat intake may ↑ diverticulitis sx/complications; not assoc w/ nuts & corn intake
- **Lifestyle:** ↑ Physical activity can ↓ risk of diverticular bleeding & diverticulitis; wt loss & smoking cessation interventions not studied but given ↑ risks assoc w/ obesity & smoking & other health benefits, reasonable to recommend; mod EtOH intake

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## DIVERTICULITIS

## Evaluation

- **General approach:** Diverticulitis primarily a clinical dx; obtain complete hx & perform thorough exam on all pts (see *"Abdominal Pain"* ); those w/ severe sx or atypical features require further testing
- **Classic presentation:** *Hx*: Low-grade fever, obstipation, LLQ abd pain, no vomiting; *PE:* May have abd or perirectal "fullness" on exam, trace ⊕ FOBT; **LLQ localized tenderness** has ⊕ LR of 10 for diverticulitis (*Dis Colon Rectum* 2010;53:896)
- **Differential diagnosis:** IBD, PID, ectopic pregnancy, cystitis, infectious colitis, colon CA
- **Labs:** CBC, BMP; consider U/A, **b**-hCG
- **Imaging:** Indicated if dx uncertain, presentation severe, or refractory; CT preferred
- **Endoscopy:** Not performed in acute setting 2/2 ↑ risk perforation, often performed afterward to r/o malignancy or IBD
- **Red flags:** Severe pain, peritonitis on exam, unable to tolerate POs, hx complicated diverticular disease in the past → ED

### Treatment (*AFP* 2013;87:612; *NEJM* 2007;357:2057)

- **Mild disease:** 7–10 d course of PO abx (1 RCT suggests may not have benefit in uncomplicated disease (*Br J Surg* 2012;99:532), but not confirmed w/ other studies)

Clear liquid diet, pain mgmt; arrange f/u (phone/in-person) at 72 h & if not improving → imaging (or re-imaging) & consider inpt mgmt

**PO Antibiotic Regimens** (*NEJM* 2007;357:2057)

| |
|---|
| Ciprofloxacin 750 mg BID (levo or moxi also okay) **and** metronidazole 500 mg TID–QID<br>TMP–SMX DS BID **and** metronidazole 500 mg TID–QID<br>*Alt:* Amox/clav 875/125 or 1000/62.5 BID |

- **All patients:** Colonoscopy at 6–8 wks if complicated episode or age-appropriate cancer screen; begin high-fiber diet 6–8 wks after resolution of acute sx
- **When to refer: If red flags** (above), e/o complications on imaging, advanced age or multiple comorbidities → ED/hospital admission; pts w/ recurrent disease (>2 episodes), complications, or younger age should have surgical eval

# DYSPHAGIA

## Background (*AFP* 2000;61:3639; *BMJ* 2003;326:433)

- **Definition:** Difficulty passing solids, liquids, or both from pharynx to stomach
- **Classification:** *Oropharyngeal*: Difficulty transferring food from OP to esophagus
  *Esophageal*: Difficulty passing food from esophagus to stomach
- **Epidemiology:** Prevalence ↑ w/ age; affects 7–10% of pts >50 y; cancer more likely when pts ♂, >40, & present w/ wt loss (*Gastrointest Endosc* 2005;61:80)
- Dysphagia can be due to wide variety of disorders, some of can → significant morbidity or mortality; it is considered an alarm system & always merits investigation of etiology

## Evaluation (*Gastroenterology* 1999;116:455; 1999;117:233)

- **General approach:** First, determine type of dysphagia, then narrow Ddx based on hx

## Presentation of Dysphagia Disorders

| | |
|---|---|
| **Oropharyngeal** | Difficulty initiating swallowing; coughing, choking/aspiration; can be<br>*Structural* (abscess, Zenker diverticulum, tumor, post-XRT)<br>*Neuromuscular* (dementia, MG, Parkinson, stroke) |
| **Esophageal** | Sensation of food ± liquids being "stuck"; can be<br>*Mechanical:* Solid > liquid dysphagia; external or intrinsic compression (stricture, tumor, web, Schatzki ring, web, mediastinal mass)<br>*Motility:* Solid & liquids affected equally (achalasia, scleroderma)<br>Solid = liquid dysphagia suggests motility d/o (achalasia, scleroderma) |

- **History:** Gradual or sudden onset, intermittent (Schatzki ring) vs. progressive (stricture, neoplasm); if sensation of food becoming "stuck," where? (lesion typically at or superior to site of sensation)
  *Assoc sx:* Heartburn, pulm infections, fever, odynophagia (esophagitis), **weight loss,** CP, xerostomia, dysgeusia (candidal infection), drooling, dysarthria, "nasal" change in speech caliber; hoarseness, tremor, ataxia, diplopia
  *PMHx:* GERD, COPD, head/neck malignancy, surgery, or XRT; stroke, autoimmune disease, celiac disease, allergy (eosinophilic esophagitis), Raynaud,
  *Meds/toxins:* Smoking, EtOH (esophageal CA) NSAIDs, alendronate, doxycycline, potassium (pill esophagitis)
- **Exam:** Neuro exam w/ careful CN eval, oral cavity: Xerostomia, posterior erythema (GERD, esophagitis), thrush; neck exam (thyromegaly, LAD), abd exam
- **Diagnostics:**

## Dysphagia Testing

| | |
|---|---|
| **Oropharyngeal** | **Modified Barium Swallow (MBS):** Pt consumes foods of varying volume/consistency coated w/ barium under fluoroscopy; images then analyzed for presence/mechanism of swallowing dysfunction<br>If nl or ?of structural cause, consider ENT eval, consider EGD |
| **Esophageal** | **EGD:** Most common findings stricture > nl ≥ esophagitis/ulcer > tumor (*Dysphagia* 2012;27:101)<br>If nl, consider MBS → if nl or ? motility d/o, consider manometry |

- **Referral:** Indicated based on hx & eval, above; *Oropharyngeal* → SLP eval & tx, ± neurology (e.g., suspected ALS, MG) or ENT (suspect

structural); *Esophageal* → GI

# GALLSTONES

## Background (*NEJM* 2008;358:2804; http://digestive.niddk.nih.gov/; *BMJ* 2007;335:295)

- **Definitions: Gallstones:** Small, crystallized concretions of bile which develop in the gallbladder; **Cholelithiasis (biliary colic):** Development of symptomatic disease due to temporary blockage in biliary tree; **Cholecystitis:** Infection or ischemia of GB, 90% of cases due to obstructing gallstone = surgical emergency; other complications include choledocholithiasis & gallstone pancreatitis
- **Pathophysiology:** Thought that bile salts precipitate into gallstones when bile has ↑ cholesterol, ↑ bili, ↓ bile salts, or incomplete/infrequent GB emptying
- **Epidemiology:** Majority of US adults have gallstones, 10–15% have sx disease
- **Natural history:** *Asx gallstones*: 10% develop sx w/in 5 y; 25% develop sx w/in 10 y (1–4% annual risk); *Biliary colic*: 20% of pts w/ biliary colic develop acute cholecystitis if left untreated
- **Risk factors:** Women (esp if pregnant, using HRT or OCPs; estrogen may ↑ cholesterol excretion & ↓ GB emptying; however, men w/ gallstones at relatively ↑ risk of cholecystitis); obesity, rapid wt loss, Native American or Hispanic ethnicity, ⊕ FHx, DM (↑ risk gallstones & ↑ risk of sx disease/complications), age >60, also TPN, sickle cell, cirrhosis, Crohn's disease
- **Increased risk of complications from gallstones:** DM, sickle cell, hereditary spherocytosis, s/p gastric bypass

## Evaluation

- **General approach:** Dependent on clinical scenario (below)

**Evaluation and Management of Gallstone Disease**

| Scenario | Evaluation |
|---|---|
| **Acute episode** | Eval for acute cholecystitis; if suspected → ED |
| **Currently asx but c/o episodes of abd pain** | Determine likelihood of cholelithiasis; if sx compatible w/ biliary colic → RUQ U/S & surgical referral |
| **Incidentally discovered gallstones on imaging** | Assess for sx or presence of complication risk factors; if present → discussion w/ pt ± surgical referral |
| **Classic Presentation of Gallstone Disease** | |
| **Cholelithiasis** | Episodic RUQ or epigastric pain, often poorly localized, w/ abrupt onset that typically resolves within several h, often after meals or in the evening; may have radiation to scapula, R shoulder or back, ±N/V, often after meals or in the evening ± RUQ/epigastric pain; may be hard to localize (nonvisceral) |
| **Acute Cholecystitis** | Often w/ hx of episodes as above; similar sx but persistent, localizes to RUQ, accompanied by fever/systemic sx |

- **Right upper quadrant ultrasound:** Se/Sp >95% for detecting stones >5 mm (Se highest when pt has been fasting, as GB then distended w/ bile); sonographic Murphy sign (pain when probe pressed against GB) + stones has high PPV of acute cholecystitis
- **Differential diagnosis:** Dyspepsia, hepatic abscess, duodenal ulcer, angina, sphincter or Oddi dysfunction, biliary dyskinesia

## Management

- **Suspected acute cholecystitis → ED**
- **History consistent with biliary colic + stones on ultrasound → surgical referral;** select pts (stone <1 cm, mild sxs, minimal calcification) who are unable to tolerate surgery may benefit from ursodiol (*Gastroenterol Clin North Am* 2010;39:245)
- **History consistent with biliary colic but no stones on ultrasound** → consider other etiologies (see Ddx, *"Abdominal Pain"*), consider GI referral
- **Asymptomatic with incidentally discovered stones** → expectant mgmt; discuss natural hx & nature of sx w/ pts; no randomized trials of elective CCY in this group, but may be considered in pts w/ features which ↑ risk of cholangioCA (GB polyps, porcelain GB) & pts may benefit from discussion w/ surgeon re: risks/benefits (*Cochrane Database Syst Rev* 2007;1:CD006230)

# GASTROINTESTINAL BLEEDING

## Background (*Essentials of Gastroenterology* 2012:317)

- The gastrointestinal tract is a frequent source of blood loss; hemodynamically significant or acute bleeding episodes warrant ED visit & likely admission; however, mild or chronic GIB may sometimes be managed on an outpatient basis
- **Definition:** *GI bleeding (GIB):* May occur anywhere in the alimentary tract; hx & risk factors guide localization for purposes of evaluation; ligament of Treitz separates upper GIB (proximal) from lower GIB (distal); *occult bleeding:* Not evident to pt but ⊕ FOBT, Fe-deficiency anemia
- Risk factors: ↑ Age, liver disease, prior hx, NSAID, or anticoagulant use
- In general, acuity of blood loss determines severity of sx

## Evaluation (*AFP* 2013;87:430; *Gastroenterology* 2007;133:1697)

- **General approach:** In pts w/ suspected bleed, first determine if inpt admission warranted; if yes → ED/admission; if not → further investigate localization
- **Bleeding symptoms:** Hematemesis, "coffee-ground emesis"—dark 2/2 prolonged exposure to gastric contents; *melena* (black, tarry, malodorous stool from digested blood), *hematochezia* (maroon-colored stool assoc w/ brisk UGIB), BRBPR
- **History: Onset, duration (acute or chronic/intermittent)**
  *Assoc sx*: Abd pain, wt loss, change in bowel habits, fever, sx of volume depletion (orthostasis, syncope) or of sx anemia (DOE/SOB, fatigue)
  *Alt source of blood:* Nosebleed, hemoptysis, menses, hematuria
  *PMHx:* Liver disease, malignancy, coagulopathy, GI or aortic surgery, IBD, prior GIB, PUD, diverticulosis, hemorrhoids, celiac disease
  *Meds/Toxins:* EtOH, ASA, NSAID, anti-PLT, anticoagulant, herbal supplements
- **Exam:** VS, general appearance; e/o volume depletion, anemia, liver disease; abd exam; *Rectal exam:* Masses, hemorrhoids, fissures, stool appearance, color (melena, bright red blood, brown stool); guaiac if no overt bleeding

**Selected Causes of Mild or Occult GI Bleeding**

| Lower GI Sources | |
|---|---|
| **Colon Cancer** | Wt loss, elderly, w/o recent colonoscopy, anemia, change in bowel habits (*Br J Cancer* 2010;102:48) |
| **Colonic Polyps** | Hx polyps, no recent colonoscopy, ↑ age |
| **Diverticular Bleeding** | Painless BRBPR or hematochezia, typically >50 y, chronic constipation (see *"Diverticular disease"*) |
| **IBD** | Episodes of tenesmus, urgency, fatigue, fevers, diarrhea w/ blood or hematochezia (see *"IBD"*) |
| **Hemorrhoids** | Pruritus, constipation hx, blood on toilet paper, not in stool; hemorrhoids on PE (see *"Hemorrhoids & Anal Fissures"*) |
| **Anal Fissure** | Visible on PE, hx constipation/straining, pain w/ defecation (see *"Hemorrhoids & Anal Fissures"*) |
| **Mesenteric ischemia** | Postprandial pain, vasculopathy (see *"Diarrhea"*) |
| **Upper GI Sources** | |
| **Esophagitis/Ulcer** | Dysphagia, odynophagia; infection, pill-induced, GERD |
| **Gastritis/GU Duodenitis/DU** | Epigastric pain, NSAID use, ASA, EtOH (see *"PUD"*) |
| **Gastric Cancer** | Early satiety, abd pain, dyspepsia (*Gut* 1997;41:142) |
| **Angiodysplasia** | CKD/ESRD; HHT, GAVE, assoc w/ ASA/NSAID use |
| **Esophageal CA** | Wt loss, older ♂, dysphagia |
| **Celiac** | Inflammatory diarrhea sx (see *"IBD"*)<br>⊕ FHx, steatorrhea, bloating (see *"Celiac"*) |

- **Lab studies:** Hb/Hct (↓ often "delayed" during acute bleed due to hemoconcentration), MCV, Fe studies; consider BMP, coags, LFTs; further labs as directed by hx/PE
- **Indications for urgent evaluation:** Concern for hemodynamically significant bleed (HoTN, tachycardia, orthostasis), comorbidities (ESLD, CHF, CAD), sx anemia → ED

## Management

- **Occult bleeding:** Referral for colonoscopy **and/or** EGD (dependent on presentation; UGI source more frequent if *no* Fe-deficiency anemia) (*NEJM* 1998;339:153); these 2 studies will determine bleeding source in 48–71% of pts (*AFP* 2013;87:430); further studies (capsule study, push enteroscopy) as determined by gastroenterology
- **If upper gastrointestinal or alarm symptoms** (e.g., abd pain, dysphagia, wt loss): Referral for EGD
- If hx/PE consistent w/ LGIB of known cause (infectious colitis, hemorrhoids), no e/o iron-deficiency anemia, & recent colonoscopy, reasonable to treat underlying cause; GI referral if bleeding persists/recurs

# GASTROESOPHAGEAL REFLUX DISEASE

## Background (*NEJM* 2008;359:16)

- **Definition:** Some degree of reflux is physiologic; GERD is when reflux of stomach contents results in troublesome sx or complications (*Am J Gastroenterol* 2006;101:1900); disease can be *esophageal:* Reflux sx ("heartburn"), esophagitis, stricture, adenoCA; or *extra-esophageal:* Laryngitis, cough, or asthma attributed to reflux
- **Complications:** ♂ > ♀; *esophageal*: Esophagitis, stricture, Barrett's, adenoCA
  *Extra-esophageal:* laryngitis, cough, asthma, (& possibly sinusitis, pulm fibrosis, pharyngitis, recurrent otitis media)
- **Epidemiology:** Symptomatic heartburn affects 14–20% of US adults; it is the most common GI-related complaint in ambulatory care
- **Risk factors:** *Clinical:* Abd obesity, smoking, EtOH use, overeating; *physiologic:* Hiatal hernia, ↓ LES pressure, delayed gastric emptying, loss of esophageal peristaltic function, gastric hypersecretion

## Evaluation (*Am J Gastroenterol* 2013;108:308; *Ann Intern Med* 2008;149:ITC2-1)

- **General approach:** GERD can be a clinical dx; in pts who p/w chest pain, cardiac causes should also be considered (see *"Chest Pain"* )

**Presentations of GERD**

| | |
|---|---|
| **Typical** | *Heartburn:* Retrosternal burning sensation, often postprandial or at evening, worse w/ fatty meals, lying down, or *after* exertion (89% Sp)<br>*Regurgitation:* Sensation of refluxed gastric contents → hypopharynx or pharynx, often assoc w/ sour taste (95% Sp)<br>Regurgitation + heartburn → 90% accurate for dx of GERD<br>Assoc sx: Sleep disturbances, dyspepsia |
| **Atypical** | Exercise-induced heartburn (must be distinguished from angina), CP (GERD >> esophageal spasm)<br>Persistent cough, wheezing/SOB, sore throat, hoarseness, CP |

- **History:** Ask about risk factors & historical features as above; also PMHx, medications which can → esophagitis (NSAIDs, alendronate → esophagitis; see *"Dysphagia"* ); meds which can ↑ GERD sx (theophylline, anticholinergics, CCBs, α-antagonists, prostaglandins,

nitrates, sedatives)

- **Features suggestive of alternative diagnosis/complications:** Weight loss, dysphagia, early satiety (gastric or esophageal CA), fevers (infectious esophagitis), odynophagia, persistent vomiting
- **Exam:** General appearance, HEENT exam (dentition, pharyngitis, LAD), cardiac, pulm, & abd exam
- **Differential diagnosis:** CAD, PUD, esophageal dysmotility, biliary colic, esophagitis 2/2 other cause
- **Diagnostics: Not required for dx of uncomplicated GERD**
  **Empiric tx:** 2 wk trial of omeprazole 20–40 mg QD as sensitive as 24 h pH monitoring in pts w/ erosive esophagitis (see *"Treatment"* below)
  **Endoscopy:** Up to 50% of pts w/ GERD have nl EGD; indicated if hx/PE suggests complications or alternative dx, sx not responsive to empiric tx, vomiting, concern for extra-esophageal sx
  **Other diagnostic techniques** (pH monitoring, Barium swallow, manometry) may be used by subspecialists if EGD unrevealing/sx refractory, but usually not useful for GERD dx
  ***H. pylori* testing:** *Not* routinely recommended for GERD sx (*Am J Gastroenterol* 2013;108:308)

## Treatment (*Gastroenterology* 2008;135:1392; *Am J Gastroenterol* 2013;108:308)

- **General approach:** Typical GERD may be treated empirically (below); those w/ suggestion of complications → EGD referral; those w/ extra-esophageal sx may benefit from GERD tx as part of full eval for those sx (e.g., cough); PPI nonresponders should be referred for further eval
- **Nonpharmacologictreatment**
  *Dietary:* Avoiding foods that ↓ LES pressure or delay gastric emptying *may* reduce sx but not a routinely recommended; e.g.: Chocolate, peppermint, onions, garlic, carbonated drinks, citrus drinks, tomato products, fatty foods, large meals
  *Behavioral:* **Weight loss**, head of bed elevation, avoid supine position 3 h after meals (e.g., eating before dinner), sleep in left lateral position, avoid EtOH & tobacco
- **Pharmacotherapy**
  **Proton Pump Inhibitors (PPI):** first-line for pts w/ mod–severe

disease; most effective tx (NNT 3–4), 80–100% efficacy; no evidence for in-class differences in efficacy

*Administration:* Take 30 mins prior to 1st meal of d

*Dosing:* No evidence for ↑ efficacy w/ ↑ dose; in pts w/o response, consider BID dosing; titrate to lowest dose which provides sx relief

*Drug interactions:* Concern for ↓ clopidogrel efficacy in observational studies, but large RCT showed *no* ↑ risk of CV event (*NEJM* 2010;363:1909); however, FDA warning remains

*Counseling:* Works as prophylactic; can take up to 4 d to take effect; *not* useful as tx in acute episode; *not* helpful if taken as intermittent "PRN"

*Side Effects:* Long-term use assoc w/ ↑ serum gastrin, atrophic gastritis, malabsorption (↓ Mg, ↓ Ca); may ↑ risk of *C. diff* infection, osteoporosis

**Antacids:** E.g., Ca carbonate (Tums); used as PRN for breakthrough sx; fastest-acting; can affect absorption of other Rx; s/e: Diarrhea or constipation (depending on compound)

**H2 receptor antagonists (H2RA):** (E.g., Ranitidine 150 mg PO BID); onset in 1 h, lasts ~9 h; 50–60% efficacy; **1st line for mild or intermittent sx;** interacts w/ phenytoin, warfarin; can → tolerance

- **Surgical therapy:** Nissen fundoplication, endoscopic suturing, or LES RFA; may be considered in pts who *have* responded to medical tx but are concerned about consequences of long-term Rx; efficacious & may ↑ QoL but medical tx likely safer/more cost-effective (*BMJ* 2013;346:f1908)
- **Barrett's esophagus:** Distal esophageal metaplasia (squamous → columnar epithelium); premalignant lesion found in 10–15% of pts undergoing endoscopy; can occur in absence of sx of chronic reflux (*Am J of Gastroenterol* 2008;103:788; *NEJM* 2009;361:2548)

  *Screening:* Via EGD; no clear consensus on whom to screen, but incidence ↑ in obese, Caucasian, men, age >50 y, ⊕ reflux sx; decision to screen may be individualized

  *Surveillance:* If diagnosed, pts generally undergo routine surveillance via EGD; no dysplasia → EGD q3–5y; low-grade dysplasia → q6–12mos; high-grade dysplasia → endoscopic mucosal resection > surveillance EGD (*Gastroenterology* 2011;140:1084; 2012;143:336)

## When to Refer

- **Gastroenterology:** If failure to respond to PPI, suspect esophageal complications, or red flags (wt loss, dysphagia), for Barrett's screening in ↑ risk pts on case-by-case basis
- **ENT, allergy, pulmonary:** For refractory extra-esophageal sx attributed to GERD which do not respond to PPI

# H. PYLORI DISEASE

## Background (*Lancet* 2009;374:1449; *AFP* 2007;75:351)

- *Helicobacter pylori* is a gram ⊖ microaerophilic bacterium found in the stomach & proximal duodenum; thought to be oral–oral, fecal–oral, & contaminated water transmission (*Epidemiol Rev* 2000;22:283)
- **Epidemiology:** Infection affects ~20% of US adults, ↑ in elderly, African-American, & Hispanic populations
- *H. pylori* infection is asx in majority of those infected & reflects colonization, *but* accounts for majority of PUD & also implicated in dyspepsia; infection also assoc w/ ↑ risk gastric Ca (but eradication *not* assoc w/ ↓ risk, so tx not indicated for that purpose)

## Evaluation & Treatment (*World J Gastro* 2011;17:3971; *Am J Gastroenterol* 2007;102:1808)

- **Indications for *H. pylori* testing:** PUD (current or prior hx), gastric MALT lymphoma, or functional dyspepsia (*not* a substitute for further eval in pts w/ alarm features; see *"Dyspepsia"*); may consider if long-term NSAID use or other ↑↑ risk of developing ulcer
- Testing should only occur if planned tx of ⊕ result

### *H. pylori* Testing Options

| | |
|---|---|
| **Serology** | Indicates current or past infection; not appropriate for pts previously treated as remains ⊕ for y; Se/Sp 85/79% (*Am J Gastroenterol* 1996;91:1138); best if ↑ pretest probability |
| **Stool Antigen** | RNA testing: ⊕ only in current infection; Se/Sp >90/90%; ↓ Se w/ PPI, ↓ Sp w/ GIB; can be used to confirm eradication; better than serology if ↓ pretest probability |
| **Urea breath test** | Radiolabeled urea ingested by pts & isotope labeled $CO_2$ generated by bacterial urease is measured in exhaled breath; can be used for initial dx or confirm eradication; expensive w/ variable reimbursement; Se/Sp 95/95% (*Gastroenterol Clin N Am* 2000;29:895) |
| **Endoscopic tests** | Rapid Urease Test, aka CLO test: Performed on tissue bx to detect for urease-splitting organism; culture, histology also used |
| ***H. pylori* Treatment Regimens** | |
| **Regimen** | **Notes** |
| **Triple Rx: PPI** (standard dose BID) + **clarithromycin** (500 mg BID) + **amoxicillin** (1 g BID) × 7–14 d | Beware ↑ clarithromycin resistance; ~70–85% eradication; consider alt. regimens |
| **Quadruple Tx: PPI** (BID) + **bismuth** (2 tab QID) + **MNZ** (500 mg TID), + **tetracycline** (500 mg QID) × 14 d | ~89% eradication |
| **Sequential Rx:** 10 d regimen. **PPI** (BID × 10 d) + **amox** (1 g BID d 1–5) + **clarith** (500 BID d 5–10), **MNZ** (500 mg TID d 5–10) | 10 d regimen >90% eradication |
| **Concomitant Rx: PPI** (BID) + **amox** (1 g BID) + **clarith** (500 BID) + **MNZ** (500 mg BID) | Superior to standard triple tx, noninferior to sequential rx |

- **Confirm eradication** by repeating stool Ag test (preferably off PPI) after 6–8 wks if tx of PUD, dyspepsia sx persist, gastric MALT lymphoma, or early gastric CA

# HEMORRHOIDS

## Background (*Dis Colon Rectum* 2011;54:1059; *JSTCR* 2011;3:68; *AFP* 2011;84:204)

- **Definition:** Swollen and/or inflamed veins of the anus & lower rectum
- **Classification:** *Internal hemorrhoids:* Viscerally innervated → painless; above dentate line; *external hemorrhoids:* Somatic innervations →

pain; below dentate line

- **Pathophysiology:** ↑ Intra-abd pressure (straining, constipation, pregnancy, ascites) → dilation of submucosal vascular tissue + weakening of supporting connective tissue → descent/prolapse of hemorrhoid
- **Epidemiology:** Est range from 4–30%; likely due to wide range in severity & whether or not mild and/or unreported disease included; peak prevalence ~45–65 y

## Evaluation

**Classical Presentation of Hemorrhoids**

| | |
|---|---|
| **History** | *Bleeding:* BRBPR w/ or after defecation, blood on toilet tissue<br>*Pruritus:* (2/2 inflammation/hygiene difficulties)<br>*Pain:* Distention from engorged vein; thrombosis can → acute discomfort |
| **Exam** | Abd exam + perineal inspection + digital rectal exam + anoscopy<br>*External hemorrhoids:* Dull pink<br>*Internal:* Dilated purple-blue veins on anoscopy, may be prolapsed |

- **History:** Ask about onset, potential precipitants (bowel habits, straining, fiber intake), if c/o bleeding, ask about ASA, anticoagulants (see *"GI Bleeding"* )
  **Exam:** Look for e/o alternative diagnosis (below), as well as classic findings (above); FOBT
- **Red flags:** Change in bowel habits, abd pain/bloating, wt loss, blood *in* stool, ⊕ FHx colorectal CA
- **Differential diagnosis:** Skin tags (may be hemorrhoidal remnant), warts, fistula (Crohn's Disease), tumor, polyp, rectal prolapse
- **Diagnostics:** Referral for colonoscopy if: (1) Pt >50 y & has not had colonoscopy in last 10 y; (2) pts >40 y w/o recent colonoscopy but ⊕ FHx colorectal CA dx before age 60; (3) pts w/ iron deficiency anemia, or ⊕ FOBT

## Treatment (*Dis Colon Rectum* 2011;54:1060, *BMJ* 2008;336:380, *AFP* 2011;84:209)

- **Nonsurgical management:** Best for mild disease (e.g., bleeding but no prolapse)
  ↑ Fiber shown to ↓ overall sx (*Cochrane Data System Rev*

2005;19:CD004649), trial of Sitz baths, limit time on commode; use of laxatives & stool softeners to avoid straining *(see "Constipation")*

*Rx:* Topical steroids (avoid prolonged use), anesthetics, astringents, and/or antiseptics

*Rx for thrombosed:* Topical lidocaine crm

- **Surgical management:** Indicated for mod–severe sx or acute thrombosis (if w/in 72 h of sx onset) offers definitive tx for existing hemorrhoids but does not prevent recurrence; frequently an office-based procedure; tx include rubber band ligation, infrared coagulation, stapled hemorrhoidopexy, & hemorrhoidectomy
- **Gastrointestinal referral:** Young pts w/ chronic constipation assoc w/ hemorrhoids, consider obstructive defecation & referral for anorectal manometry

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### ANAL FISSURES (*Gastroenterol Clin North Am* 2008;37:627)

- **Definition:** Tear in distal anal canal, often painful; may be acute or chronic
- **History:** Pain w/ defecation, bright red blood on toilet tissue or streaking stool surface
- **Exam:** Visible tear, posterior midline > anterior midline, off of midline suggests alternative dx, e.g., anal CA or IBD; in chronic fissures, may see indurated edges, hypertrophied anal papillae, or sphincter fibers visible at fissure base
- **Etiology:** Not clearly understood, thought to be 2/2 anal canal trauma from hard stool → pain w/ defecation → ↑ resting internal anal sphincter tone (involuntary) → more trauma
- **Treatment:** Stool softeners (see *"Constipation"*); for chronic/refractory sx → GI for consideration of alt tx (can include topical CCB, botulinum injection); no role for manual sphincter dilatation (can damage sphincter → incontinence)
- **When to refer:** Chronic, refractory to stool softeners, fissure off of midline

# INFLAMMATORY BOWEL DISEASE (IBD)

## Background (*NEJM* 2009;361:2066; *Lancet* 2012;380:9853)

- **Definition:** Inflammatory bowel diseases are the clinical syndromes of chronic, idiopathic, inflammatory d/o which primarily affect the gastrointestinal tract
  **Crohn's Disease (CD):** Systemic & transmural intestinal inflammation which can occur throughout the GI tract
  **Ulcerative Colitis (UC):** Inflammatory d/o of the colonic mucosa
- **Pathophysiology:** Both CD & UC are thought to result from dysregulation of immune system's response to intestinal microbes; however, much of the genetic predispositions, clinical risk factors, presentation, complications, & tx are distinct
- **Epidemiology** (*Gastroenterology* 2012;142:46)
  **UC:** Peak incidence in 20s, ♂ > ♀; *Risk factors:* ⊕ FHx, Ashkenazi Jewish heritage, s/p bacterial colitis (e.g., Salmonella, Shigella), ? NSAIDs, OCPs; appendectomy + current smoking protective
  **CD:** Bimodal, w/ peak incidence in 20s & 50s; ♀ > ♂, ↑ prevalence; *Risk Factors:* Smoking, ⊕ FHx, recent gastroenteritis, Ashkenazi Jewish heritage

## Evaluation (*Gut* 2011;60:571)

- **General approach to diagnosis:** Determine if IBD plausible explanation for sx, & if so, refer to GI for endoscopy; this can be done primarily w/ hx but impression can be honed w/ exam & selected lab studies

**Initial Presentation of IBD**

| | Ulcerative Colitis | Crohn's Disease |
|---|---|---|
| **Distribution** | Proctosigmoid (~40–50%), left-sided colitis (~30–40%), pancolitis (~20%) | Small intestine (~40%), ileocolitis (~40%), colitis (~20%) |
| **History** | May present as mild diarrhea, intermittent **rectal bleeding,** or as inflammatory **diarrhea** or proctitis (multiple loose stools, hematochezia, **tenesmus**)<br><10% p/w fulminant disease (appear systemically ill → ED) | Variable, can involve entire GI tract; indolent **crampy abd pain** ± fluctuating mucoid **diarrhea,** hematochezia, fatigue, fevers, wt loss, oral ulcers |

- **History:** Onset, severity, pattern of sx, bowel habits; systemic sx (fevers, chills, wt loss)

*PMHx:* Autoimmune disease, DVT, liver disease, recent gastroenteritis/colitis, gallstones (CD), nephrolithiasis (CD)
*Other:* FHx IBD, medications, smoking, travel hx
*Assoc sx:* Rashes, eye pain/irritation, arthritis, jaundice

- **Exam:** VS, BMI, general appearance; *HEENT:* aphthous ulcers, episcleritis; *Derm* jaundice, erythema nodosum, pyoderma gangrenosum; *Abd exam:* RLQ mass: Ileocecal inflammation or phlegmon in CD; *Rectal exam:* Perineal exam for fissures, fistulas, or induration suggestive of abscess; rectal masses, presence of blood in stool
- **Labs:** CBC w/ diff, LFTs, ESR, CRP, Fe/$B1_2$/Folate, Vit D

  *Stool studies:* If diarrhea prominent, consider culture, O + P, fecal leukocyte testing, fecal calprotectin (Se/Sp 93/96%) or lactoferrin (*BMJ* 2010;341:c3369)
- **Imaging:** KUB if ? obstruction, **CT** indicated if ?of abscess, colitis, alt dx (diverticulitis)
- **Endoscopy:** Flex sig (UC, distal CD) vs. colonoscopy to establish extent of disease
- **Differential diagnosis:** Extensive, dependent on presenting sx, but can include infectious colitis, diverticulitis, CRC, celiac disease, chronic pancreatitis, & IBS

## Treatment (*BMJ* 2008;336:1062; *Lancet* 2012;380:1590)

- **When to refer:** If concern for severe disease (unstable VS, clinically ill, inadequate PO intake, concern for abscess, obstruction) → to ED; if suspect IBD based on above → to gastroenterology
- **Monitor for complications:**
  *Stricture (CD or UC):* Obstructive sx, usually in terminal ileum if 2/2 CD
  *Fistula (CD):* Entero-vesicular (recurrent polymicrobial UTIs), cutaneous, vaginal, enteric
  *Abscess (CD):* Fevers + peritonitis/abd pain (intra-abd) or perirectal pain/inflammation
  *Peri-anal disease (CD):* Seen in 1/3 of CD pts; perirectal abscess, fissures, fistulas
- **Health maintenance**

*Immunizations:* Ensure up-to-date (flu, pneumococcal, HBV, ± HPV) caution w/ live vaccines if on or anticipating immunosuppresants in next ~8 wks (see *"Immunizations"*)

*Colorectal CA screening:* Overall risk of CRC higher in pts with PSC, early age at IBD dx, or long disease duration; consider screening after 8 y of disease, w/ surveillance q1y or as set by gastroenterologist (*Gastroenterology* 2012;143:375)

*Other CA screening:* Age-appropriate, also at ↑ risk of lymphoma, melanoma (*Clin Gastroenterol Hepatol* 2013;pii:S154)

*ID screening:* Annual TB testing if on anti-TNF tx

- **Nonpharmacologic treatment** (*IBD* 2008;14:1597)

  *Probiotics:* Data incomplete but may ↓ risk of pouchitis (UC), no benefit proven in CD

  *Diet:* No uniform modifications proven effective, but reasonable to trial eliminating foods pt assoc w/ sx

  *Smoking cessation:* Important in CD; likely overall health benefit in UC but may → flare

- **Pharmacotherapy:** Generally managed by gastroenterologists, divided into induction & maintenance Rx; drug classes below

**Pharmacologic Agents Used in Treatment of IBD**

**5-ASA compounds:** Often 1st-line tx for mild UC as induction + maintenance; limited data on efficacy in CD; often trialed for 3–4 wks; small proportion (<5% of pts) experience idiosyncratic worsening of sx on 5-ASA at any time during tx
*Route:* PO for ileal, R or transverse colon disease; PR for distal disease (proctitis → suppository; proctosigmoiditis or L-sided colitis → enema)
*Specific Agent:* Mesalamine (ext release, pH sensitive), Pentasa (small intestine + colon); Asacol (terminal ileum + boluses into right colon), Lialda (terminal ileum + delays to release throughout colon), Sulfasalazine (colon), Olsalazine/Balsalazide (colon)
*Monitoring:* Annual CBC, LFT, U/A (risk of interstitial nephritis), BUN/Cr

**Thiopurines:** Used as maintenance in UC & CD
*Specific Agents:* 6-MP, AZA
✔ TPMT genotype prior to initiating tx to assess if ↑ risk of toxicity (leukopenia, ↑ LFTs)
*Monitoring:* CBC w/ diff, LFTs, amylase/lipase every 2 wks, then q1–3 mos; metabolites also assessed if concerns for toxicity or nonadherence (6-TG, 6-MMP)

**Corticosteroids:** Typically used as induction, not maintenance
*Budesonide:* High 1st-pass liver metabolism → ↓ systemic s/e ("targeted"); used in active ileitis or R-sided colon CD
*Prednisone:* 40–60 mg/d used as induction, 60–80% of pts responds in 2–3 wks

**Other:** For mod—severe disease (frequently hospitalized), used if above tx fail for induction & as maintenance
*Anti-TNF* (UC/CD): Infliximab, adalimumab, certolizumab pegol, golimumab (UC); anti-integrin: natalizumab (CD); calcineurin inhibitors

# IRRITABLE BOWEL SYNDROME

## Background (*NEJM* 2003;349:2136; *Gastroenterology* 2006;130:1377)

- **Definition:** Abd pain or discomfort occurring 3 d/mo × last 3 mos (w/ sx onset >6 mos prior to dx) **&** at least 2 of the following:
  1. Improvement of sx w/ defecation
  2. Onset assoc w/ change in stool frequency
  3. Onset assoc w/ change in stool form or appearance
- **Classification:** Subtype based on bowel habits; **IBS-C** (constipation) hard stools ≥25%; **IBS-D** (diarrhea) loose stools ≥25%; **IBS-M** (mixed) hard stools ≥25% & loose stools ≥25%, sometimes called "alternators"; **Unsubtyped:** Does not fit subtype criteria
- **Pathophysiology:** Thought to be multifactorial; genetic predisposition, mucosal barrier disruption, stress response, ?altered gut microbiota → dysfunction of neurohormonal CNS–GI system & altered neurotransmitter release
- **Epidemiology:** IBS is estimated to affect 12% of US adults, ♀ > ♂ 2:1, onset typically prior to age 50; over half of pts have comorbid Ψ d/o (mood, anxiety)
- IBS pts have ↓ QoL & often receive ↑ meds, ↑ tests, & more provider visits than other pts w/o IBS; however, many also do not seek medical attention

## Evaluation (*Nat Rev Gastroenterol Hepatol* 2010;7;565)

- **General approach:** IBS is a clinical dx based on classic hx & benign PE; features suggestive of alt dx should prompt further eval; as sx frequently chronic, attempt to determine what prompted pt to seek care now (↑ in sx, ↑ stress) & what they attribute sx to (e.g., fear of malignancy) as this will be important in guiding tx
- **History:** Hallmark sx are abd pain/bloating (96%); ask about bowel habits, hard/loose stools, frequency, urgency, straining, sense of incomplete evacuation, mucous in stool; aggravating/alleviating factors (defecation, stress, diet)
  *Assoc sx:* Fever, chills, wt loss, bloody stools
  *PMHx:* Depression, anxiety, thyroid disease, autoimmune disease,

immunosuppression, travel hx

*Meds:* Assess for medications which can → altered bowel habits (see *"Constipation"* & *"Diarrhea"* )

*FHx:* Autoimmune, GI malignancy, celiac, IBS, IBD

*Social hx:* Exercise, current stressors, hx abuse/IPV

- **Exam:** Complete exam at time of initial dx, including exam of thyroid, skin, oropharynx, abd & rectal exam, ⊕ FOBT; this reassures pt & provider that alternative dx is not missed
- **Features suggestive of alternative diagnosis ("alarm" symptoms):** New sx at ≥50 y, progressive sx, unintentional wt loss, nocturnal diarrhea, anemia, bloody stools, ⊕ FHx of colorectal CA, celiac disease, IBD
- **Differential diagnosis:** Hypo/hyperthyroidism, celiac disease, IBD, infection, malignancy, diverticular disease, medication effect, lactose intolerance, chronic mesenteric ischemia
- **Diagnostics** (*Am J Gastroenterol* 2009;104:S1): Not recommended if pt meets IBS criteria w/o alarm signs; may consider celiac serology (below)

**Diagnostic Screening in IBS** (*Nat Rev Gastroenterol Hepatol* 2010;7:565)

| | |
|---|---|
| Celiac disease serology | Recommended in IBS-D & IBS-M |
| Colonoscopy | *Indications:* Alarm sx present; or for age-appropriate (>50 y) routine screening<br>If IBS-D or IBS-M pt referred for screening colonoscopy: Ask GI MD to get random bx for ? of microscopic colitis |
| BMP, CBC, TSH, stool tests, abd imaging | Low yield; should only be performed if alarm sx or features suggestive of alternative dx |

## Management (*Gastroenterology* 2006;130:1377; *AFP* 2012;86:419)

- **Counseling:** Effective mgmt of IBS requires effective pt–provider relationship

*Support:* Express belief that sx are result of real d/o

*Education:* Explain current understanding of disease; intestine under complex neuroregulation, & overly responsive to stimuli (food, hormones, medication, stress) → spasm or stretching → pain & changes in GI function

*Reassurance:* Explain eval & assessment that this does not reflect dangerous d/o

- **Complementary/Alternative therapies:** Acupuncture no more effective than sham acupuncture in meta-analysis; however *both* more effective than no intervention (*Am J Gastroenterol* 2012;107:835)
- **Diet:** Many IBS pts believe that diet plays a role in their sx, but there is no evidence that exclusion diets or food allergy testing are efficacious (*AJG* 2009;104;Suppl 1:S1)
  - **Fiber:** Although bulking agents (see below) have some efficacy, no evidence that dietary fiber supplementation is more effective than placebo for global IBS sx
  - **Allergies/Intolerance:** Pts w/ IBS have a ↑ prevalence of lactose intolerance than healthy controls; pts should keep a food diary to see if their sxs are related to dairy intake; fructose intolerance also increasingly recognized in IBS; true food allergies usually coexist w/ IBS rather than reflect the 1° cause of sx
- **Exercise:** Evidence that physical activity can ↓ IBS sx (*Am J Gastroenterol* 2011;106:915)
- **Psychotherapy:** CBT, psychotherapy, hypnotherapy, & stress mgmt all ↓ sx of IBS; most benefit in pts willing to accept psych component of sx or those who prefer talking Rx over medications (*Nat Rev Gastroenterol Hepatol* 2010;7:565)
- **Probiotics:** Vary in species, strains, preps, & doses, but studies demonstrate that tx w/ *Bifidobacterium* improves IBS sx. *Lactobacillus* not effective (*AJG* 2009;104;Suppl 1:S1)
- **Pharmacotherapy:** Tailored to pt's symptoms & their severity

**Pharmacotherapy in IBS** (*Nat Rev Gastroenterol Hepatol* 2010;7:565)

| Symptoms | Drugs | Comments |
|---|---|---|
| Pain/Bloating | TCAs | Likely impact on central/visceral pain sensation<br>NNT is 3.2 to benefit 1 pt (*NEJM* 2003;349:2136)<br>Caution in IBS-C given potential constipation |
| | SSRIs | Less e/o efficacy in IBS, may offer ↑ benefit to pts w/ comorbid mood/anxiety d/o |
| | Antispasmodics (e.g., hyoscyamine, dicyclomine) | Effective for short-term relief (*Cochrane Database Syst Rev* 2011(8):CD003460); ↓ postprandial sxs if given 30 mins before meals; s/e: Dry mouth, dizziness, blurred vision<br>Long-term effects unknown |
| Diarrhea | Antidiarrheals | Helpful for sx control, no imprvmt in global sxs |
| | Rifaximin (2 wk course) | Global ↓ in sxs/↓ bloating in IBS-D, but not yet approved by FDA for IBS (*NEJM* 2011;364:22) |
| Constipation | Bulking Agents | ↓ Straining/hard stools primarily seen w/ psyllium, but caution given potential bloating |
| | Laxatives | IBS efficacy not well-established, polyethylene glycol best-studied (see "*Constipation*") |
| | Other (usually Rx'd by GI) | Lubiprostone: $Cl^-$ channel activator for IBS-C<br>Linaclotide: cGMP activator, used for IBS-C |

- **When to refer:** Severe/refractory sx, dx uncertain, or presence of alarm sx → GI

# JAUNDICE

## Background (*BMJ* 2001;322:33)

- **Definition: Jaundice:** Yellowish discoloration of the skin, sclera, & mucous membranes due to hyperbilirubinemia (usually appears when total bili >3 mg/dL); H**yperbilirubinemia:** Accumulation of bili above nl limits (>1.5 mg/dL)
- **Heme metabolism:**
  1. Hb (from RBCs) broken down in RES → *unconjugated ("indirect") bili*
  2. Unconjugated bilirubin (UCB) bound to albumin in blood & transported to liver
  3. UCB then conjugated w/ glucuronic acid → water-soluble *conjugated ("direct") bili*
  4. Conjugated bilirubin (CB) then excreted in bile
- **Pathophysiology:** Excess heme breakdown or defective conjugation → unconjugated ("indirect") hyperbilirubinemia; impaired excretion, biliary obstruction or epithelial damage → conjugated ("direct") hyperbilirubinemia
- Etiologies range from benign to life-threatening; full evaluation & discussion of assoc sx needed for triage

## Evaluation (*AFP* 2004;69:299)

- **General approach:** Characterize type of bilirubinemia (predominantly indirect or mixed) to guide differential; consider ED referral/admission for anyone clinically ill w/ new jaundice
- **History:** Determine any assoc sx: fatigue, fevers, confusion, bleeding; SOB, DOE; RUQ pain, pruritus; epigastric pain, wt loss; any recent illness, travel, injection drug hx
  *Meds/Toxins:* EtOH, medications (see *"Abnormal LFT"* )
  *PMHx:* Liver disease, HIV, gallstones, wt loss, autoimmune disease, abd surgery (e.g., CCY), FHx liver disease
- **Exam:** Jaundice (conjunctiva, SL), stigmata of ESLD (ascites, spider angiomata, splenomegaly, gynecomastia), xanthomas, hyperpigmentation

- **Initial diagnostics:**
  **Labs:** TB + DB, CBC for all jaundiced pts, along w/ ALT, AST, Aφ, PT/INR, Alb
  **Imaging:** If conjugated, RUQ U/S often next step (see *"Abnormal LFTs"* )

## Differential Diagnosis (*Best Pract Res Clin Gastroenterol* 2010;24:555)

**Selected Causes of Hyperbilirubinemia**

| | |
|---|---|
| **Indirect (unconjugated) hyperbilirubinemia** | |
| **Overproduction** | **Hemolytic,** ineffective erythropoiesis, hematoma reabsorption, large PE |
| **Defective conjugation** | **Gilbert's:** Conjugation enzyme insufficiency, affects 5% of US; often detected incidentally when TB slightly ↑ despite nl LFTs; can present w/ jaundice during stress/illness/fasting, but resolves w/ sx; can offer reassurance<br>Crigler–Najjar: Conjugation enzyme deficiency, rare |
| **Direct (conjugated) hyperbilirubinemia** | |
| **Obstruction** | *Intrahepatic:* PBC, medications (OCPs, erythromycin)<br>*Extrahepatic:* Choledocholithiasis, stricture, cholangioCA, pancreatic CA, PSC |
| **Epithelial damage** | **Hepatitis (viral, EtOH, autoimmune), cirrhosis** |
| **Defective excretion** | Genetic d/o: Dubin–Johnson, Rotor syndrome, abnl biliary transport proteins |

## Management

- As per underlying cause; may offer reassurance to pts w/ Gilbert's disease
- If etiology unknown & LFT abnormalities persistent → GI referral; see *"Abnormal LFTs";* if pt appears clinically ill w/ acute presentation of jaundice or e/o altered hepatic function → ED

# PANCREATITIS

## Background (*Lancet* 2008;371:143)

- **Definition:** Inflammation of pancreas, ranging from mild/interstitial to extensive necrosis
- **Epidemiology:** Acute pancreatitis: incidence ↑ w/ age, ♂ : ♀; incidence ↑ in African-Americans; majority of cases mild but 20% are sev (assoc

w/ morbidity/mortality)

- **Risk factors:** Smoking (↑ risk of EtOH & idiopathic pancreatitis); abd obesity (↑ severity & incidence); DM2 (1.5–3× ↑ risk), EtOH → 4× ↑ risk of acute pancreatitis, ↑ risk of progression to chronic pancreatitis

**Selected Etiologies for Pancreatitis**

| | |
|---|---|
| **Obstructive** | **Gallstones** (35–40% of all cases), cysts, pancreatic divisum |
| **Meds/Toxic** | **EtOH** (~30%; often >5 y heavy consumption), organophosphates<br>*Meds:* TMP/SMX, furosemide, HCTZ, steroids, AZA, mesalamine, opiates, VPA, carbamazepine, estrogens, 6-MP, tetracycline, HAART (lamivudine, nelfinavir) erythromycin, APAP; ? of GLP-1 & DPP-4 inhibitors |
| **Metabolic** | **Hyperlipidemia** (TG >1000 mg/dL), hypercalcemia |
| **Genetic, Autoimmune** | Autoimmune (IgG4 disease; more commonly presents as pancreatic mass), SLE, Sjögren |
| **Other** | *Postsurgical:* ERCP, abdominal, or cardiac surgery<br>*Infection:* Mycoplasma, legionella, salmonella, mumps, coxsackie, HBV, CMV, VZV |

- **Complications:** Systemic (AKI, ARDS, DIC), metabolic (↓ Ca, hyperglycemia), acute fluid collection, necrosis, pseudocyst
- Most pts who p/w acute pancreatitis require inpt tx; f/u visits after an acute episode should focus on ↓ recurrence

## Evaluation (*Ann Intern Med* 2010;153:ITC51-5; *AFP* 2007;75:1513)

- **General approach:** Determine if suspected case consistent w/ pancreatitis & if so if requires hospital admission; attempt to establish etiology

**Typical Presentation for Acute Pancreatitis**

| | |
|---|---|
| **History** | Abd pain (upper abdomen radiating to back, often w/o alleviators), nausea, vomiting, aggravated by PO intake |
| **Exam** | Epigastric and/or periumbilical TTP; may radiate to chest, back, flank ± ↓ bowel sounds; pt may bend forward ("knee–chest" position) to ↓ pain |

- **PMHx & risk factors:** Known gallstones, EtOH use, smoking, prior CCY (↑ gallstone pancreatitis), ↑ TG, DM prior pancreatitis or similar episodes, prior ERCP
  *Meds:* Rare, but possible
- **Labs: Lipase** or amylase (combining doesn't ↑ diagnostic accuracy),

LFTs, TG, CBC, BMP

*Lipase:* More specific than amylase & ↑ for longer time; also ↑ in head trauma, intracranial masses, CKD, & in pts on heparin

*Amylase:* ↑ Se/↓ Sp; also ↑ in CKD, salivary gland or fallopian tube d/o, intestinal ischemia, perforated peptic ulcer

- **Imaging:** RUQ U/S in all pts w/ first episode (visualizes gallstones, not pancreatitis itself)

  CT if unsure of dx or concern for complications (fluid collection, necrosis)

  Urgent ERCP (typically done as inpt) indicated for e/o sepsis, comorbid biliary obstruction (e/o cholangitis, ↑ TB, worsening pain in setting of biliary dilatation)
- **Red flags:** Unstable VS (fever, HoTN), peritonitis (guarding), inability to take adequate PO, multiple comorbidities, elderly, severe pain → ED
- **Ddx** (see *"Abdominal Pain");* PUD, chronic pancreatitis, biliary colic, cholecystitis, biliary colic, renal colic, appendicitis, ectopic pregnancy
- **Predicting severity:**
  1. *Harmless Acute Pancreatitis:* No rebound tenderness, nl Hct, & nl serum Cr predicts a non-severe course w/ 98% accuracy
  2. *Bedside Index of Severe Pancreatitis Score:* BUN > 25, GCS < 15, SIRS, age >60, pleural effusion (1 pt each); calculate w/ in 24 h: If 0–2 pts, mortality <2%; if 3–5 pts, mortality >15% (*Am J Gastroenterol* 2009;104:966)

## Treatment (*Gastroenterology* 2007;132:2022)

- Most acute pancreatitis managed in inpt setting (see Red Flags above); mild cases *may* be managed as outpt if fluid status, nutrition, & analgesia can be managed on PO basis
- **Prevention of future episodes:**

  *Counseling:* ↑ Likelihood of recurrence w/ EtOH (even if pancreatitis felt to be 2/2 another cause) → EtOH cessation/reduction (see *"Alcohol Use Disorders"* ); smoking cessation; adherence to lipid-lowering medication if ↑ TG

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# Chronic Pancreatitis

## Background (*Gastroenterology* 1998;115:763)

- **Definition:** Chronic inflammation which leads to fibrosis & destruction of pancreatic cells; can → endocrine and/or exocrine insufficiency & ↑ risk of pancreatic CA
- **Etiology:** Toxic-metabolic (45–80% from **EtOH**), recurrent/severe acute pancreatitis, genetic, autoimmune (hypergammaglobulinemia, ↑ IgG4), obstructive, idiopathic
- **Risk factors:** Recurrent acute pancreatitis necessary but not sufficient; tobacco ↑ risk of idiopathic CP & accelerates progression of EtOH-induced CP
- **Complications:** Chronic pain, DM, pseudocyst/abscess, malnutrition; pancreatic CA incidence 4% over 20 y

## Evaluation (*Clin Gastroenterol Hepatol* 2012;10:108)

- **Presentation:** Sx develop over years; diagnosed based on imaging + lab findings
  - **Signs and symptoms:** Intermittent → chronic epigastric pain, e/o pancreatic insufficiency (steatorrhea, wt loss, hyperglycemia)
  - **Labs:** Amylase/lipase often nl; may have ↑ AΦ, TB, ↑ glc, ↑ fecal fat, Vit D; consider fecal elastase (↓ ) or serum trypsin (↓ ) if ? of exocrine insufficiency
  - **Imaging:** Typically diagnosed by EUS, MRI w/ MRCP, or CT; ERCP ↑ Se but often not needed for dx
  - **Functional tests:** Secretin test (typically performed by GI if imaging tests equivocal)
- **Differential diagnosis:** Pancreatic CA, IPMN, BD/duodenal obstruction

## Treatment (*Gastroenterology* 2013;144:1282)

- **Referral:** Consider GI referral if suspected (or if dx unclear); if sx persistent/severe, refer for evaluation & consideration of endoscopic/surgical tx; low threshold for admission (new fever, new jaundice, major change in sx all merit further eval)
- **Lifestyle treatment:** All pts w/ chronic pancreatitis should be counseled re: low-fat diet, EtOH & tobacco abstinence, receive Ca/Vit D supplementation (consider BMD testing)

- **Analgesia:** Consider APAP/NSAID, then tramadol, pregabalin/gabapentin, SSRI/SNRI/TCA (see *"Chronic Pain"*)
- **Exocrine treatment:** If insufficient, pancreatic supplementation (e.g., pancrelipase w/ meals; can add PPI, H2RA to ↑ activity)

# PEPTIC ULCER DISEASE

## Background (*Lancet* 2002;360:933; *J Clin Gastroenterol* 1997;24:2)

- **Definition:** PUD refers to focal mucosal damage in the stomach (GU) or proximal duodenum (DU); can also occur in esophagus or more distal duodenum in pts w/ hypersecretory states
- **Epidemiology:** Lifetime prevalence up to 10%; ♂ > ♀; most commonly affects 25–64 yo; incidence is ↓ w/ widespread use of PPI & *H. pylori* eradication (*J Glob Infect Dis* 2011;3:366)
- **Risk factors: *H. pylori* infection** (involved 48% of ulcers), **NSAID/ASA use** (24%) (these 2 factors have synergistic effect); smoking (23%); some combination of the 3 accounts for 89–95% of all ulcers (*J Clin Gastroenterol* 1997;24:2); other causes include malignancy, hypersecretory states (Zollinger–Ellison syndrome), stress ulcers from serious illness ± corticosteroid use, postsurgical anastomotic ulcer

## Evaluation (*AFP* 2007;76:1005)

- **General approach:** Suspect ulcer disease in pts who p/w following sx; ask about risk factors (above) & red flags

### Classical Presentation of PUD

| | |
|---|---|
| **History** | Episodic gnawing/burning epigastric pain; occurring 2–5 h after meals or on empty stomach (classically GU has sx worst w/ food, DU sx worst after meal, but not reliable); nocturnal pain which can → awakening<br>*Alleviating sx:* prior to Relieved by food intakes, antacids, or anti-secretory agents<br>*Assoc sx:* Bloating, fullness |
| **Exam** | Sx often minimal, may have epigastric TTP, ⊕ FOBT, or melena |

- **Red flags:** Melena (see *"GI Bleeding"*), peritoneal signs, intractable vomiting → ED

- **Differential diagnosis:** Dyspepsia, GERD, pancreatitis, biliary colic; see respective chapters
- **Diagnostics: EGD** indicated if pt has occult bleeding or alarm sx (wt loss, early satiety, anemia, dysphagia)
  ***H. pylori*** testing (see *'H. pylori'*)

## Postulcer Care

- **Treat underlying cause**(s) to promote healing & reduce risk of recurrence: Treat *H. pylori* (see *"H. pylori"*), ↓ or hold NSAIDs; smoking cessation, avoid EtOH; generally okay to continue cardioprotective ASA (for 1° prevention, should weigh risk of bleeding vs. potential benefits; see *"CAD"* )
- **Gastric acid suppression:** 8 wks for DU & 8–12 wks for GU; PPI > H2RA but both >90% resolution at f/u; consider long-term suppressive tx in pts on dual anti-PLT agents or o/w at ↑ risk of recurrence (*Dig Dis* 2011;29:465)
- **Mucosal protectants:** For gastroprotection, not as acute treatment: Sucralfate (coats ulcer bed), misoprostol (stimulates mucus & bicarbonate secretion, can → diarrhea), antacids (neutralizes gastric acid)
- **Follow-up esophagogastroduodenoscopy:** 6–12 wks after initial tx for gastric ulcer; indicated if ulcer large/complicated or sx (including bleeding) persist despite tx; repeat EGD not routinely needed for duodenal ulcers
- **When to refer:** Indications for EGD, above; GI referral for persistent/severe sx

# NOTES

# ABNORMAL WBC COUNT

## LEUKOPENIA

### Causes of Neutropenia (*Hematology ASH Educ Program* 2004:63; 2012:174)

| |
|---|
| **Infectious:** Viral (HIV, HBV, HCV, EBV, CMV); bacterial (Shigella, Brucellosis, TB); parasitic; tick-borne (Ehrlichia, Rickettsial, RMSF) |
| **Medications:** Suppress BM or trigger autoimmune reaction; ACEI, APAP, ACV, abx (ampicillin, bactrim, ceph, macrolides, vancomycin), AZT, chemotherapy, clopidogrel, clozapine, digoxin, dipyridamole, fluoxetine, furosemide, ganciclovir, immunosuppressants, methimazole, NSAIDs, prednisone, propranolol, propylthiouracil, ranitidine, spironolactone, sulfasalazine, thiazides, TCAs, valproate, & many others (>125) (*Ann Intern Med* 2007;146:657); Cocaine & heroin may be "cut" w/ levamisole (chemo drug) (*Ann Intern Med* 2009;150:287) |
| **Autoimmune:** Collagen vascular, aplastic anemia, Fanconi anemia, Felty syndrome (RA + splenomegaly + neutropenia), sarcoid |
| **Malignancy:** Leukemia, myelodysplasia, cancers that metastasize to bone, amyloidosis |
| **Other:** Vit $B_{12}$, folate, copper deficiency, EtOH, CVID, pure white cell aplasia, hypersplenism; Myeloperoxidase deficiency will result in artificially low ANC as this enzyme is used to identify neutrophils in automated counters |
| **Congenital:** Chediak–Higashi, Kostmann syndrome, glycogen storage disease, cyclic neutropenia (autosomal dominant, occurs q14–35d) (*NEJM* 2009;360:3; *Semin Hematol* 2002;39:89) |
| **Benign chronic neutropenia/Chronic idiopathic neutropenia:** Seen in 4.5% of pts w/ African ancestry → no further w/u needed (*Ann Int Med* 2007;146:486) |

### Causes of lymphocytopenia

| |
|---|
| **Infectious:** Viral (HIV, measles, HBV/HCV), bacterial (TB, histoplasma, brucella), malaria |
| **Medications:** Rituximab, steroids, chemotherapy (fludarabine, cladribine) |
| **Autoimmune:** Lupus, RA, Sjögren |
| **Malignancy:** Lymphoma, cancers that metastasize to bone |
| **Other:** EtOH, zinc & Vit deficiency, physiologic stress (i.e., post-op, sepsis) |

- **History:** Most important aspect of evaluation - leukopenia assoc w/ other Sx or a hx recurrent infections is the most concerning; most asx leukopenia is chronic & familial/ethnic; often asx/incidental; may present w/ fevers, chills, diarrhea, abdominal pain, joint pain, opportunistic/recurrent infection, FTT, food allergies; fatigue, pallor, easy bruising/bleeding, petechiae (if RBC or PLT affected); complete medication & supplement hx; cyclic sx (i.e., q3wks may suggest cyclical neutropenia)
- **Exam:** LNs, spleen, dental exam to r/o abscesses & gingivitis

- **Workup:** CBC w/ diff, peripheral smear; *consider:* viral serologies (HIV, HepB & HCV, EBV), $B1_2$, folate, MMA, homocysteine, copper/ceruloplasmin level, ESR/CRP, ANA, complement, flow cytometry, reticulocyte count; *Per clinical suspicion:* RMSF, & ehrlichia serologies, PPD, RF, & anti-CCP Ab; may need hematology referral for BM bx if above w/u unrevealing, neutropenia is persistent, & ANC <1000; role of antineutrophil Ab for autoimmune disease unclear; Neutrophil function assays include bacterial killing, nitroblue tetrazolium (to r/o chronic granulomatous disease), chemotaxis; if congenital cause suspected, consider referral to geneticist for specialized testing
- **Neutropenia:** Categorized by absolute neutrophil count (ANC); *Mild:* ANC 1000-1500; *Mod:* ANC 500-1000; *Severe:* ANC <500; Infectious risk ↑ w/ ↓ ANC, especially for ANC <500 (*Ann Int Med* 1966;64:328)
  **Benign chronic neutropenia/Chronic idiopathic neutropenia:** Seen in 4.5% of pts w/ African ancestry → no further w/u needed (*Ann Int Med* 2007;146:486)
  **Asx:** D/c offending meds, monitor CBC w/ diff q2–12wks, counsel pt about importance of reporting signs of infection; consider neutropenic diet if ANC <500
  **Febrile:** Admit for IV abx; most often GI/GU source (GNRs, *Staph aureus*) or candida
  **G-CSF (filgrastim):** In consultation w/ hematology, consider for pts w/ recurrent infections, congenital neutropenia, fever/infection w/ medication associated neutropenia, or HIV- or AIDS-associated neutropenia (*AIDS* 1998;12:65; *Blood* 1993;81:2496); acute s/e include bone pain, myalgias, flu-like sx; chronic G-CSF use assoc w/ osteoporosis & possibly ↑ malignancy; Pegfilgrastim is given as a single injection, in contrast to filgrastim which is dosed daily for up to 14 d
- **Lymphocytopenia:** D/c offending med & treat supportively; Lymphocyte count will almost always return to nl unless malignancy involved (*Aust N Z J Med* 1997;27:170)

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## LEUKOCYTOSIS

- **History:** Hx recent infection, fevers, chills, night sweats, wt loss; complete medication & supplement hx; allergic reactions & exposures; travel hx; hx asthma, bronchiectasis, IBD; smoking hx
- **Exam:** LNs, spleen, skin (rash)
- **Workup:** CBC w/ diff, peripheral smear, viral serologies (HIV, EBV, CMV), flow cytometry (for chronic lymphocytic leukemia [CLL] & other leukemias), peripheral blood for FISH for BCR–ABL (Philadelphia chromosome, chronic myelogenous leukemia [CML]), ESR, CRP, SPEP, TSH; stool culture, ova, parasites depending on clinical scenario; the presence of blasts or numerous atypical lymphocytes on the peripheral smear is concerning for malignancy; hematology referral for BM bx if above w/u unrevealing or suggestive of malignancy
- **Management:** Identification & emergency referral of pts w/ acute leukemia is key; acute leukemia is suggested by suppression of other cell lines (RBC, PLT), coagulopathy (bleeding, petechiae), fevers, & circulating blasts; treatment o/w directed at underlying cause (e.g., withdrawal of offending med(s)), referral to heme/onc for chronic leukemias, smoking cessation, mgmt of infection or autoimmune disease

**Causes of Neutrophilia (*AFP* 2000;62:2053)**

**Infection:** Any acute infectious process, esp *C. diff*, pneumococcus, Staph

**Smoking:** Most common cause of ↑ ANC, likely due to chronic inflammation; WBC in population studies of smokers 27% higher than nonsmokers (*Am J Clin Pathol* 1997;107:64); Leukocytosis may persist for up to 5–10 y after cessation (*Arch Med Res* 2004;35:246)

**Medications:** Steroids, lithium (*Semin Hematol* 1983;20:129)

**Malignancy:** Leukemia, MDS, MM, large cell lung CA (*Cancer* 1987;60:903)
**Chronic myelogenous leukemia (CML):** Proliferation of mature/immature granulocytes (mainly neutrophils, but also basophils & eosinophils) due to *BCR–ABL* translocation (t9;22) found in 90–95% of pts (*Hematology ASH Educ Program* 2003:132; *NEJM* 2007;357:258)

**Other:** Pregnancy, physiologic stress (vigorous exercise, surgery, sepsis), IBD, bronchiectasis, thyroid storm, asplenia, PCV (in assoc w/ ↑ Hct), postseizure, heatstroke, sickle cell anemia, PLT clumping, or cryoglobulinemia (both may result in spurious ↑ ANC) (*J Clin Pathol* 1987;40:120), hereditary neutrophilia, chronic idiopathic neutrophilia

## Causes of Lymphocytosis

**Infectious:** Viral (HIV, EBV, CMV, HTLV-1, HepB & C, enterovirus), bacterial (pertussis, brucella, TB, toxoplasmosis, babesia, typhus)

**Medications:** Serum sickness & other drug hypersensitivity reactions

**Malignancy:** Thymoma, lymphoma (mantle cell, follicular, lymphoplasmacytic, splenic marginal zone), prolymphocytic leukemia, hairy cell leukemia
**Chronic lymphocytic leukemia (CLL):** Sustained absolute lymphocyte count ≥5000 w/ clonality on flow cytometry (*Blood* 2008;111:5446)
**Monoclonal B-cell lymphocytosis:** Clonal lymphocyte count ≤5000 w/o cytopenias, LAN, organomegaly, or sx; pts w/ MBL & CLL phenotype cells have a ~1% annual risk of developing CLL requiring tx (*NEJM* 2008;359:575)

**Other:** Hyperthyroidism, postsplenectomy, post-transplant lymphoproliferative d/o, cigarette smoking, RA, Addison disease, splenomegaly

## Causes of Monocytosis

**Infectious:** Brucellosis, VZV, TB, malaria, bacterial endocarditis, syphilis, trypanosomiasis, typhoid fever

**Malignancy:** Leukemia, HL, MDS
**Chronic Monocytic Myelogenous Leukemia [CMML]:** Absolute peripheral monocytosis >1000 that persists ≥3 months w/ myelodysplastic/myeloproliferative features in BM; important to r/o CML & PDGFR rearrangements (*Am J Hematol* 2012;87:611)

**Other:** Steroids, pregnancy, asplenia, sarcoidosis, IBD, lupus

## Causes of Eosinophilia

Leukemia (usually CML), lymphoma, PCV, myelofibrosis, adrenal insufficiency, solid tumors, allergic reactions, RA, lupus, Addison disease; Asthma, Churg–Strauss; drug hypersensitivity; infections (HIV, scarlet fever, leprosy, GU, fungi)

## Causes of Basophilia

Leukemia (usually CML), myelofibrosis, PCV, essential thrombocytosis, MDS, allergic reactions, UC, RA, hypothyroidism, estrogen supplementation, ovulation, infection (viral, TB, helminth, varicella, chronic sinusitis)

# ANEMIA

## Background (*NEJM* 1999;341:1986; 2005;352:1011; 353:1135)

- **Definition:** ↓ In RBC mass; threshold depends on age, sex, race: White ♂ Hgb <13.5 g/dL; African ancestry ♂ Hgb <12.8 g/dL; White ♀ Hgb <12.2 g/dL; African ancestry ♀ Hgb <11.5 g/dL (*Blood* 2006;107:1747); other factors affecting RBC mass include high altitude, smoking, athletics, volume status

### Causes of Anemia (*AFP* 2000;62:2255; 2009;79:203; 2010;82:1117)

| |
|---|
| **Microcytic:** Iron deficiency (common), copper deficiency (very rare), lead poisoning, congenital/acquired sideroblastic anemias; Thalassemias & hemoglobinopathies |
| **Normocytic:** Anemia of chronic disease, early iron deficiency, CKD, hypothyroidism, bleeding, hypersplenism, hemolysis (spherocytosis, sickle cell, G6PD, autoimmune, mechanical) |
| **Macrocytic:** Vit $B_{12}$, folate deficiency, ↑ reticulocytes, medications (hydroxyurea, AZT, chemotherapy), EtOH, liver disease, hypothyroidism, myelodysplastic syndrome |

- **Pathophysiology:** Erythropoietin (Epo) produced in kidney stimulates hematopoiesis in the BM; nl RBC life ~120 d

### Anemias with Increased Erythrocyte Destruction (*AFP* 2004;69:2599)

**Differential diagnosis:** Sickle cell, thalassemia major, hereditary spherocytosis, autoimmune, infectious (malaria, babesia, bartonella), G6PD deficiency, hypersplenism, medications (dapsone), liver disease, autoimmune hemolytic anemia (AIHA), microangiopathy PNH; hemolysis may be intravascular (mechanical trauma, infection, complement fixation) or extravascular in liver/spleen (Ab fixation, inability to deform)

**Autoimmune:** ⊕ Direct Coombs; *cold* agglutinins (IgM, found in mycoplasma PNA, mononucleosis) or *warm* (IgG, found in autoimmune disease, drug exposure [dozens reported, common culprits include PCNs, NSAIDs]) target RBC surface proteins → destruction; cold or warm agglutinins found in malignancy (CLL, lymphoma, Waldenström)

**Evan syndrome:** Warm AIHA + Idiopathic Thrombocytopenic Purpura (ITP)

**Fragmentation hemolysis:** ↑ Schistocytes (>1%) found in DIC, TTP/HUS, & HELLP syndrome (*Am J Hematol* 2004;75:18); fragmentation may also be seen w/ faulty prosthetic heart valves, malignancy-associated DIC, severe HTN

**Glucose 6-phosphate dehydrogenase (G6PD) deficiency:** NADPH produced by G6PD protects RBC from oxidative stress; X-linked; ↑ oxidants from physiologic stress, meds (i.e., APAP, ASA, chloroquine, colchicine, nitrofurantoin, phenazopyridine, primaquine, sulfamethoxazole) → ↑ oxidative damage in → RBC destruction (*Blood* 1994;84:3613); G6PD heterozygosity found in 20 & 12% of African-American ♂ & ♀, respectively (*Mil Medicine* 2006;171:905); degree of deficiency & consequences vary

**Thalassemia:** ↓ or absent synthesis of α or β Hgb chains → ineffective erythropoiesis + hemolysis → microcytic, hypochromic anemia; classified into major (transfusion dependent) & minor (heterozygotes = trait, tend to be asx & mildly anemic); pts who are transfusion-dependent susceptible to *Yersinia* infection 2/2 to ↑ iron

**Anemias with Decreased Erythrocyte Production (Low Reticulocyte Count)**

**Differential diagnosis:** Iron, $B_{12}$, folate deficiency (see *"Folate & Vitamin B 12 deficiency"*) due to malnutrition, malabsorption (celiac disease, *H. pylori*, atrophic gastritis, gastric bypass); marrow problems (MDS, tumor, aplastic anemia, medications, XRT); ↓ Epo (renal failure), hypothyroidism, hypogonadism; chronic disease (↓ absorption, ↓ Mϕ release)

**Iron deficiency:** Iron deficiency w/ anemia found in 1–2% of US adults; iron deficiency w/o anemia in 11% ♀, 4% ♂ (*AFP* 2007;75:671; *JAMA* 1997;277:973); Nonanemic ♂ have ~3–4 g in iron stores, ♀ have 2–3 g, most of which stored in Hb; Iron stores (mg) may be estimated by 8–10 × ferritin (ng/mL); inflammatory disease (e.g., RA) ↑ ferritin by ~3-fold (*Blood* 2003;101:3359; *Semin Hematol* 1982;19:6)

**Anemia of chronic disease:** ↓ Marrow RBC production 2/2 to chronic illness

**Elderly:** 20–30% of elderly pts have anemia of ? etiology, likely multifactorial & related to ↓ stem cell function, hypogonadism, ↓ Epo, & early MDS (*AFP* 2010;82:480; *Blood* 2004;104:2263)

**Sideroblastic anemia:** Congenital or acquired (myelodysplasia, drugs [chloramphenicol, INH, linezolid]), EtOH, ↓ copper, lead/zinc poisoning) deficiency in synthesis of heme or Hgb → microchromic, typically microcytic anemia + iron overload

**Alcohol abuse:** Inhibition of heme synthesis, malnutrition, variceal bleeding; macrocytosis occurs via unclear mechanisms

| |
|---|
| **Acquired pure red cell aplasia:** ↓RBC production & absence of RBC precursors in marrow; most cases idiopathic; may be assoc w/ leukemia, MDS, thymoma, drugs (INH, VPA, mycophenolic acid), parvovirus, & autoimmune disease; reticulocytes are absent in blood; treated w/ supportive transfusions, immunosuppression |
| **Aplastic anemia:** Hematopoietic stem cell deficiency/failure → pancytopenia w/o splenomegaly → anemia + recurrent infections & bleeding; congenital (Fanconi anemia), acquired (*Meds:* chloramphenicol, sulfonamides, phenytoin, carbamazepine, VPA, indomethacin; *Infection:* parvovirus, EBV, hepatitis, HIV), & idiopathic (*Lancet* 1995;346:228); diagnosed by bone marrow biopsy; treated w/ removal of causative agent, supportive care (transfusions, abx), stem cell transplant, immunosuppression |
| **Anemias Due to Bleeding** |
| GI, menorrhagia, blood donation, hemorrhage into thigh or retroperitoneum, iatrogenic (multiple blood draws) |

## Evaluation

- **History:** Duration of sx; exertional dyspnea, fatigue, dizziness, HA, palpitations, ↓ concentration, syncope, menorrhagia, melena, hematochezia, bone pain, diet; signs of systemic disease (fevers, night sweats, anorexia, wt loss, malaise); meds (especially NSAIDS, ASA), EtOH, alt meds; pica (craving items not suitable as food), geophagia (craving clay/dirt), pagophagia (craving ice); restless leg syndrome (Fe deficiency); ethnicity (Mediterranean) & FHx of hematologic disease/malignancy or bleeding d/o; blood transfusion/donation hx; symptoms precipitated by cold exposure (cold agglutinin hemolytic anemia); *H. pylori*, PUD, celiac disease or autoimmune disease
  **Menorrhagia**: Changing pads >q3h; >21 pads/cycle, need to change pad at night (see *"Abnormal Uterine Bleeding"*) (*Am J Obstet Gynecol* 2004;190:1216)
- **Exam:** Pallor (skin, palmar creases, oral mucous membranes, nail beds, palpebral conjunctiva), tachycardia, orthostatic VS, systolic flow murmur (↑ CO), atrophic glossitis (Fe, folate, $B1_2$ def), angular cheilosis, jaundice (hemolysis), splenomegaly, koilonychia (spoon-like fingernails seen in Fe deficiency); LN exam
- **Workup:** CBC w/ diff & RBC indices, retic count, peripheral smear (*NEJM* 2005;353:498), Chem-12, FOBT; further w/u based on clinical suspicion: Iron, TIBC, ferritin, folate, $B1_2$, Hgb electrophoresis, TSH, Epo, SPEP, H. pylori, colonoscopy/EGD, ANA; referral to hematology for bone marrow biopsy if dx unclear despite above w/u
  **Reticulocyte index (RI):** Equal to reticulocyte count × (Pt Hct/nl Hct)/maturation factor; HCT dictates maturation factor; HCT 45 →

maturation factor 1, 35 → 1.5, 25 → 2, 20 → 2.5; RI >2% = appropriate BM response; RI <2 = inadequate BM response

**Screening:** USPSTF recommmends ✓ CBC in pregnant women at 1st prenatal visit (*AFP* 2006;74:464); CDC recommends ✓ CBC in premenopausal ♀ q5–10y (*MMWR Morb Mortal Wkly Rep* 1998;47:1); consider CBC q5y in asx pts >50 y & annually in pts w/ chronic disease (*Curr Med Res Op* 2006;22:385)

### Anemia Testing

| Disease | Test and Comments |
|---|---|
| Iron deficiency | Microcytosis, ↓ Fe, ↓ ferritin, ↓ transferrin sat, ↑ TIBC, ± reactive thrombocytosis; Ferritin <41 ng/mL 98% sensitive/specific (*Blood* 1997;89:1052) |
| Anemia of chronic disease | ↓ Fe, nl or ↓ TIBC, nl or ↑ ferritin, ↓ retic index |
| α- or β-thalassemia minor | Hgb electrophoresis; FHx anemia, nl or ↑ ferritin, Fe |
| $B_{12}$ or folate deficiency | Macrocytosis + neutrophil hypersegmentation (see *"Folate and Vitamin $B_{12}$ Deficiency"*) |
| Hemolysis | ↑ LDH, ↓ haptoglobin, ↑ indirect bili, ± ↑ retic; ↑ urine Hb & ↑ urine hemosiderin in intravascular hemolysis |
| Hypersplenism/bleeding | ↑ Retic count, retic index >2% w/o e/o hemolysis |
| Autoimmune hemolytic anemia (AIHA) | ⊕ *Direct Coombs:* Detects offending Ab bound to pt RBC; washed pt RBCs mixed w/ antiserum or Abs specific to Igs (Indirect Coombs: Pt serum mixed w/ nl RBC; primarily used to test for transfusion compatibility) |

## Treatment (*AFP* 2009;80:339; 2013;87:98; *Am J Med* 2008;121:943)

- **Transfusion:** Consider if Hgb <8 g/dL or if pt symptomatic (*Ann Intern Med* 2012;157:49); 1 unit packed RBC contains 200 mg iron, ↑ Hgb by 1 g/dL, & Hct by 3–4% (*Ann Intern Med* 1994;121:278)
- **Iron deficiency anemia:** Co-administration of oral iron w/ ascorbic acid or orange juice ↑ Fe absorption; Ca supplements/antacids, tea, & soy protein ↓ Fe absorption; avoid taking w/ food; Goal: Daily dose of elemental iron 150–200 mg/d; IV iron may be used for pts unable to absorb or tolerate oral iron (i.e., IBD, s/p gastric bypass, HD, profound deficiency); Tx may continue until Hgb normalizes, unless profoundly deficient & iron stores need repletion; Reticulocytosis ~1 wk after beginning PO iron repletion suggests response

  **Prevention:** Pregnant pts should take a 30 mg/d iron supplement; if Fe deficiency found then Rx a 60–120 mg supplement

  **Failure to respond:** May be due to co-morbid disease (i.e., anemia of

chronic disease, MDS, RA), $B1_2$/folate deficiency, malignancy, thalassemia, compliance issues, ↓ absorption (antacids, s/p bypass), bleeding

**Iron Repletion (*Lancet* 2007;369:1502; *NEJM* 2007;357:93)**

| | Form | Elemental Fe | Comments |
|---|---|---|---|
| Oral | Ferrous fumarate | 106 mg/tablet | Highest "concentration" of iron/tablet |
| | Ferrous sulfate | 65 mg/tablet | Least expensive |
| | Ferrous gluconate | 28–38 mg/tablet | ↑ GI tolerance due to ↓ Fe, but more pills/d |
| | Ferrous sulfate elixir | 44 mg/5 mL | Better GI tolerance than sulfate tablet |
| | Carbonyl iron | 45–60 mg/tablet | Elemental iron in microscopic spheres→ ↑ GI tolerance |
| | Heme iron polypeptide | 28 mg/tablet | May be combined w/ iron polysaccharide (Feosol Complete w/ Bifera); unlike elemental iron, heme iron may be taken w/ or w/o food; ↑ GI tolerance |
| IV | Iron sucrose | 200 mg/ infusion | Equal in safety (*Nephrol Dial Transplant* 2006;21:378); test dose not necessary *unless* pt has reacted previously to iron dextran |
| | Ferric gluconate | 125 mg/ infusion | |
| | Ferumoxytol | 510 mg (max) | Rapidly given (30 mg/s); used in HD |
| | Iron dextran | 50 mg/mL | Highest rate of local or systemic s/e (4.7%), & anaphylactic reactions (1%) (*Am J Kid Dis* 1999;33:464); requires 25 mg test dose |

- **Anemia of chronic disease:** Treat underlying condition; may coincide w/ iron deficiency anemia, which should be treated; see *"Chronic Kidney Disease"* for mgmt in CKD
- **Hemolytic anemias:** Managed in conjunction w/hematology
  **Immune:** D/c culprit drug; **Warm agglutinins:** Steroids; Immunosuppression, cytotoxic meds, IvIg; Splenectomy in severe cases (*Am J Hematol* 2002;69:258); **Cold agglutinins:** Avoidance of cold, cytotoxic agents, rituximab, plasmapheresis in sev cases (*Br J Haematol* 2011;153:309)
  **G6PD deficiency:** D/c culprit drug; folate supplementation
  **Hereditary spherocytosis:** Folate; transfusion w/ iron overload Ppx; splenectomy
  **Thalassemia major:** Transfusion w/ iron overload Ppx & folate; manage endocrinopathies, osteopenia; **Minor:** Preconception

genetic counseling

- **Patient information:** *AFP* 2000;62:2265; *JAMA* 2012;307:2448

# FOLATE & VITAMIN $B1_2$ DEFICIENCY

## Background (*Blood* 2008;112:2214; *J Nutr* 1999;129:779; *Neurology* 1995;45:1435; *NEJM* 2013;368:149)

- **Epidemiology:** Prevalence of $B1_2$ deficiency = 5–400/10,000 people; more common in the elderly & in pts of African/European ancestry; folate deficiency mainly found in pts >65 y (5–10% prevalence) (*Age Ageing* 2004;33:34) & in alcoholics

### Vitamin $B1_2$ vs Folate Deficiency

| $B_{12}$ Deficiency | Folate Deficiency |
|---|---|
| 2 µg/d RDA, 2–5 mg body stores | 400 µg/d RDA (600 µg/d in pregnant ♀, 500 µg/d in lactating ♀); 5–10 mg in body stores |
| Deficiency takes years to develop | Deficiency takes 4–5 mos |
| Absorbed in terminal ileum | Absorbed in jejunum |
| ↑ Homocysteine & ↑ MMA | Only homocysteine elevated |
| Found exclusively in animal products | Found in animal products & leafy vegetables |
| Develops mainly due to malabsorption | Develops mainly due to malnutrition/EtOH |
| Megaloblastic anemia | Megaloblastic anemia |
| Neurologic changes may be present | Neurologic changes absent |

- **Pathophysiology of B12 deficiency:** $B1_2$ (cobalamin) is a cofactor for conversion of homocysteine to methionine; deficiency ↑ homocysteine (cytotoxic), ↓ methionine (neurotoxic), ↓ tetrahydrofolate (↓ DNA synthesis → delayed RBC maturation → megaloblastic anemia); Cyanocobalamin is a prodrug of cobalamin; $B1_2$ absorption requires: (1) Adequate intake, (2) Gastric acid & pepsin to release $B1_2$ from protein & allow it to bind R factor, (3) Pancreatic proteases release $B1_2$ from R factors, (4) Intrinsic factor (IF) to bind $B1_2$, (5) Functional $B1_2$-IF receptors to facilitate ileal uptake

  **"Pernicious anemia":** Loss of IF due to IF Ab & autoimmune atrophic gastritis → destruction of parietal cells (which secrete IF)

by Ab; present in up to 2% of pts >60 y (*NEJM* 1997;337:1441); most common cause of severe $B1_2$ deficiency

**Risk factors:** Vegetarian diet during pregnancy, strict vegans, tropical sprue, gastrectomy, chronic gastritis, HIV, chronic antibiotic use → bacterial overgrowth, PPI/antacid/H2 blocker use, metformin, EtOH abuse, bariatric surgery, Sjögren

- **Pathophysiology of folate deficiency:** Inadequate intake or EtOH (↓ absorption); folate (**Vit B9**) is the naturally occurring form; folic acid is the therapeutic Vit

  **Risk factors:** Conditions that ↑ folate demand (i.e., pregnancy, hemolytic anemia, sev dermatitis) or meds that interfere w/ metabolism (trimethoprim, pyrimethamine, methotrexate, phenytoin); eating d/o, depression → malnutrition; ↓ absorption in celiac disease, IBD, short bowel syndrome, gastric bypass

  **Neural tube defects:** Folic acid supplementation ↓ incidence of NTDs

## Evaluation (*NEJM* 2013;368:149)

- **History:** Sx of anemia (see *"Anemia"*) or of pancytopenia in severe cases; symmetric paresthesias, numbness, gait instability, memory loss, personality or MS Δ (found only in $B1_2$ deficiency); *malabsorption* (wt loss, diarrhea); *blood clots*, including cerebral venous sinus due to ↑ homocysteine; *diet:* screen for eating d/o & depression which can lead to poor PO intake; *medications; GI hx:* gastritis, gastrectomy, Crohn's, intestinal surgery, pancreatitis, IBD; EtOH; *autoimmune disease:* DM1, thyroid, vitiligo
- **Exam:** Wt; prematurely graying hair; glossitis; gait, peripheral sensation (including vibratory/position sense; check Romberg), motor strength; MMSE, depression screen; pallor, vitiligo, hyperpigmentation; vaginal atrophy

**Common Tests Used to Assess $B1_2$ and Folate Deficiency** ( *J Clin Pathol* 2003;56:924)

| |
|---|
| **$B_{12}$ levels:** <200 pg/mL = likely deficiency (Se/Sp = 65–95%/50–60%), >350 pg/mL = nl; falsely ↓ in pregnancy, OCP use, MM, folate deficiency, excessive Vit C intake; falsely ↑ in liver disease, myeloproliferative d/o; cannot r/o deficiency on basis of a nl $B_{12}$ level alone if clinical suspicion high; **measure before treating folate deficiency** |
| **Folate levels:** >4 ng/mL = nl; serum folate represents short-term folate balance, may be influenced by eating, & is a good initial screening test; RBC folate representative of tissue stores & is useful for pts w/ borderline serum folate/suspected folate + $B_{12}$ deficiency |
| **Methylmalonic acid and homocysteine:** Both ↑ in $B_{12}$ deficiency (Se 94%, Sp 99%) (*Am J Med* 1994;96:239); nl MMA & ↑ homocysteine suggestive of folate deficiency (Se 86%, Sp 99%); if both MMA & homocysteine are nl then $B_{12}$ & folate deficiency unlikely; useful for intermed $B_{12}$ (200–350 pg/mL) or folate values, or pt has a condition that falsely ↑ or ↓ $B_{12}$ levels, but clinical picture consistent w/ deficiency; measure *before* $B_{12}$ repletion; Homocysteine ↑ w/ nl MMA suggestive of folate deficiency, renal disease, or homocystinuria; MMA falsely ↑ in renal failure |
| **Anti-intrinsic factor antibody:** Sens 60–70% for pernicious anemia, Sp >95%; anti-parietal cell Ab ↑ Se but ↓ Sp, limiting use; has supplanted Schilling test in dx of pernicious anemia |

- **Workup:** Serum $B1_2$ & folate (& RBC folate if serum folate borderline), CBC w/ diff, MCV, peripheral smear (hypersegmented neutrophils), reticulocyte count, anemia w/u if anemic (see *"Anemia"*)

## Treatment (*AFP* 2011;83:1425; *Blood* 2008;112:2214; *Cochrane* 2005;20:CD004655)

- **B12 repletion:** *Asx:* Cobalamin 1 mg PO QD until serum level normalizes; *Symptomatic:* 1 mg IM QD × 7 d then weekly × 4 wks; prompt recognition & tx needed to prevent permanent neuro damage; neuro recovery may take 1.5–3 mos if sx due to $B1_2$ deficiency

  **Maintenance:** 1 mg PO QD or 1 mg IM monthly (if neuro symptoms → 2×/mo × 6 mo, then monthly); indefinite IM tx may be needed for pts permanently unable to absorb $B1_2$ (i.e., as in pernicious anemia, gastrectomy, bariatric surgery)

  **Monitoring:** CBC 1–2 mos after tx starts (anemia normalizes in ~6–8 wks), then q6–12mos; follow $K^+$ in severely $B1_2$ deficient pts as ↑↑ BM erythropoiesis may lead to ↓ K +
- **Pernicious anemia:** IM $B1_2$ due to poor GI absorption to correct initial deficiency; maintenance IM $B1_2$ or high dose oral (i.e., 1–2 mg/d) may be used; ✓ TFTs since thyroid disease often present; chronic atrophic gastritis due to pernicious anemia assoc w/ ↑ risk of gastric CA, carcinoid; age-appropriate CA screening; American Society for GI Endoscopy recommends 1× EGD to confirm dx & r/o CA/carcinoid,

consensus lacking

- **Folate deficiency:** Oral folate 1 mg PO QD until Hct/Hb normalizes on CBC; test for $B1_2$ deficiency prior to folate supplementation
- **Bacterial overgrowth:** Poor movement of stool → ↑↑ bacteria; may be 2/2 to IBS, diverticulosis, dysmotility (i.e., narcotics); treat bacterial overgrowth w/ abx (rifaximin, norfloxacin) & restore motility (i.e., d/c offending medication, or Rx metoclopramide)
- **Tropical sprue:** Found in warm-climate developing countries; toxins from bacterial overgrowth/gastroenteritis → small bowel damage → Vit malabsorption; ✓ stool cx; Rx appropriate abx/anthelminthic + folic acid + $B1_2$ (if deficient) (*Dig Dis* 2007;25:237)
- **Prevention:** $B1_2$ supplementation in vegetarians, pregnant & breastfeeding ♀, pts who have had bariatric or other major intestinal surgery; nitrous oxide irreversibly oxidizes the cobalt in cobalamin & may precipitate altered mental status in pts deficient at baseline (*Neurology* 1995;45:1435); initiate folic acid supplementation (i.e., prenatal vitamins w/ 0.4–0.8 mg QD) 1 mo prior to conception in ♀ planning to become pregnant; continue through 1st trimester (*Am J Clin Nutr* 2006;83:993); folic acid supplementation neither ↑ nor ↓ risk of CA

# BLEEDING DISORDERS

## Background (*AFP* 2009;80:1261; *Mayo Clin Proc* 2002;77:181; *NEJM* 2009;361:1887)

- **Etiology:** A bleeding disorder may be due to abnormalities in the coagulation cascade, PLT (see *"Platelet Disorders"*), blood vessels, or fibrinolysis

### Distinguishing Features of Bleeding Disorders

| Symptoms | Platelet Disorders | Coagulation Disorders |
|---|---|---|
| Location | Mucosal/cutaneous (oral, nasal, GI, GU) | Deep tissue (muscle & joints = hemarthroses) |
| Bleeding after trauma | Immediate | Delayed |
| Petechiae | Common | Rare |
| Ecchymoses | Small, superficial | Large SC/soft tissue |

- **von Willebrand disease:** Most common inherited bleeding d/o (prevalence ~1%, ♂:♀ 7:3) 2° to deficiency or dysfunction of vWF which binds PLTs to endothelium → PLT & clotting defect; vWF binds factor VIII & protects it from proteolysis; common cause of unexplained menorrhagia
  **Type 1:** Autosomal dominant (60–80% cases); mild to mod quantitative deficiency of vWF & factor VIII
  **Type 2:** Autosomal dominant or recessive (10–30% cases), 4 subtypes of qualitative vWF abnormalities
  **Type 3:** Sev (1–5% cases), autosomal recessive; sev or complete vWF deficiency & mod to severe VIII deficiency
  **Acquired:** Rarely caused by Ab to or destruction of vWF in myeloma, lymphoma, CML, CLL, uremia, autoimmune dz (hypothyroidism, SLE), ET, valvular heart dz, drugs
- **Liver disease:** ↑ Bleeding risk (2/2 to ↓ coag factor synthesis, ↓ PLT (splenic sequestration, ↓ Tpo) & ↑ clotting risk (↓ synthesis of protein C, S, antithrombin) (*NEJM* 2011;365:147)
- **Hemophilia:** Factor VIII deficiency (type A), factor IX deficiency (type B, Christmas disease); X-linked recessive w/ bleeding in joints, muscles, GI tract; highly variable phenotype depending on factor level

## Evaluation (*AFP* 2008;77:1117; *NEJM* 2008;359:938)

- **History:** Bleeding after surgery, dental work, minor trauma, childbirth, epistaxis (>10 mins), menorrhagia, anemia, melena, BRBPR; FHx bleeding; hx transfusion; medications (esp abx, ASA, NSAIDs, steroids, SSRIs + ASA/clopidogrel, warfarin)
- **Exam:** Purpura (purple or red patches/spots caused by bleeding, typically from broken/injured capillaries), petechiae (small purpura, typically 1–3 mm, may appear pinpoint), ecchymosis (large purpura = bruise); LAN, splenomegaly
- **Workup:** Peripheral smear (*NEJM* 2005;353:498); Fibrinogen, factor VIII, vWF Ag, vWF activity (ristocetin cofactor activity); coags (below); referral to hematology for further classification testing if vWF Ag & activity suggest vWD
  **Prothrombin time (PT):** Measures extrinsic (factor VII,

thromboplastin [tissue factor]) & common pathways (prothrombin [factor II], factors V, X, fibrinogen); **INR** = Pt PT ÷ control PT

**Activated partial thromboplastin time aPTT:** Measures intrinsic (VIII, IX, XI, XII) & common pathways

**Mixing studies:** Combine pt & nl plasma to identify factor deficiencies & inhibitors

**Thrombin time:** Measures conversion of fibrinogen to fibrin & clot formation by thrombin

**Expected Lab Values in Selected Bleeding Disorders**

| Diagnosis | PT | aPTT | [Platelet] |
|---|---|---|---|
| Prothrombin, fibrinogen, factor V or X deficiency, liver dz, severe Vit K deficiency | ↑ | ↑ | Nl |
| Factor VII or mild vit K deficiency, liver disease, warfarin | ↑ | Nl | Nl |
| Hemophilia A or B, vWD, factor XI, XII deficiency | Nl | ↑ | Nl* |
| Vasculopathies, connective tissue dz, collagen d/o, PLT dysfunction, scurvy, steroid-induced purpura, vasculitis | Nl | Nl | Nl |

*PLT count may be low in type 2B vWD

## Treatment (*Blood* 2009;114:1158; *NEJM* 2004;351:683)

- **von Willebrand disease:** Hematology referral; aminocaproic acid or tranexamic acid may be used orally or topically for mild mucous membrane bleeding (dental work, menorrhagia); topical thrombin for epistaxis or gingival bleeding; Desmopressin (dDAVP, promotes vWF release from endothelial cells), Factor VIII/vWF concentrate; combined OCPs or levonorgestrel IUD for pts w/ menorrhagia; consider family eval/screening
- **Hemophilia:** Comprehensive care at a designated hemophilia center (cdc.gov/ncbddd/hemophilia/htc.html)
- **Patient information:** *AFP* 2009;80:1269; *JAMA* 2012;308:1492

# DVT AND PULMONARY EMBOLUS

## Evaluation (*AFP* 2012;86:913; *NEJM* 2003;349:1227; 2008;358:1037; 2010;363:266)

- **Differential diagnosis of deep vein thrombosis:** Varicose veins, superficial thrombophlebitis, muscle strain, cellulitis, lymphedema, Baker cyst (see "*Chest Pain*" for Ddx of PE)

- **History:** Edema, calf/thigh pain, venous distention, dyspnea, pleuritic CP, cough, hemoptysis, syncope, orthopnea or asx; hx previous thrombosis; OCP or tamoxifen use; fetal losses; cancer hx, including compliance w/ CA screening; pregnancy; FHx DVT/PE, cancer (*Am J Med* 2007;120:871)
- **Exam: DVT:** Edema, redness, warmth, palpable cord, ⊕ Homans sign (calf pain w/ passive foot dorsiflexion), difference in calf diameter; **PE:** Tachypnea, **tachycardia,** ↓ $O_2$, rales, pleural rub, ↑ JVP, fever; stool guaiac prior to any anticoagulation
- **Workup:** D-dimer (96–99% NPV in pts w/ low-intermed pretest probability) & PE-CT or LE U/S as below; Se of LE U/S 94% (proximal DVT), 63% (distal DVT), Sp 94% (both); if clinical suspicion for DVT is high & LE U/S ⊖, repeat in 5–7 d or ✓ MRV (nearly 100% sensitive); ✓ ECG, coags, CBC w/ diff, Chem-12, UA (nephrotic syndrome); V:Q scan in pts who are morbidly obese, have CKD, or cannot undergo PE-CT

  **Hypercoagulability workup:** Controversial (*JAMA* 2005;293:2352); consider in idiopathic VTE, FHx VTE, recurrent pregnancy loss, recurrent VTE; Factor V Leiden & prothrombin gene mutations, antiphospholipid antibodies (IgG, IgM), & UA (nephrotic syndrome) may be checked during anticoagulation; Antithrombin, factor VIII, lupus anticoagulant, proteins C/S affected by anticoagulation or acute thrombosis → check once DVT resolves & pt off anticoagulation; role of homocysteine screening unclear

  **Malignancy workup:** Pts w/ unprovoked VTE should be current w/ routine cancer screening (see *"Disease Screening," "Prostate Cancer"*), be carefully asked about FHx of CA, & be followed closely; prevalence of occult CA 6% at time of VTE dx & 10% 12 mos after (*Ann Intern Med* 2008;149:323); aggressive w/u not cost-effective & has unclear effect on outcome (*NEJM* 1998;338:1169)

  **Dx of PE in pregnant pts:** Consider LE U/S 1st then CXR to r/o other causes (*NEJM* 2008;359:2025); Spiral CT has ↓ fetal radiation compared to V:Q scan (*AFP* 2008;77:1709)

**Wells Criteria in VTE Disease**

| For DVT (points) | For PE (points) |
|---|---|
| Entire leg swollen (1) (*JAMA* 2006;295:199) | Clinical sx of DVT (3) (*JAMA* 2006;295:172) |
| Asymmetric swelling ≥3 cm (1) | Other dx less likely than PE (3) |
| Immobilization of leg (1) | HR >100 (1.5) |
| Bedridden >3 d or recent (1 mo) surgery (1) | Immobilization ≥3 d or surgery in previous 4 wks (1.5) |
| Tenderness along venous system (1) | |
| Pitting edema (1) | Hx DVT/PE (1.5) |
| Active malignancy (1) | Hemoptysis (1) |
| Collateral superficial vein (1) | Malignancy (1) |
| Alt dx more likely (subtract 2 points) | **PE unlikely (≤4 points):** D-dimer ⊖ or <500 ng/mL: PE effectively ruled-out<br>D-dimer ⊕ or ≥500 ng/mL → ✓ PE-CT<br>**PE likely (>4 points):** ✓ PE-CT |
| **Low (0 points) & mod (1–2 points) risk:** D-dimer ⊖: DVT r/o; D-dimer ⊕ → ✓ LE U/S<br>**High risk (≥3 points):** ✓ LE U/S | |

## Management (*AFP* 2011;83:293; 2013;87:556; *Ann Intern Med* 2007;146:204; 2008;149:ITC3–1; *Chest* 2012;141:e419S; *JAMA* 2011;305:1336; *Lancet* 2010;375:500; *Mayo Clin Proc* 2013;88:495)

- **Outpatient management of PE/DVT:** In reliable pts w/ good social support, no $O_2$ requirement, nl VS, no hx bleeding or serious comorbid disease (esp CKD); scoring systems available to guide pt selection for outpt PE tx (*Lancet* 2011;378:41)
- **Duration of VTE treatment:** 1st episode of a provoked VTE (i.e., surgery, immobilization) or unprovoked *distal* DVT (i.e., calf): 3 mos; 1st episode of an unprovoked proximal DVT (i.e., popliteal, femoral, iliac) or PE & recurrent VTE: 3 mos then reassess risk/benefit of bleeding vs. recurrent VTE: Pts w/ low risk of bleeding → indefinite anticoagulation; mod risk → shared decision-making; High → 3 mos total

  **Bleeding risk:** Various scoring systems reported, but none more effective than provider subjective assessment (*Am J Med* 2012;125:1095); risk factors for bleeding include age >75 y, hx GIB or ICH, CKD, hepatic disease, antiplatelet Rx, hx supratherapeutic INR

  **Cancer pts:** Indefinite (metastatic) or until the patient is cancer-free

  **Compression stockings:** 30–40 mmHg prevent post-thrombotic syndrome after DVT

  **D-dimer testing:** Pts w/ 1st unprovoked PE or proximal DVT & an abnl D-dimer 1 mo after discontinuation of warfarin had ↑ risk of recurrent VTE (15% vs. 6%) compared to pts w/ a nl D-dimer

(PROLONG, *NEJM* 2006;355:1780)

**Aspirin:** 100 mg PO QD ↓ risk of recurrent VTE in pts w/ a 1st unprovoked VTE who stopped anticoagulation (6% vs. 11%) compared to placebo w/o ↑ risk of major bleeding (WARFASA, *NEJM* 2012;366:1959)

**Repeat U/S:** Pts w/ 1st proximal DVT & residual thrombus after 3 mos of anticoagulation who received continued anticoagulation had ↓ rate of recurrent VTE (12% vs. 17%) & ↑ major bleeding (1.5% vs. 0.7%) compared to pts who received fixed-duration anticoagulation (*Ann Intern Med* 2009;150:577)

### Anticoagulant Dose & Monitoring Reversal/Contraindications/Notes

| Drug | Notes | Reversal |
|---|---|---|
| **Warfarin** (INR goal 2–3) *Review pt med list for drugs that interfere w/ warfarin; Diarrhea, fever may potentiate anticoagulation* | Initial: 5 mg PO then dose by INR; use lower starting doses in elderly<br>Requires bridge for 5 d + INR 2–3 for >24–48 h<br>Referral to anticoagulation monitoring service (↓ complications, ↑ time in therapeutic range) | Asx: INR <4.5: Lower or hold dose, ↑ freq of monitoring, resume at lower dose once in range<br>INR 4.5–10: Hold 1–2 dose(s), ↑ freq of monitoring, resume at lower dose once in range<br>INR >10: Vit K<br>INR >20 or bleeding → ER |
| **Dalteparin** or **enoxaparin** (LMWH) *Superior to warfarin for VTE in CA* (*Arch Intern Med* 2002;162:1729; CLOT, *NEJM* 2003;349:146) | Dalteparin: 100 U/kg q12h or 200 U/kg QD<br>Enoxaparin: 1 mg/kg q12h (preferred in CA, extensive clot, obese) or 1.5 mg/kg QD<br>Anti-Xa not required unless wt <50 kg or >150 kg or in pregnancy | Protamine reverses<br>Contraindications: CrCl <30, HIT<br>Relative contraindications: Wt <50 kg or >150 kg<br>Preferred for outpt anticoagulation in pregnant pts |
| **Fondaparinux** (Synthetic Xa inhibitor) | <50 kg → 5 mg QD<br>50–100 kg → 7.5 mg QD<br>>100 kg → 10 mg QD; no monitoring required | No antidote<br>Contraindicated in bacterial endocarditis (↑ risk ICH), wt <50 kg, CrCl <30; Safe in HIT |
| **Rivaroxaban** (Factor Xa inhibitor) *FDA approved for DVT & PE* | 15 mg BID × 3 wks → 20 mg PO QD noninferior to enoxaparin → warfarin in acute PE, w/ ↓ bleeding (EINSTEIN-PE, *NEJM* 2012;366:1287) | CrCl 30–49: 15 mg daily<br>Contraindicated in pregnancy, hepatic impairment, CrCl <30; unlike warfarin, single missed dose → subtherapeutic anticoagulation |

- **Patient information:** *JAMA* 2012;308:2531

# HEMOCHROMATOSIS

## Background (*AFP* 2013;87:183; *BMJ* 2011;342:c7251; *Clin Pathol* 2011;64:287)

- **Genetics:** Autosomal recessive syndrome of ↑ iron absorption → iron overload + organ damage; penetrance (symptomatic hemochromatosis) is variable, ranging from 1–28% in homozygous ♂ & ~1% in homozygous ♀ likely due to the protective effect of iron loss w/ menstruation (*Lancet* 2002;359:211; *NEJM* 2008;358:221)
  *HFE C282Y mutation:* Missense mutation found in 70–90% of pts w/ hemochromatosis
  **Other:** *HFE* C282Y/H63D compound heterozygotes (3–5%), H63D homozygotes (1%)
- **Epidemiology:** Caucasians: 10% heterozygotes, 0.5% homozygotes (*JAMA* 2001;285:2216; *NEJM* 1988;318:1355); **most common genetic disease in Caucasians;** presents at age 40–50 y, w/ later onset in ♀ due to iron loss w/ menstruation; age of symptomatic onset related to gradual accumulation of iron to toxic levels over decades (*WJM* 1995;162:370); ♀ who have early menopause (i.e., due to hysterectomy or prolonged OCP use) may present earlier
- **Pathophysiology:** Normally, ~1–2 mg iron absorbed from diet balance losses in GI tract, skin, menses, & sweat; iron stores regulated by absorption as no excretion mechanism exists; ↓ hepcidin expression due to *HFE* mutations → ↑ iron absorption

### Consequences of Iron Overload (Rare in Heterozygotes)

| |
|---|
| **Liver:** 20–220-fold ↑ in HCC (*Gastroenterology* 2003;125:1733; *NEJM* 1985;313:1256); Cirrhosis (esp if pts consume >30–60 g EtOH/d), hepatomegaly, abnl LFTs; C282Y homozygotes w/ ferritin >1000 µg/L have a 20–45% risk of developing cirrhosis, while pts w/ ferritin <1000 µg/L have a 0–2% risk (*Hepatology* 2011;54:328) |
| **Endocrine:** DM2 due to iron accumulation in pancreas; hypogonadism (impotence in ♂, amenorrhea in ♀, ↓ muscle & bone mass) due to pituitary iron overload; hypothyroidism |
| **Rheumatology:** Excess iron in joints → inflammation & calcium crystal formation; Arthropathy, esp in 2nd & 3rd MCP joints & wrists; osteoporosis |
| **Cardiovascular:** CMP/CHF due to iron accumulation; Arrhythmias (SSS, AF) |
| **Dermatology:** "Bronze" hyperpigmentation due to melanin/iron deposition |

- **Differential diagnosis:** Iron overload anemias due to chronic transfusion, hemolytic anemias, liver disease (HepC, NASH, EtOH), dialysis, α1-antitrypsin deficiency, aceruloplasminemia, porphyria, African iron overload (due to consumption of iron-rich beer)

## Evaluation (*Gastroenterology* 2010;139:393; *Hepatology* 2011;54:328; *NEJM* 2012;366:348)

- **History:** Weakness, impotence, joint pain, fatigue; most pts asx
- **Exam:** Skin exam, palpation of liver, spleen
- **Workup:** CBC, LFTs, ECG, AFP, A1c, stool guaiac if anemic (GIB due to varices), EGD if cirrhotic to screen for varices; hepatitis serologies if risk factors present; TTE if cardiac sx
  - **Iron studies:** Transferrin saturation ([serum iron], μmol/L/TIBC, g/L) ≥50% in ♀ or ≥60% in ♂ and/or ferritin >200 ng/mL in ♀ & >300 ng/mL in ♂ prompt suspicion for hemochromatosis (*Lancet* 1997;349:73); American Association for the Study of Liver Disease (AASLD) advocates cutoff transferrin saturation >45% in ♀ & ♂; transferrin saturation <45% w/ nl ferritin is 97% specific to r/o hemochromatosis (*AFP* 2013;87:183)
  - **Other causes of ≠ ferritin:** EtOH, HIV, **inflammation**, malignancy, metabolic syndrome, hepatitis, autoimmune disease, renal insufficiency
  - **Gene testing:** Indicated in pts whom hemochromatosis is suspected when transferrin saturation >45% *or* ferritin is abnormally ↑ w/o explanation; *HFE* C282Y & H63D most common; if these are nl & hemochromatosis still suspected, ✓ liver MRI or bx; high liver iron suggests rare hemochromatosis mutations → refer to geneticist for specialized testing; nl liver iron suggests inflammation or other iron loading anemias (i.e., thalassemia, sideroblastic anemia, hemolytic anemia, aplastic anemia); *HFE* heterozygotes w/ ↑↑ ferritin should be tested for mutations found in type II–IV hemochromatosis & consider liver bx if these are ⊖ (*NEJM* 2004;350:23)
  - **Liver bx:** Consider if pt is >40 y & has ↑ LFTs or ferritin >1000 ng/mL
  - **Liver MRI:** Useful in pts who test ⊖ for *HFE* mutations but have clinical/lab signs of iron overload disease (*Best Pract Res Clin Gastroenterol* 2009;23:171); may help quantify hepatic Fe concentration
- **Screening:**
  - **General population:** USPSTF & AAFP recommend *against* screening asx individuals; ACP concluded there was insufficient evidence to

make a recommendation (*Ann Intern Med* 2005;143:517; 2006;145:204)

**First-degree relatives of hemochromatosis pts:** ✓ Fasting transferrin saturation, ferritin level, & *HFE* mutation (if proband has an *HFE* mutation); ~50% of ♂ relatives & 10% of first-degree ♀ relatives who are also homozygotes for hemochromatosis have disease-related conditions (*NEJM* 2000;343:1529); probands who are symptomatic are likely to have relatives who become symptomatic, which is why screening is recommended

**DM2:** Screening not recommended since incidence of hemochromatosis not enriched in pt populations w/ DM2 (*J Lab Clin Med* 2000;135:170)

**Pts w/ liver disease:** AASLD recommends all pts w/ liver disease be evaluated for hemochromatosis (*Hepatology* 2011;54:328)

- **Prognosis:** Nl life expectancy in pts who do not develop cirrhosis or DM2 (*Gastroenterology* 1996;110:1107); men homozygous for C282Y mutation & w/ ferritin >1000 µg/L more likely to have sx or liver disease (*NEJM* 2008;358:221); tx may reverse cirrhosis, cardiac dysfunction, hypogonadism, & varices

## Treatment (Ann Intern Med 1998;129:932; Blood 2010;116:317; Hepatology 2011;54:328)

- **Observation:** Appropriate for asx pts w/ ferritin <1000 µg/L; F/u includes annual H&P, iron studies; these pts should be especially encouraged to donate blood; screen for hepatocellular CA w/ U/S ± AFP q6mos (*Hepatology* 2011;53:1020)
- **Indications to treat:** Sx and/or end-organ damage; consider in asx pts w/ ferritin >1000 µg/L; consider in pts at risk for liver disease (EtOH, obesity, hepatitis), regardless of ferritin
- **Phlebotomy:** 500 mL of blood contains 200–250 mg iron & removal will ↓ ferritin by 30 ng/mL (*AFP* 2013;87:183); Hb & Hct should remain >80% of baseline level during phlebotomy; ✓ Ferritin q3mos

  **Schedule:** Remove 1 U q1–2wks until ferritin <50–150 µg/L, transferrin saturation <30–50%; it may take 1–3 y of weekly phlebotomy to achieve this; time to achieve nl iron levels may be estimated: (pt ferritin – 150)/30 = # of phlebotomy sessions needed; lifelong maintenance phlebotomy q2–6mos to target ferritin 50–300 µg/L (optimal level unclear) (*Best Pract Res Clin*

*Gastroenterol* 2009;23:171)

**Blood donation:** Centers that accept blood from hemochromatosis pts may be found at hemochromatosis.org; this may be alternative to phlebotomy in provider's office if ferritin & transferrin saturation closely monitored by supervising MD

**Impact of phlebotomy:** In asx pts, phlebotomy may prevent complications of iron overload; phlebotomy improves fatigue, arthralgias, skin hyperpigmentation, normalize LFTs, & ↓ hepatomegaly/RUQ pain; not effective at restoring pituitary/thyroid function, lowering the risk of liver CA or infection; may improve CMP, cirrhosis (rarely), & DM (*Ann Intern Med* 1998;129:932)

- **Diet:** Avoid iron & Vit C supplements (contributes to oxidant damage, iron mobilization) (*Ann Intern Med* 1999;131:475), uncooked seafood (*V. vulnificus* infection), & EtOH (due to risk of cirrhosis) (*Gastroenterology* 2002;122:281); o/w no restrictions
- **Heterozygotes:** Most never come to medical attention; observe w/ annual ferritin levels w/ tx implemented if signs of iron overload develop (*NEJM* 2004;350:23)
- **Patient information:** hemochromatosis.org, irondisorders.org, americanhs.org

# LYMPHADENOPATHY & SPLENIC DISORDERS

## Background (*AFP* 1998;58:1313; 2002;66:2103; *Hematol Oncol Clin N Am* 2012;26:395)

- **Definitions:** >600 lymph nodes exist; malignancy found in 1.1% of pts w/ unexplained LAN in primary care; risk ↑ w/ age (*J Fam Pract* 1988;27:373); risk of malignancy or granulomatous disease 0% if LN <1 cm, 8% 1–2.25 cm, 38% >2.25 cm (*Semin Oncology* 1993;20:570)

**Lymphadenopathy (LAN):** >2 cm inguinal, >5 mm epitrochlear, any palpable supraclavicular/iliac/popliteal LN, & >1 cm for all others; inguinal & cervical LN often palpable in healthy pts; **Generalized LAN:** ≥2 LN regions

**Lymphangitis: Inflammation** of lymphatics, typically presenting w/ red streaks from a wound toward the nearest LN; typically caused by *S. pyogenes*

**Lymphadenitis:** Inflammation of a LN which may be enlarged, red, or tender

**Splenomegaly:** Greatest dimension >11–13 cm; size of spleen proportional to ht; up to 3% of healthy college students have splenomegaly (*JAMA* 1993;270:2218)

- **Asplenia/hyposplenism:** The spleen phagocytoses bacteria & senescent RBC, & produces IgM Ab against encapsulated bacteria (*S. pneumoniae*, *N. meningitidis*, & *H. influenzae* type b); assoc w/ ↑ prevalence of infection (3.2%) & mortality (1.4%), usually due to fulminant *Streptococcal* sepsis in a 7 y obsv study (*J Infect* 2001;43:182)

  **Hyposplenism:** Caused by sickle cell, IBD, celiac disease, Whipple disease, hepatitis, EtOH, cirrhosis, BMT, leukemia, myeloproliferative disease, autoimmune disease, HIV, high-dose steroids, thrombosis of splenic vasculature, TPN, amyloidosis; dx by ↓ spleen size, Howell–Jolly bodies (erythrocytes w/ nuclear remnants) on smear (*Lancet* 2011;378:86)

## Evaluation (*AFP* 1998;58:1313; 2002;66:2103)

- **History:** Duration, fatigue, infections, easy bruising, pruritus, new/changing skin lesion or rash, joint pain, weakness, *exposures:* travel, sick contacts, pets, rabbits (Tularemia), cats (cat scratch disease); EtOH, allergies, IVDU, sexual behavior, meds, ingestion of raw or undercooked food/milk (Toxoplasma or Brucellosis), dental procedures; personal or FHx of infections, malignancy, autoimmune disease, connective tissue disease; painful LAN after EtOH (Hodgkin lymphoma)

  **Diagnostic clues:** Rate of growth (benign LAN suggested by duration <2 wks or >1 y w/o change); pain (infectious or inflammatory), B-type symptoms (fever >38°C, night sweats, >10% wt loss in previous 6 mos) → suspect lymphoma

  **Splenomegaly sx:** Early satiety, left abdominal fullness/pain, L shoulder pain

- **Exam:** Description of LN: Size, consistency (firm, rubbery, shotty, matted/confluent, tender, warm); Valsalva maneuver w/ supraclavicular palpation ↑ detection of supraclavicular LAN; skin exam to r/o melanoma; eval of dentition

**Diagnostic clues:** Rubbery LN → lymphoma; Firm, "rock hard" LN → metastatic CA; LAN can wax & wane w/ lymphoma/CLL; ∴ important to follow even after resolution

**Waldeyer ring:** Pharyngeal lymphatics formed by palatine, pharyngeal, & lingual tonsils

**Examination of the spleen:** Wide inter-observer variability; nl-sized spleen typically difficult to palpate; Splenomegaly may be detected by percussion of Traube space (formed by the 6th rib, midaxillary line, & left costal margin w/ the pt supine); tympanic/resonant percussion is nl due to the lung or gastric bubble while splenomegaly is suspected by dull sounds; percussion Se/Sp ↑ when pt is nonobese & has not recently eaten (*JAMA* 1993;270:2218)

- **Workup:** *Directed by clinical hx:* CBC w/ diff, peripheral smear, Chem-12, HIV, CMV (PCR & IgM), EBV serologies, HepB, LDH, CRP, ESR, RF, ANA, RPR, PPD, toxoplasma IgM, throat Cx, Lyme; CXR or CT if malignancy suspected; ultrasound/MRI may distinguish LN from other anatomic structures

  **Biopsy:** Consider in pts w/ unexplained LAN, if LN is large, rapidly growing, persistent, or o/w suspicious; select the most suspicious LN (i.e., largest, most abnl) for highest yield; bx of inguinal or axillary LN have highest likelihood of being nondiagnostic due to reactive hyperplasia; excisional bx preferred due to difficulty of diagnosing lymphoma from an FNA which does not capture enough tissue to eval LN architecture; if LN is not accessible for excisional bx then core preferred; bx of spleen generally avoided due to risk of hemorrhage

  **Flow cytometry:** Consider if LAN & lymphocytosis w/o signs of infection

## Treatment (*AFP* 1998;58:1313; 2002;66:2103)

- **Primary treatment cause-related:** Close f/u to ensure resolution

  **Empiric tx:** Steroids not recommended due to effect of glucocorticoid on LN which may complicate pathologic interpretation if bx needed; abx recommended only infection suspected

- **Lymphadenopathy of unknown etiology: Low suspicion for malignancy:** Observation ×4–8 wks

**High suspicion for malignancy or persistent enlargement:** (i.e., older age, firm or fixed LN, constitutional sx, duration >4–6 wks, supraclavicular) → bx

### Differential Diagnosis of Lymphadenopathy & Splenomegaly

| | |
|---|---|
| **Splenomegaly** (*NEJM* 2008;359:2707) | **Benign:** PV thrombosis/HTN, CHF, cirrhosis, hemolysis, chronic anemia, malaria, infection, autoimmune, CTD, sarcoid, amyloid, Gaucher/Niemann–Pick dz, thalassemia; **Malignant:** Leukemia, lymphoma, myeloproliferative d/o, metastases |
| **Generalized LAN** | **Benign:** *Infection:* viral (EBV, CMV, HIV, HHV8 [Castleman], HBV, strep), fungal, bacterial, protozoal, tick borne, toxoplasma; *autoimmune:* RA, lupus, sarcoid; *drug hypersensitivity:* allopurinol, atenolol, captopril, carbamazepine, ceph, hydralazine, indomethacin, PCN, phenytoin, primidone, pyrimethamine, quinidine, sulfonamides, sulindac, silicone; **Malignant:** Leukemia, lymphoma |
| **Head & neck** | **Benign:** URI, skin/scalp/ear/eye sinus/dental/soft tissue infection, EBV, CMV, HIV, toxoplasma, rubella, *B. henselae*, mycobacterial, CTD; **Malignant:** Head & neck CA, melanoma, lymphoma, leukemia |
| **Supraclavicular** | Most worrisome for malignancy: Left LN drains abdomen, R drains mediastinum/lungs; **Benign:** Fungal, mycobacterial, CTD; **Malignant:** *Left* (Virchow Node): Abdominal/thoracic/testicular/pelvic malignancy, breast cancer, lymphoma, leukemia; *Right:* Esophageal, lung, breast, thyroid, or laryngeal cancers, lymphoma, leukemia |
| **Epitrochlear** | **Benign:** Infection of hand/forearm, tularemia, sarcoid, 2° syphilis ("sailor's handshake"), CTD; **Malignant:** Melanoma, lymphoma, leukemia |
| **Axillary** (drains L neck, UE, lateral breast, chest wall) | **Benign:** Skin & soft tissue infection of arm, chest wall, or breast, *B. henselae*, tularemia, CTD; **Malignant:** Breast or lung cancers, melanoma, lymphoma, leukemia |
| **Inguinal** (drains genitals, perineum, lower anal canal, lower abd wall) | Drains LE, genitals, buttock, abdominal wall below umbilicus; **Benign:** STI, skin & soft tissue infection of the lower extremities; **Malignant:** Squamous cell carcinoma of the penis, vagina or vulva, melanoma, lymphoma, leukemia |
| **Thoracic** (hilar & mediastinal) | **Benign:** PNA, mycobacterial, sarcoid, CTD; **Malignant:** Lung, esophageal, breast CA, melanoma, lymphoma, leukemia |
| **Abdominal** (mesenteric & RP) | Paraumbilical LN drains abdomen (Sister Mary Joseph node) → may be sign of abdominal/pelvic CA; **Benign:** Mycobacterial, sarcoid, CTD; **Malignant:** GI & GU cancers, melanoma, lymphoma, leukemia |

(*AFP* 1998;58:1313; 2002;66:2103; *Hematol Oncol Clin N Am* 2012;26:395)

## Care of the Asplenic or Hyposplenic Patient (*Lancet* 2011;378:86)

- **Patient education:** Pts should seek medical attention *immediately* w/ any fevers or rigors

- **Prophylactic antibiotics:** Pts should be given Rx for amoxicillin–clavulanate 875 mg PO BID, levofloxacin 750 mg PO QD, or moxifloxacin 400 mg PO QD, & instructed to use if they develop fevers/rigors *in addition to promptly seeking medical attention;* role for prophylactic dental abx unclear; role for *daily* abx unclear & not supported by RCT; some groups recommend amoxicillin 250–500 mg PO QD, esp if pt has survived pneumococcal sepsis, has HIV, or is immunosuppressed post-transplant
- **Vaccines: Pneumococcal** (*both* PPSV-23 & PCV13, given 8 wks apart) preferably 2 wks before or at least 2 wks after splenectomy; PPSV-23 again after 5 y (*MMWR Morb Mortal Wkly Rep* 2012;61:816); **Meningococcal** (Menactra or Menveo if <55 y; Menomune [MPSV4] if >55 y) q5y; Menactra should not be administered w/ pneumococcal vaccine (*Ann Intern Med* 2012;156:211; *MMWR Morb Mortal Wkly Rep* 2011;60:72); **Influenza** annually, esp to prevent secondary bacterial infections; there is no contraindication to live attenuated vaccines (e.g. shingles); **Tetanus** q10y; 1-time doses of **diphtheria, *H. influenzae* type b**

# PLATELET DISORDERS

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## THROMBOCYTOSIS (*NEJM* 2004;350:1211)

### Etiology of Thrombocytosis

| | |
|---|---|
| Reactive (85%) | **Acute/chronic inflammation: Infectious** (TB, osteomyelitis), **Rheum** (RA, vasculitis, sarcoid), **IBD** (UC, Crohn); **Asplenia** (see *"Lymphadenopathy & Splenic Disorders"*), **CKD/nephrotic syndrome;** response to vigorous exercise |
| | **Nonmalignant hematologic conditions: Anemia** (iron deficiency, bleeding, acute hemolysis), **Rebound:** Following Rx of ITP, $B_{12}$ deficiency, chemo |
| | **Malignancy:** Metastatic disease, lymphoma |
| | **Tissue damage:** Surgery, trauma, burns, postexercise, acute pancreatitis, MI |
| | **Drugs:** ATRA, epinephrine, glucocorticoids, vincristine, interleukin 1-b |
| Primary (15%) | **Myeloproliferative neoplasms:** Essential thrombocytopenia, PCV, CML, CMML, refractory anemia with ring-sideroblasts assoc w/ marked thrombocytosis (RARS), primary myelofibrosis (initial state), myelodysplasia (*JAMA* 2010;303:2513); **Familial thrombocytopenia** |

- **Essential thrombocythemia:** Chronic ↑ PLT (>450K) not due to

myeloproliferative d/o or reactive thrombocytosis (dx of exclusion); assoc w/ ↑ risk of stroke, PE, DVT, retinal artery thrombosis, bleeding, & acute myeloid leukemia; ~50% of pts have a *JAK2* V617F mutation (*Blood* 2007;110:1092); Vasomotor sx may be treated w/ low dose ASA (81–100 mg); PLT counts may be ↓ w/ hydroxyurea or anagrelide Rx (*NEJM* 2005;353:33)

- **Symptoms of thrombocytosis:** HA, CP, sx assoc w/ thrombosis/bleeding, visual disturbances

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## THROMBOCYTOPENIA (*AFP* 2012;85:612)

| PLT Count | Bleeding Risk |
|---|---|
| 149–50K | Asx, no increased bleeding risk even w/ major trauma |
| 40–20K | Minimal bleeding after trauma |
| 20–10K | Major bleeding after trauma, mild spontaneous bleeding |
| <10K | Spontaneous bleeding |
| <5K | Critical spontaneous bleeding |
| Bleeding risk also depends on PLT function (ASA, uremia) & age | |
| **PLT goals:** >50K for surgery, endoscopy; >100K for neuro/ocular surgery/epidural interventions; >30–50K for dental work; goal may need to be higher if pt febrile/septic; Anticoagulation (ASA, clopidogrel, warfarin, etc.): Balance risk/benefit of anticoagulation vs. bleeding, generally >50K cutoff (*Semin Thromb Hemost* 2011;37:267) | |

### Causes of Thrombocytopenia (*JAMA* 2004;292:2263)

| | | |
|---|---|---|
| **Destruction** | **Immune-mediated**<br>**Drugs:** Heparin (HIT-II), indomethacin, thiazides, sulfonamides, quinine (Tonic water), quinidine, (comprehensive listing at ouhsc.edu/PLT)<br>**ITP** (dx of exclusion)<br>**Infection:** HIV, HCV, *H. pylori*<br>**Rheumatologic:** SLE, APLS, RA, sarcoid<br>**Neoplasm:** CML, Hodgkin, solid tumors<br>**Globulins:** IgA-deficiency, hypogammaglobulinemia | **Nonimmune-mediated**<br>**Drugs**<br>**Infection:** Sepsis, mononucleosis, CMV, HSV, RMSF, ehrlichiosis, babesiosis<br>**MAHA:** TTP, HUS, DIC, HELLP, vasculitis<br>**Others:** HELLP, DIC, TTP-HUS, giant hemangioma |
| **↓Production** | **Drugs/toxins:** EtOH, thiazides, estrogen, IFN, chemotherapy, many others; **XRT**<br>**Infection:** Sepsis, parvovirus, CMV, HSV, influenza, HIV, rubella, mononucleosis<br>**Cancer:** Leukemia, lymphoma, myeloma, CLL, myelofibrosis, myelodysplasia, CML, aplastic anemia, PNH<br>**BM infiltration:** Solid tumors, TB, osteopetrosis<br>**Nutritional deficits:** $B_{12}$ & Folate, rarely iron<br>**Hereditary:** Wiskott–Aldrich syndrome, May–Hegglin anomaly | |
| **Misc** | **Hypersplenism:** Portal HTN, hepatic/portal/splenic vein thrombosis, lymphoma, PE, myelofibrosis, sarcoidosis; Gestational; **Pseudothrombocytopenia:** Clotted specimen or EDTA-mediated PLT clumping (occurs in 0.1% healthy pts) | |

**Causes of platelet dysfunction**

| |
|---|
| ASA, NSAIDs, liver disease, uremia, multiple myeloma, Waldenström's macroglobulinemia |

- **Immune (idiopathic) thrombocytopenic purpura:** Dx of exclusion for isolated ↓ PLT (*NEJM* 2002;346:995); incidence of 1 in 10,000/y; IgG against PLT membrane proteins/megakaryocytes → ↓ production, ↑ destruction; Antiplatelet Ab testing not recommended
- **Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome:** ↓ PLT + MAHA (≥2 schistocytes on 100× HPF) of otherwise unexplained etiology ± neuro/renal dysfunction, fever (*Blood* 2010;116:4060; *NEJM* 2006;354:1927); urgent referral for plasmapheresis

## Evaluation (*NEJM* 2007;357:580)

- **History:** Mucosal bleeding (epistaxis, hematemesis, bleeding gums, hemoptysis, melena, BRBPR), menorrhagia, metrorrhagia; recent viral illnesses, diarrhea (esp bloody), new meds (including alt therapies, supplements), nutrition, B symptoms, FHx of bleeding/leukemia, cancer screening, HIV/TB risk factors; hx DVT; hx bleeding w/ minor trauma, dental work, easy bruising, blood transfusions
- **Exam:** Splenomegaly, LAN, petechiae, purpura, ecchymoses, stool guaiac
- **Workup:** Peripheral smear (*NEJM* 2005;353:498); CBC w/ diff in citrate if there is evidence of PLT clumping. PLT count of 50–100K w/o bleeding may be rechecked in 1–2 wks before further w/u; consider: Chem-12, retic, LDH, coags, D-dimer, fibrinogen, ANA, H. pylori, direct Coombs, $B1_2$/folate, HIV, HCV, Abd U/S (for splenomegaly);

  bone marrow biopsy for severe unexplained thrombocytopenia, age >60 y, multilineage involvement

## Treatment (*Blood* 2011;117:4190; *NEJM* 2003;349:903; 2011;365:734)

- **General principles:** Treat underlying disease (i.e., autoimmune, infectious)
- **Medication induced:** D/c offending med; PLT typically recover after

1–2 wks

- **Idiopathic thrombocytopenic purpura:** Tx depends on bleeding risk/hx, typically tx begun if PLT <30K or bleeding sx at dx; glucocorticoids 1st-line tx; IvIg & anti-Rh(D) are temporary tx; pts w/ persistent ↓ PLT may be treated w/ splenectomy, rituximab, or TPO agonists
- **Patient information:** *AFP* 2012;85:623

# POLYCYTHEMIA

## Background (*Ann Intern Med* 2010;152:300; *Blood* 2007;110:1092; *NEJM* 2007;356:444)

- **Definition:** ↑ RBC mass (Hgb >18.5 g/dL ♂, >16.5 g/dL ♀, or Hct >52% ♂, 48% ♀); pts w/ thalassemia trait may have ↑ RBC count w/ a nl or ↓ Hgb/Hct and/or ↓ MCV
- **Pathophysiology:** Relative polycythemia is due to ↓ plasma volume; usually asx; **2° polycythemia:** ↑ RBC mass in response to ↓ oxygen (COPD, high altitude, smoking, OSA, chronic CO exposure, R → L shunt); may also be due to Epo secretion 2/2 renal-vascular disease, renal/uterine/ovarian/cerebellar/hepatocellular CA, fibroids, renal transplant, or testosterone/anabolic steroid use

  **Polycythemia vera (PCV):** ↑ in RBC mass due to clonal expansion ± ↑ granulocytes & PLT in absence of physiologic stimulus; chronic myeloproliferative d/o due to *JAK2* gain of function mutation V617F (95–97% pts) or exon 12 mutation; *JAK2* V617F is found in ~50% of pts w/ essential thrombocytosis & myelofibrosis

## Evaluation and Prognosis (*AFP* 2004;69:2139; *Br J Haematol* 2013;160:251)

- **History:** Hx thrombosis, erythromelalgia (burning pain, erythema & swelling in extremities); hyperviscosity (HA, dizziness, tinnitus, blurred vision); bleeding (easy bruising, epistaxis, GI bleed, hemoptysis); pruritus after bathing, gout; smoking hx; occupational/home CO exposures
- **Exam:** Plethora, splenomegaly, HTN, purpura, engorged retinal veins, cyanosis, $SaO_2$ at rest & w/ activity (i.e., walking)

- **Workup:** CBC w/ diff (repeat testing to confirm ↑ RBC mass); Epo level (↑ in 2° polycythemia; ↓↓ in PCV); carboxyhemoglobin level (↑ in 2° polycythemia due to CO); *JAK2* mutation analysis; CXR if pulm disease suspected
- **Prognosis:** Relative survival (mortality assoc w/ PCV) 72% at 10 y, 46% at 20 y from dx; various prognostic indexes proposed; ↑ risk of AML, MDS, CV death, stroke

## Treatment

- **All patients:** Low-dose ASA (75–100 mg/d) unless contraindicated.
- **Secondary polycythemia:** Treat underlying cause (smoking cessation, COPD [see "*Tobacco Use*" & "*Chronic Obstructive Pulmonary Disease*"])
- **Polycythemia vera:** Hematology referral for phlebotomy (goal Hct <45%) (*NEJM* 2013;368:22) & hydroxyurea if ↑ risk thrombosis (age >60 y, hx thrombosis) or severe sx (pruritus, bone pain, wt loss, splenomegaly) (*Br J Haematol* 2005;130:174); avoid iron supplementation; allopurinol if ↑ uric acid; pruritus may be treated w/ antihistamines, avoiding hot showers & starch baths
- **Patient information:** *AFP* 2004;69:2146

# BITES AND INFESTATIONS

## Animal Bites *Clin Infect Dis* 2005;41:1373)

- **Background**: Only 20% brought to medical attention; dog bites more common; cat bites often deeper & ↑ risk of infection
- **Microbiology:** Wound infections usually polymicrobial; pathogens reflect flora of animal oral cavity (*Pasteurella* spp, *Capnocytophaga canimorsus*, anaerobes) & human skin (staph, strep)
- **Evaluation:** *History:* Timing of bite, location, depth, immunization hx
  *PMHx:* Immunocompromised, s/p splenectomy, sickle cell (functional asplenia)
  *Exam:* Wound severity, signs of local & systemic infection (fever, erythema, edema, drainage, LAD), distal neurovascular exam
  *Workup:* If severe, ✔ CBC, BCx, U/S; consider radiograph
- **Management:** Irrigate, assess for FB, consider superficial debridement; 1° closure for simple superficial lacs <12 h old w/o sx of infection; **do not close** cat bites or hand/foot wounds; referral to surgery for complex wounds & any bite affecting hands or joints; consider plastic surgery referral for facial wounds
- **Antibiotics:** Tx for clinical infection or ppx if deep puncture, on hand, near joints, or compromised host; *Choice of abx:* **Amoxicillin/clavulanate** (875/125 mg BID × 3–5 d for ppx, longer for clinical infection); alternatively doxycycline, TMP–SMX, or FQ + clindamycin (for anaerobic coverage); consider MRSA coverage if ↑ risk (e.g., known MRSA carrier, immunosuppressed), or if ⊕ purulent drainage/surrounding cellulitis
- **Immunization: Tetanus toxoid IM** if out-of-date (>5 y or <3 lifetime doses) or uncertain, tetanus Ig if vaccine hx unknown for severe wounds (>6 h old & >1 cm deep, & signs of infection or debris); **Rabies ppx** (human diploid cell vaccine + HRIg) for all wild animal bites (incl raccoons, etc.); for domestic animals, observation of animal × 10 d → if nl behavior, no rabies tx, if animal becomes ill → sacrificed & brain tissue tested for rabies

## Human Bites (*CID* 2005;41:1373)

- **Background:** Risk of infection ↑ compared to animal bites

- **Microbiology:** Pathogens = oral & skin flora; strep, staph, haemophilus, eikenella most common; anaerobes often ⊕ in mixed cultures
- **Management:** Same as above for dog & cat bites; **no 1∞ closure** for human bite; **all pts should receive prophylactic abx;** clenched-fist bites (injury from striking teeth) often require IV abx & consultation w/ hand surgeon
- **Bloodborne pathogens:** HCV, HIV transmission risk very low; however, if there is blood in saliva → counseling about HIV PEP warranted; HBV transmission possible; unvaccinated or undetectable anti-HBs should receive HBIg & HBV series

## Insect Bites and Stings (*J Allergy Clin Immunol* 2011;127:852)

- Usually self-limited local reaction, rarely can → systemic reaction/anaphylaxis
- **Local reaction:** Remove stinger, apply cold compresses, nonsedating antihistamines; for severe edema, consider oral steroids; expectant mgmt regarding infection
- **Systemic reaction:** Inpt eval, at d/c prescribe epinephrine auto-injector, refer to Allergy for skin testing & consideration of immunotherapy

## Lice (*NEJM* 2002;346:1645; *JAAD* 2004;50:1; *CID* 2007;44:S153)

- **Head lice** (pediculosis capitis): Children > adults, spread through shared items, infestation
  *S/sx:* Scalp pruritis or asx; dx by visualization of louse ± nit w/ fine-toothed comb
  *Tx:* Heat-wash sheets/clothes + topical **permethrin, 2 applications 7 d apart** (alt: Malathion, benzyl EtOH, 0.5% ivermectin lotion); TMP–SMX w/ permethrin or PO ivermectin (off-label) for tx failure
- **Body lice** (pediculosis corporis): Vector for typhus, trench, & recurrent fever; ↑ prevalence in poverty, war, natural disaster settings, infested clothes ↑ risk *S/sx:* Waist & axillae pruritic papules; visualize louse or nit on body or clothes *Ddx:* Scabies, allergic dermatitis; skin scraping useful if dx unclear
  *Tx:* Bathe, heat-wash sheets/clothes, 10 h application of permethrin

to entire body if nits on body

- **Genital lice** (pediculosis pubis, "crabs"): Transmitted during sexual activity, screen for co-infection w/ other STIs; *S/sx:* Pubic & axillae pruritus, louse or nits on hair
  *Ddx:* Scabies, trichomycosis axillaris, white piedra
  *Tx:* **1% permethrin,** Return in 1 wk, re-treat PRN; tx partner, heat-wash sheets & clothes

## Spider Bite (*Lancet* 2011;378:2039; *NEJM* 2005;352:700)

- Most spiders are not toxic to humans & not medically important; severe reaction should prompt consideration of differential; often misdiagnosed **soft-tissue MRSA infection**
- Black widow, brown widow (southern US), & false black widow (worldwide) usually cause unremarkable local reaction (papules, pustules) ± local pain; recluse spider (US) bites **rarely** can → local necrosis, systemic sx & hemolytic anemia; supportive care

## Bedbugs (Cimex lectularius) (*JAMA* 2009;301:1358)

- **Background:** ↑ Prevalence of infestations worldwide; 5 mm in size → visible w/ naked eye; yellow/reddish color; feed at night; live close to host in furniture, mattresses, floorboards; can live 1 y w/o feeding; no evidence serves as disease vector
- **Signs and symptoms:** Usually no reaction to bite; most rashes brought to attention are 2–5 mm pruritic, maculopapular, erythematous; excoriation can → superinfection; case reports of more severe reaction (hypersensitivity, complex rashes)
- **Treatment:** If sx, may consider topical corticosteroids; if superinfected → oral/topical abx
- **Eradication:** Very difficult; requires systematic effort & often professional assistance; prevention (inspection of hotels rooms, items purchased 2nd-hand, library books) advised

## Scabies (see *"Scabies"*)

# BACTERIAL ENDOCARDITIS PROPHYLAXIS

## Background

- **Pathogenesis:** Nonbacterial thrombotic endocarditis (NBTE) forms on valve surface → during bacteremia, bacteria adhere to NBTE → bacteria proliferate within vegetation → infectious endocarditis (IE)
- **Incidence:** Estimated at 3–9 cases/100,000 persons annually; significantly ↑ risk in pts w/ valvular disease or IVDU (*NEJM* 2013;368:1425)
- **Prophylaxis:** Periprocedural bacteremia can → IE in pts w/ diseased valves; abx are used to ↓ bacterial load → ↓ risk of IE; however, most cases not post-procedural
- **Historical context:** Pre-procedure ppx used to be recommended more widely, but 2007 AHA guidelines narrowed scope to those at highest risk

## Rationale for Limited Prophylaxis (*Arch Intern Med* 1992;152:1869; *Lancet* 1992;339:135)

- Controversial whether decreasing peri-procedure bacteremia reduces overall IE risk; "high-risk" procedures cause only a small proportion of IE cases (*CID* 2006;42:e102)
- Episodes of bacteremia from dental disease far more common; can occur w/ daily activities (eating, brushing); mgmt of poor oral hygiene may be more effective than antibiotic ppx (*Am J Cardiol* 1984;54:797; *Pediatr Cardiol* 1999;20:317)
- Antibiotic ppx has adverse effects: GI upset, diarrhea, allergic reactions, selection of resistant organisms
- Postimplementation of 2007 AHA Guidelines → ↓ use of ppx → no ↑ incidence of *S. viridans* IE (*Circulation* 2012;126:60)

## When to Use Prophylaxis: AHA 2007 Guidelines (*Circulation* 2007;116:1736)

- Ppx is recommended in patients w/ high-risk **condition** undergoing high-risk **procedure** (*must meet both criteria*)

**High-risk Conditions and Procedures**

| Conditions | Procedures |
|---|---|
| • Prior IE<br>• Prosthetic cardiac valve or prosthetic material used for cardiac valve repair<br>• Congenital heart disease if:<br>1. Unrepaired cyanotic CHD (may have palliative shunts & conduits)<br>2. Repaired w/ prosthetic material or device w/in past 6 mos<br>3. Repaired but w/ residual defects near a prosthetic patch or device<br>• Cardiac transplantation recipients who develop cardiac valvulopathy<br>• Native valve disease **not** an indication for ppx | • Dental procedures w/ manipulation of gingival tissue/periapical region of teeth, perforation of oral mucosa<br>• Surgical procedures of **infected** skin, skin structures, or MSK tissue*<br>• Respiratory tract procedures that involve *incision or bx of the respiratory mucosa* (such as tonsillectomy or adenoidectomy)<br>• GI & GU procedures (including EGD & colonoscopy) **during active GI/GU infection only** (Note: these pts should receive *anti-enterococcal* abx [e.g., amoxicillin]; any GI/GU procedures w/o an active infection do not require ppx) |

*These pts should receive regimen active against GAS and *S. Aureus*.

## Prophylactic Antibiotic Regimens (*Circulation* 2007;116:1747)

- **Antibiotic should be given as a single dose 30–60 mins prior to procedure**
- Do not use cephalosporins if hx of anaphylaxis, angioedema, or urticaria to penicillin

### Prophylactic Regimens for Dental Procedures

| Situation | Regimen |
|---|---|
| Oral | Amoxicillin 2 g PO |
| Unable to take oral meds | Ampicillin 2 g IM/IV **or** (Cefazolin or Cftx) 1 gm IM/IV |
| Allergic to PCN/ampicillin | Cephalexin 2 g PO **or** Clindamycin 600 mg PO **or** (Azithromycin or Clarithromycin) 500 mg PO |
| Allergic to PCN/ampicillin & unable to take oral meds | (Cefazolin or Ceftriaxone) 1 gm IM/IV **or** Clindamycin 600 mg IM/IV |

# FEVER OF UNKNOWN ORIGIN

## Background (*Arch Int Med* 2003;163:545; *Medicine* 2007;86:26)

- **Definition:** (1) Illness of >3 wks duration; (2) Fever >38.3°C (101°F) on several occasions during that time; (3) Uncertain dx after 1 wk of intensive evaluation (*Medicine* 1961;40:1; *Arch Intern Med* 1992;152:21)
- **Etiology:** Usually an uncommon presentation of a common illness, rather than rare disease; likely cause varies by age, geography,

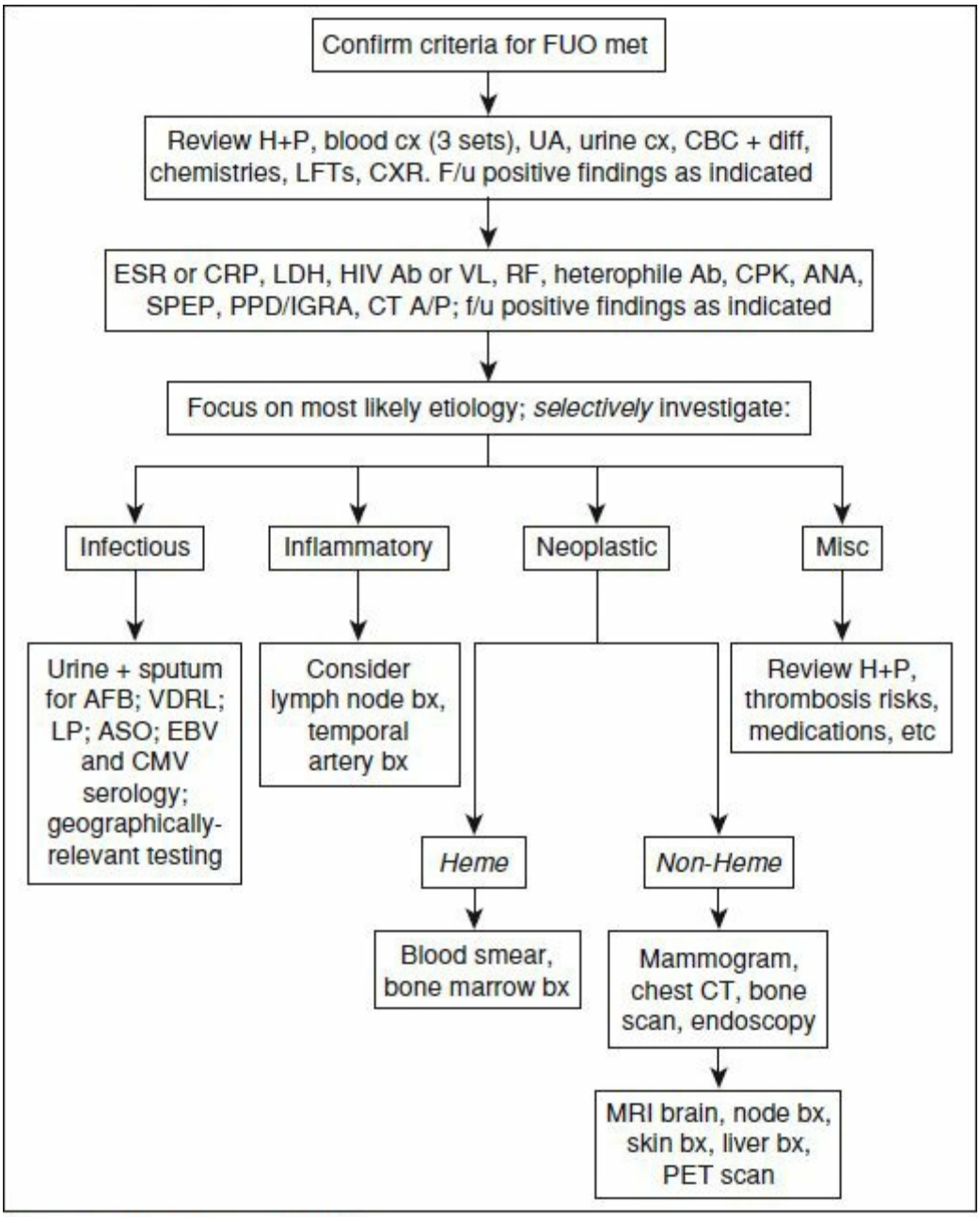
immune status; generally, infectious 25–30%, inflammatory 20–25%, malignant 15%, miscellaneous 5%, no dx in 20–30%; nosocomial, neutropenic, HIV-associated FUO should be considered separately

**Etiologies of FUO (*Arch Int Med* 2003;163:545)**

| Category | Common Etiologies |
|---|---|
| Infectious | **TB:** Most common infectious etiology worldwide; may have ⊖ PPD, CXR, IGRA, blood cx, sputum AFB; bx of nodes, marrow or liver may → dx (*Int J Infect Dis* 2008;12:71; *J Infect* 2006;52:399)<br>**Abscess:** Usually abd or pelvic: (E.g., liver, splenic, renal, prostatic); also retroperitoneal, dental, paraspinal; risk factors include ESLD, immunosuppressants, recent surgery, DM<br>**Osteomyelitis:** E.g., vertebral, mandibular, DFI; local sx may be min<br>**Endocarditis** (*Cardiovasc Clin* 1993;23:139): Culture ⊖ in 5%; consider up to 21 d incubation ± special media to detect fastidious organisms; use serology for *Bartonella* & Q fever (*Coxiella*); TTE detects 90% of endocarditis presenting as FUO |
| Inflammatory | **GCA:** 15% of FUO cases in the elderly; see *"Vision Complaints"*<br>**Adult Still's:** (Adult JRA, younger adults) fever + macular truncal rash often precede arthritis<br>Also PAN, Takayasu arteritis, RA, SLE, granulomatosis w/ polyangiitis (Wegener's), mixed cryoglobulinemia (*Clin Rheumatol* 2012;31:1649) |
| Neoplastic | **Leukemia, Lymphoma** (esp non-Hodgkin)<br>**Renal cell CA:** 15–20% of cases have fever (*Lancet* 1997;350:575)<br>HCC or liver metastases (*Heart Lung* 2013;42:67)<br>**Atrial myxomas:** Fever in ~33%, arthralgias, emboli, ↑ IgM |
| Other | **Drug fever:** Antimicrobials (PCN, carbapenems, cephalosporins, sulfa, nitrofurantoin, INH), antiepileptics, H1 & H2 blockers, antiarrhythmics, NSAIDs, antihypertensives (hydralazine, ACEI), antithyroid (PTU); Eosinophilia & rash in only 25% (*Arch Intern Med* 1996;156:618)<br>**Endocrine:** Hyperthyroidism, thyroiditis, pheo, adrenal insufficiency<br>**Other:** Hereditary periodic fever syndromes (FMF); **clot** (PE, DVT, hematoma); factitious fever |

## Diagnosis (*Infect Dis Clin North Am* 2007;21:867)

- **Detailed history:** Travel, sick contacts, animal exposure, outdoor exposure (forest, lake, ocean), immunosuppression, med & toxin hx unusual foods, localizing symptoms
- **Careful exam:** LAD, skin rash or lesions, new murmur, HSM, arthritis, jaw claudication
- CT abdomen/pelvis may reveal etiology in up to 20% of cases (*Radiology* 1980;136:407)
- Biopsy (marrow, liver, nodes, temporal artery) as final step or if localizing symptoms



(Adapted from: *Am Fam Physician* 2003;68:2223)

Figure 7-1 Diagnostic Approach to FUO

## Management (*Arch Intern Med* 1996;156:618)

- Empiric antimicrobials generally unhelpful, except in neutropenic fever
- Up to 50% of cases remain idiopathic, most of those recover spontaneously
- **Referral:** As appropriate if dx made; if uncertain, consider ID consultation

# HEPATITIS B

## Background (*Hepatology* 2009;50:661; *NEJM* 2008;359:1486)

- Hepatitis B is a double-stranded DNA retrovirus which primarily infects hepatocytes; 8 known genotypes
- **Transmission:** Blood, sexual contacts, vertical transmission
- **Natural history: Most chronically infected pts acquired HBV during childhood in endemic areas;** only 5% of acute infection in adults → chronic infection
- **Risk factors for HBV infection: 2 different populations at ≠ risk**
  *Early* infection (↑ risk of → chronic infection): From endemic regions: Africa, Asia, S. Pacific, often acquired perinatally, 90% of exposed neonates will develop chronic infection
  *Late* infection (↓ risk of → chronic): Sexual/household contacts, IVDU, MSM, prisoners, HD

## Acute Infection (*Hepatology* 2009;49:S28; cdc.gov/hepatitis/HBV)

- **Epidemiology:** 2.1/100,000 new cases/y in US, most cases among pts 25–44 y; (↓ 80% from 1987–2004 2/2 vaccine availability & universal/needle precautions)
- **Incubation:** Range of 6 wk–6 mos, average 90 d
- **Presentation: Often mild but wide range** of manifestations; only 30–50% adults develop sx (< 1% fatal); typical sx = fatigue, fever, jaundice/dark urine (at bili levels >2.5), pruritus, RUQ pain, N/V, loss of appetite; aminotransferase levels often >1000; ↑ risk of severe disease in elderly; Ddx: CMV, EBV, other viral hepatitis, acute HIV
- **Diagnosis: For acute infection, initially** obtain HbsAg, Anti-Hbc IgM: expect ⊕ HbsAg: (May be ⊖ during "window period" lasting 2–8 wks after exposure) ⊕ **Anti-HbcIgM** (must be interpreted clinically; can also be ⊕ in chronic dz flare)
- **Treatment:** Supportive care for mild cases; suspicion of ALF warrants emergent referral → ED, consider antiviral therapy; reportable to CDC/local health dept
- Recombinant Hep B vaccine should be administered as near to the time

of exposure as possible; HBIg ↓ incidence & severity of infection if given w/in 7 d of exposure (*Expert Rev Clin Immunol* 2011;7:429)

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## CHRONIC INFECTION

### Background

- **Epidemiology:** 1.25 million carriers in US (most asx); 15–40% will develop serious sequalae (cirrhosis, ESLD, HCC) over their lifetime
- **Sequelae: HBV Æ 100¥ ≠ risk of HCC, even if no e/o cirrhosis** (*NEJM* 2004;350:1118)
- **Risk factors for cirrhosis:** ≠ Age, genotype C, ↑ HBV DNA, ♂, EtOH, HCV, HDV or HIV ⊕
- **Risk factors for HCC:** ↑ Age, EtOH, HCV ⊕, smoking, ♂, ⊕ FHx, cirrhosis

### Diagnosis

- **Definition:** ⊕ HBsAg for >6 mos
- **Screening:** Those at ↑ risk of infection or complications, including pregnant women, HCV ⊕, HIV ⊕, pts starting immunosuppressant tx, chemotherapy, chronic ↑ ALT/AST, DM
- **Laboratory Testing**
  *Anti-HBs* (HBs**Ab**): Indicates immunity; can be from vaccination or prior cleared infection
  *Anti-HBc* (HBc**Ab**): Indicates previous or ongoing infection
  *Anti-HBc IgM:* Indicates acute infection (<6 mos), converts to *Anti-Hbc IgG* at 6 mos
  *Anti-HBe* (HBe**Ab**): Presence indicates → nonreplicative state; "seroconversion": HBeAg ⊕ pts who → HBeAg ⊖ & develop Anti-HBeAb ⊕; good prognosis but must distinguish from HBeAg ⊖ chronic HBV, which typically has HBV DNA >2000
  ***HBs*Ag***:* ⊕ Indicates acute or chronic infection; will turn ⊕ approx 4 wks from exposure
  ***HBe*Ag***:* ⊕ In acute & chronic infection; indicates active viral replication
  *HBV DNA:* (Copies/mL); viral load correlates w/ viral replication (marker of dz activity)

### Hepatitis B Initial Lab Evaluation

| Clinical Question | Expected values/notes |
|---|---|
| **Does pt have immunity?** | ⊕ **Anti-HBs,** ⊖ **HbsAg** |
| … 2/2 vaccination? | ⊖ Anti-Hbc IgG |
| … 2/2 infection? | ⊕ Anti-Hbc IgG |
| **Does pt have chronic HBV?** | ⊖ **Anti-HBs,** ⊕ **HBsAg** |
| Carrier state? | ⊖ HBeAg, & HBV DNA |
| Active state? | ⊕ HBV DNA >2000 IU/mL, HBeAg ⊕/⊖ |

## Evaluation (*Hepatology* 2009;50:661)

- **History:** Assess for presence of risk factors of complication, sx of ESLD
- **Exam:** Eval for e/o liver dysfunction: jaundice, ascites, spider angiomata, HSM
- **Initial Studies:** LFTs, CBC, PT/INR, HBV DNA, HBeAg/anti-HBe,HCV, HIV, for those at ↑ risk: HDV, AFP (U/S in ↑ risk pts)

## Management (*AFP* 2010;81:965)

- **Immunization:** HAV in all nonimmune pts
- **HCC screening: U/S (preferred) w/ or w/o AFP q6–12 mos**
  **Who:** Cirrhosis, ⊕ FHx HCC, African descent >20 yo, or Asian descent ♀ >50 yo, ♂ >40 yo, or anyone >40 yo w/ ALT elevation or serum HBV DNA >2000 copies/mL
- **Disease monitoring:** See below

### HBV Serial Disease Monitoring

| HbeAg ⊕ | | HbeAg ⊖ | |
|---|---|---|---|
| **ALT nl** | q3–6 mos ALT<br>q6–12 mos HbeAg | **ALT nl, HBV DNA <2000** | q3mos ALT × 3, then q6–12mos if still nl |
| **ALT 1–2× ULN** | q3mos ALT, q6mos HbeAg<br>Consider bx if >40; if ↑ ALT persistent, consider bx/ Rx | **ALT 1–2× ULN<br>HBV DNA 2000–20,000** | q3mos ALT & HBV DNA; consider bx or Rx if persistent |
| **ALT >2× ULN** | q1–3mos ALT, q3mos HbeAg<br>Tx if persistent or if ↓ liver function | **ALT >2× ULN<br>HBV DNA >20,000** | Tx if persistent, bx optional |

(*Hepatology* 2009;50:661)

- **Pharmacologic treatment: Should be considered & initiated in**

**conjunction w/ specialist;** tenofovir, entecavir pegylated IFN-α 1st-line; **Goal:** ↓ Complications, incidence of liver failure, cirrhosis, & HCC by suppressing HBV replication; not considered curative

- **Indications:** E/o liver disease 2/2 HBV infection (jaundice, decompensated liver disease, cirrhosis) ALT persistently >2× ULN **and** HbeAg ⊕ **or** HBV >20,000 IU/mL; consider liver bx if ALT 1–2× ULN & HBV >2000 IU/mL to guide mgmt

## When To Refer

- Consideration of initiating therapy; persistent ↑ of LFTs or HBV DNA; abnl liver bx

## Prevention

- **Counseling:** Advise immunization of sexual partners, condoms use; cover open cuts/scratches; ineligible for blood/sperm/organ donation; do not share toothbrushes or razors; no other restrictions (day care, contact sports okay)
- **Immunize:** See *"Immunizations";* n.b. if schedule is interrupted after 1st dose, give 2nd dose ASAP, no need to start over; 2nd & 3rd dose should be at least 8 wks apart
- **Postexposure prophylaxis:** Initiate vaccine in unvaccinated; can consider HBIg + booster if inadequate response

# HEPATITIS C

## Background (*Hepatology* 2009:49:1335; 2011;54:1433; cdc.gov)

- **Microbiology:** ⊕ ssRNA flavivirus, 7 major genotypes w/ assoc subtypes; in US, 1 most common >> 2 > 3
- **Transmission:** Via direct blood contact (IVDU, transfusions, needlestick); vertical transmission; sexual transmission extremely rare except HIV ⊕ MSM
- **Incubation:** Typically 4–12 wks
- **Natural history:** Acute infection typically asx; **for those infected Æ ~80% chronic carrier** state **Æ ~20% cirrhosis over 20–30 y Æ 1–5% annual risk of dying from HCC or ESLD**

- **Prevention:** No vaccine available; prevention dependent on ↓ exposure

## Epidemiology and Risk Factors (*cdc.gov; Hepatology* 2009:49:1335)

- **Prevalence:** Estimated 3.2 million people anti-HCV ⊕ in US; leading cause of death from liver disease & leading cause for liver transplantation in US
- **Risk factors for infection: IVDU** (30% young users & >70% older uses infected, risk ↑ even w/ single injection), blood tx or organ transplant recipient prior to 1992, clotting factor recipient before 1987, ESRD on HD, **HIV**
- **Risk factors for disease progression:** ETOH use, older age, ↑ duration of infection, HIV, HBV, obesity

## Evaluation (*cdc.gov*)

- **Screening:** Those w/ risk factors for infection (above) & **one-time screening of all adults born between 1945–1965,** pts w/ unexplained elevated aminotransferases, sexual partners of HCV ⊕ individuals, postexposure, pts receiving regular transfusions (or any blood transfusion before July 1992), HD, transplant candidates/recipients
- **Symptoms of acute infection** (only ~20% have sx): Jaundice, RUQ pain, fatigue
- **Symptoms of chronic infection:** Many pts asymptomatic but fatigue common, later may develop symptoms due to hepatitis or cirrhosis; extrahepatic manifestations can include hematologic (cryoglobulinemia), dermatologic (PCT), renal (MPGN), endocrine (thyroiditis, DM)
- **Diagnostic labs**
  *Anti-HCV:* Current **or** past infection, ⊕ 1–3 mos post-infection, 97% sensitive after 6 mos
  *HCV RNA:* Active disease; can be quantitative, ⊕ 2–3 wks postinfection
  *Indications:* ⊕ Anti-HCV, ↑ LFTs in immunocompromised pt, consideration of tx, dx during acute infection before anti-HCV ⊕
- **Further studies:** If HCV RNA ⊕, → obtain LFTs (incl albumin, INR),

genotype (guides tx choices), consider liver bx or indirect (serum-based) fibrosis assessment (e.g., FibroSure, Hepascore) if it will influence decision to treat

- **Management of acute hepatitis:** Supportive care (can consider early antivirals); if concern for acute liver failure (rare) → **prompt ED referral**

## Chronic HCV Management (*Hepatology* 2009:49:1335)

- **General approach:** Involves surveillance & management to ↓ likelihood of disease progression, as well as consideration of pharmacotherapy
- **Immunization:** HAV, HBV (if not infected), Tdap, influenza annually, *S. pneumo* (*Ann Intern Med* 2010;152:36)
- **Screen for coinfections:** HIV, HBV, sexually transmitted infections
- **Counseling:**
  *Preventing infecting others:* Discuss modes of transmission, must avoid blood donation or activities that would expose others to blood, advise vaccination of close contacts (HBV); sex between monogamous couples: risk ~1 in 190,000 acts
  *Preventing disease progression:* Avoid other RFs for liver fibrosis (EtOH, tob, obesity), avoid NSAIDs, limit APAP (<2 g in 24 h), vertical transmission in ♀
- **HCC screening: Indicated only in pts w/ cirrhosis** (unlike HBV): U/S every 6 mos
- **Pharmacologic Treatment**
  *Contraindications:* Uncontrolled depression, hx of transplant (other than liver), pregnancy, some autoimmune conditions, severe concurrent medical disease
  *General approach:* Regimen specifics depend on genotype; mainstay is Peg-IFN + Ribavirin (+ protease inhibitor Telaprevir or Boceprevir for genotype 1) for 24–28 wks; *S/e:* IFN/ribavirin: Fatigue, flu-like sx, depression, N/V, anemia; PIs: anemia, rash, pruritus
  *Efficacy:* Also depends on genotype; genotype 1, noncirrhotic → sustained virologic response (SVR) in 75% of Caucasians, ~40% of African-Americans; genotype 2 → SVR in 80% of pts

- **When to refer:** Refer for initiation of tx if persistently abnl LFTs, hepatitis on liver bx, advanced fibrosis/cirrhosis, or sx attributable to HCV

# HIV/AIDS

## Definitions

- **Human immunodeficiency virus infection (HIV):** ⊕ HIV Abs by ELISA w/ confirmation by Western blot **or** detectable plasma HIV RNA
- **Acquired immunodeficiency syndrome (AIDS):** HIV infection + CD4+ T-lymphocyte count $<200$ cells/mm$^3$ **or** an AIDS-defining opportunistic infection or malignancy (see below)

## Background

- **Microbiology:** ssRNA lentivirus; retrovirus (inserts itself into host genome); 2 types; HIV-2 infections in US rare (limited primarily to pts born in W. Africa)
- **Transmission:** Bloodborne pathogen—sexual, vertical, transfusion, or occupational (e.g., needlestick) transmission possible, ↑ risk w/ ↑ viral load
- **Natural history:** Wide variability, usually progresses to sx over 1–10 y if untreated
- **Prevention:** No vaccine available; to prevent must ↓ exposure

## Epidemiology (www.unaids.org; *cdc.gov* 2013)

- **Prevalence:** 34 million people infected worldwide, 1.1 million in US; 20% are unaware of dx → they account for 50% of all transmissions
- Sexual contact most common transmission route in US; 20× ↑ risk for each sexual act when condoms are **not** used
- HIV disproportionately affects gay, bisexual, & other MSM, IVDU, as well as people of African-American > Hispanic ethnicity; however, significant transmission occurs among all demographic groups
- **Routes of transmission:** Sexual (vaginal insertive/receptive ~0.05/0.1% risk, anal insertive/receptive ~0.06/0.5%), IVDU (0.7%), vertical transmission (10–40% w/o ARVs), transfusion (now

in US <1/2,000,000), occupational (needlestick ~0.3%); all dependent on viral load

## Acute Retroviral Syndrome (http://www.aidsinfo.nih.gov; *NEJM* 2011;364:1943)

- Occurs in ~40% to 90% of infections, when viral load peaks (~$10^6$ copies/μL) 2–6 wks after viral transmission
- **Presentation:** "Mono-like illness," w/ fever, viral exanthem (erythematous maculopapular lesions, face, & trunk), LAN, nonexudative pharyngitis, myalgia/arthralgia
- **Diagnosis:** Order viral load (or p24 Ag test); ELISA may be ⊖ or weakly ⊕, WB <1 band
- **Treatment:** Supportive; prompt referral for consideration of antiretroviral tx
- **Secondary prevention:** Pts w/ ARS have very high infectivity 2/2 high viral load; proper dx can → reduction of high-risk behavior → reduced transmission

## Diagnostic Studies

- **Screening:** Screen routinely all pts aged 15–64 y once; repeat in pts initiating tx for TB, pts seeking tx for STIs, all pregnant women, & pts w/ ongoing risk as judged on individual basis (*MMWR* 2006;55:1; *Ann Intern Med* 2013;159:51)
- **Lab tests**
  *Antibody testing:* ELISA is initial screen (>99% Se for chronic infection, becomes ⊕ 2–8 wks after acute infection) → confirmed w/ Western blot
  *Rapid test:* Uses oral fluid (also available as home test kit: OraQuick), blood, plasma, or serum; result in 10–20 mins; Se & Sp 98.4–100%; must confirm by routine ELISA + Western blot (cdc.gov/hiv/topics/testing/rapid/rt-comparison.htm)
  *HIV RNA:* Measures by PCR; current detection range 20–10 million copies/mL
- If suspect **acute infection**, must test for HIV RNA or p24 Ag

## New Diagnosis of HIV

- **Delivering diagnosis:** First, assess pt's understanding of likelihood of HIV dx & their anxiety (see "Breaking Bad News" in *"Pt Counseling"*); deliver news simply/briefly & await their response; avoid "jumping ahead" to intake or specifics of tx options; assess individual coping skills & family/community resources; offer access to counselor/peer group/social work; emphasize HIV's transformation to a chronic disease & set up a plan for next steps in mgmt (http://hivinsite.ucsf.edu; *AFP* 2006;73:271)
- **Partner notification/case reporting:** Consider timing of exposure for partners to determine appropriate testing; be aware of local dept of public health reporting requirements & resources (many offer anonymous partner notification)
- **Initial medical evaluation:** Goals are (1) assess the risk of disease progression; (2) assess the risk for OI, to guide prevention education & Ppx; (3) eval current symptoms based on HIV stage; (4) screen for common comorbidities; & (5) target appropriate health maintenance interventions

## Initial Evaluation of HIV ⊕ Patient

- **History:** Full PMHx, including HLD, CAD, DM, CKD, neuropathy, depression, anxiety, PTSD, TB, hx hepatitis, HSV, shingles, immunizations, prior CA screening
  *HIV staging:* Current viral load, current & nadir CD4, date of dx (& route/date exposure, if known)
  *HIV treatment hx:* Prior regimens (including adverse effects), resistance testing (obtain medical records whenever possible), current/prior adherence: "Do you sometimes forget to take your medications?" "How many times in the past 2 weeks have you missed a dose?"
  *Substance use:* Tobacco, EtOH, street drugs, Rx drugs
  *Social hx:* Occupation, housing, social supports, country of origin, partner stability
  *Sexual hx:* Emphasize behaviors (e.g., "do you have sex w/ men, women, or both?" rather than using labels such as "gay" or "homosexual"), assess sexual practices (vaginal, oral, anal) & condom use, hx other STIs, contraception use
- **Exam:** Full PE, including weight, skin exam, OP exam, LN exam

- **Labs/Studies**
  *HIV:* CD4+ count, quantitative HIV RNA, HIV genotyping for ART resistance
  *Medical:* CBC w/ diff, electrolytes, BUN, Cr, LFTs, fasting glucose + lipids, G6PD, U/A
  *ID:* GC/CT; TB (see *"TB"*); serologies for syphilis, toxo, CMV, VZV, HAV, HBV, HCV
  *Diagnostics:* Baseline CXR, fundoscopy, cervical + anal PAP smear in ♀, anal PAP in MSM
- **Immunization:** CD4 cells affect vaccine efficacy → defer vaccination in pts w/ CD4 <200 who will soon start ART; live-virus vaccines should **not** be used (e.g. intranasal influenza) when alternatives exist; may be used (MMR, VZV) if CD4 >200 (*MMWR* 2013;62(01):2)
  *Recommended:* Inactivated influenza, DTaP, HBV (may repeat series, if anti-HBS remains ⊖, HAV, HPV (if <26 y), pneumococcal (PCV13 & PPSV23); MMR, VZV, intimate partner violence (IPV) as indicated if CD4 >200; discuss w/ ID specialist if uncertain (see *"Immunizations"* for dosing details)
- **Health maintenance** (*CID* 2009;49:651; *MMWR* 2010;59:1)
  *Annual screening:* BP; lipids; ECG in ♀ >40 y or ♀ >50 y; U/A; assess for lipodystrophy
  *Monitor if on ART:* Glucose, eGFR q6–12 mos; ALT/AST, Aφ q3–6mos
  *STIs:* annual screening for GC/CT & syphilis in all sexually active pts
  *Psych/Neuro:* Screen pts periodically for neurocognitive impairment and/or depression
  *CA screening:* Colon, breast as in HIV ⊖ pts; annual cervical Paps recommended (see *"Cervical Cancer Screening"*); consider anal PAP q6–12mos in MSM

## CAD risk in HIV ⊕ patients (*JAMA Intern Med* 2013;173:614; *AIDS* 2013;27:973)

- Patients w/ HIV have ↑ risk of death from CAD; this is multifactorial: (1) ↑ Risk factors (e.g., tobacco), (2) HIV treatment toxicity (can ↑ lipids, ↑ insulin resistance), & (3) HIV itself (inflammation → atherogenesis; risk appears ↑ w/ optimal HIV mgmt); this warrants focused prevention efforts (e.g., smoking cessation, ASA when

indicated; see *"Coronary Artery Disease"*)

- Statins often indicated to manage HLD; however, caution w/ statins & PIs (PIs can → ↑ serum concentration of statins; pravastatin least affected; NNRTIs can → ↑ serum concentration of statins); requires more frequent monitoring for s/e (LFTs, CK) (hab.hrsa.gov/deliverhivaidscare/clinicalguide11/)

## Antiretroviral Therapy (DHHS February 2013 aidsinfo.nih.gov)

- Antiretroviral therapy (aka highly active antiretroviral therapy, or HAART) should only be initiated by a clinician experienced in HIV care; all pts should have HIV genotyping to assess for pre-existing resistance before starting ART
- **Indications for ART initiation:** Recommended for **all** HIV-infected individuals regardless of CD4 count; recommendation strength ↑ w/ ↓ in CD4 (definitely for CD4 $<350$, strongly consider for CD4 350–500, consider for CD4 $>500$)
- **Other definite ART indications:** Pregnancy (prevents perinatal transmission; specialized OB/GYN referral recommended); current or prior AIDS-defining illness; HIV-associated nephropathy (HIVAN); HBV co-infection when HBV tx is indicated

**Antiretroviral Agents**

| Class & Drug | | Side Effects & Key Facts |
|---|---|---|
| NRTI | Abacavir (ABC; Ziagen) | Hypersensitivity syndrome: fever, myalgia, GI sx & rash (strong assoc w/ HLA B*5701) |
| | Didanosine (ddI;Videx) | Pancreatitis, peripheral neuropathy, ↑ lactic acidosis & hepatic steatosis when combined w/ stavudine |
| | Emtricitabine (FTC; Emtriva) | HA, nausea, insomnia, palm/sole hyperpigmentation |
| | Lamivudine (3TC; Epivir) | HA, dry mouth; also active against HBV |
| | Stavudine (d4T, Zerit) | Peripheral neuropathy, lactic acidosis, pancreatitis, dyslipidemia, diarrhea |
| | Tenofovir (TDF;Viread) | AKI, Fanconi syndrome, CKD, osteomalacia, GI sx |
| | Zidovudine (AZT; Retrovir) | Cytopenias, fatigue, malaise, HA, GI sx, lipoatrophy myalgia/myopathy, skin/nail hyperpigmentation |
| NNRTI | Rilpivirine (RPV; Edurant) | Rash, depression, insomnia |
| | Efavirenz (EFV; Sustiva) | CNS sx (abnl dreams, drowsiness, dizziness; caution w/ driving), ↑ LFTs, ↓ methadone levels, **teratogenic** |
| | Etravirine (ETR; Intelence) | ↑ LFTs, rash, med interactions (ok w/ methadone), SJS |
| | Nevirapine (NVP; Viramune) | Hepatitis – more common at ↑ CD4 counts, in ♀, & in pts w/ HBV/HCV; ↓ methadone levels; rash |
| Protease-Inhibitor | Atazanavir (ATZ; Reyataz) | ↑Bili, ↑ LFTs, ↑ PR interval, rash, contraindicated w/ PPI, causes less hyperlipidemia than other PIs |
| | Darunavir (DRV; Prezista) | ↑LFTs, risk for rash in pt w/ sulfa allergy,↑statin levels except atorvastatin |
| | Fosamprenavir (FPV;Lexiva) | ↑LFTs, ↑ lipids, GI sx |
| | Indinavir (IDV; Crixivan) | Nephrolithiasis, ↑ bili, ↑ LFTs, alopecia, insomnia |
| | Lopinavir/ ritonavir (LPV/r; Kaletra) | GI sx, HA, fatigue, dyslipidemia, ↑ LFTs, pancreatitis; med interactions |
| | Nelfinavir (NFV;Viracept) | Diarrhea, N/V, ↑ LFTs |
| | Ritonavir (RTV; Norvir) | Med interactions,↑LFTs, GI sx |
| | Saquinavir (SQV; Invirase) | ↑LFTs, GI sx, HA, ↑ QT |
| | Tipranavir (TPV;Aptivus) | ↑LFTs, ↑ lipids, risk of rash if sulfa allergy, GI sx, med interactions |
| FI | Enfuvirtide (ENF; Fuzeon) | Local reaction incl nodules at injection site, neutropenia |
| EI | Maraviroc (MVC; Selzentry) | Med interactions, GI sx, ↑ LFTs, hepatitis, liver failure, joint/muscle pain, ↑ URI, HoTN |
| II | Raltegravir (RAL; Isentress) | GI sx, ↑ LFTs & amylase, CNS sx, myalgia, rash/pruritus/ SJS; generally well tolerated |

FI, Fusion inhibitor; EI, Entry inhibitor; II, Integrase inhibitor

- **Preferred initial antiretroviral regimens** (*DHHS February* 2013, *aidsinfo.nih.gov*)

  *NNRTI-based:* EFV/TDF/FTC
  *PI-based:* ATV/r + TDF/FTC, **or** DRV/r + TDF/FTC
  *Integrase inhibitor-based:* RAL + TDF/FTC

## Infectious and Malignant Complications of HIV/AIDS (*Guidelines for Prevention and Tx of Opportunistic Infections in HIV-Infected Adults and Adolescents,*

*aidsinfo.nih.gov* 5/7/2013)

- **General approach:** Pts w/ HIV/AIDS are at ↑ risk of both unusual & "typical" infections; low threshold for eval of new/persistent complaints; **if red flags present, prompt consultation w/ ID specialist vs. ED eval** depending on chronicity/severity
- **Selected diseases commonly encountered in ambulatory setting**
  *Mucocutaneous candidiasis:* Oral burning/pain, white patches; can be dx clinically or w/ KOH prep: Tx is fluconazole, clotrimazole troches, or pastilles; if suspect esophageal involvement (odynophagia, dysphagia) → referral to ID/GI
  *VZV*, *HSV:* See respective chapters; refer to ID/Derm if severe disease
- **Red flags:** Fever, fatigue, night sweats, wt loss, new HA, vision changes, persistent cough, diarrhea

## Opportunistic Infections

| CD4 Count at Risk (cells/mm$^3$) | Opportunistic Infections or Malignancies | Recommended 1° Ppx (if none listed, only preventive therapy is ART) |
|---|---|---|
| <500 | Recurrent **bacterial** PNA/infections, MTb infection, mucocutaneous candidiasis (oral **thrush**, vaginitis)<br>Kaposi sarcoma, oral hairy leukoplakia, cervical CA | If ⊕ latent **TB** screen (& no active TB or MDR risk): INH + Vit $B_6$ for 9 mos, *or* RIF/RFB for 4 mos<br>Vaccination as per above for VZV, PSV23, PCV13, flu, HPV, etc. (see *"Immunizations"*) |
| <100–200 | **PCP,** ***Toxoplasma*** *gondii* encephalitis, HSV, VZV, *Histoplasma capsulatum* infection, *Cryptosporidium* enteritis, ***Cryptococcus*** *neoformans* encephalitis, isosporiasis<br>Visceral Kaposi's sarcoma, non-Hodgkin's lymphoma, PML | For **PCP** (when **CD4 <200**): TMP–SMX DS or SS daily or DS 3×/wk, or dapsone 100 mg daily, *or* atovaquone 1500 mg daily, *or* *aerosolized* pentamidine 300 mg monthly (see *"PCP prophylaxis"*)<br>For **Toxo** (if **IgG+** & **CD4 <100**): TMP–SMX DS daily, *or* (dapsone 50 mg daily + pyrimethamine 50 mg weekly + leucovorin 25 mg weekly)<br>For **histoplasmosis** (in hyperendemic areas when **CD4 <150**): Itraconazole 200 mg daily |
| <50–100 | Invasive candidiasis/aspergillosis, disseminated MAC, CMV (retinitis, esophagitis, colitis), penicilliosis, CNS lymphoma | For **MAC** (when **CD4 <50**): Azithromycin 1200 mg weekly *or* Clarithromycin 500 mg BID *or* Azithromycin 600 mg 2×/wk<br>For **Penicilliosis** (in **SE Asia**): Fluconazole 400 mg qwk |

## Prophylaxis

- **Pre-exposure prophylaxis:** Eligible if high risk for sexual acquisition (mainly MSM), HIV ⊖ (RNA & Ab), HBV ⊖, & nl GFR; Prophylaxis w/ Truvada 300/200 once daily; check renal function regularly (*MMWR* 2011;60:65)
- **Nonoccupational PEP:** (*MMWR* 2005;54:1)
  Clean exposure site w/ soap & water; flush mucous membranes w/ water; review exposure & regimen w/ HIV expert w/in 48–72 h; if initiation delayed >72 h postexposure, PEP not recommended
  *Monitoring:* Assess HIV status (+ HBV/HCV serologies) of exposed person at 0, 1, 3, & 6 mos; monitor weekly for s/e & adherence while on PEP
  Counsel pt about need for risk-reduction measures until testing excludes HIV infection
- If **occupational exposure**, occupational health services should eval & document

# HERPES SIMPLEX VIRUS

## Background (*JAMA* 2006;296:964; 2011;305:1441)

- **Microbiology:** dsDNA herpesviridae; herpes simplex viruses 1 (HSV-1) & 2 (HSV-2) are common causes of mucocutaneous disease, characterized by lifelong infection w/periods of latency & reactivation
- **HSV-1:** Responsible for essentially all cases of clinical orolabial disease & most new genital infections in US; can also → skin (e.g., eczema herpeticum), eye (keratitis), & CNS (encephalitis) disease (*JAAD* 2007;57:737; *CID* 2013;56:344)
- **HSV-2:** Responsible for genital lesions but can also infect oral mucosa; infection in ♀ → ↑ risk of neonatal HSV
- **Transmission:** Typically via direct contact w/ mucus membranes; oral–oral, oral–genital, genital–genital; can also occur via shared utensils or towels; most transmission occurs during asx periods of viral shedding
- **Natural history:** Incubation period 2–20 d (*AFP* 2010;82:1075);

**primary infection**: Ranges from subclinical to ulcers & ⊕ constitutional signs (pharyngitis, mono-like sx) → **latency**: in CNV ganglia (orofacial) or sacral (genital) → **reactivation**: usually 1—6 episodes/y, milder, shorter in duration than **primary episode**

## Epidemiology and Risk Factors (*JAMA* 2006;296:964; 2011;305:1441; *JAAD* 2007;57:737)

- Annual incidence 23.6 million cases/people 15–49 y old; US seroprevalence of HSV-1/HSV-2 ~58/17%; of these people, only 10–25% have ever had clinical disease)
- **Risk factors for acquisition:** African-American (HSV-1 &2), ♀ (HSV-2), prior STI (HSV-2), ↑ number lifetime partners (HSV-2), uncircumcised men (♂ circumcision ↓ HSV-2 acquisition by 25%) (*NEJM* 2009;360:1298); early acquisition assoc w/ ↓ SES
- **Risk factors for reactivation:** Immunosuppression → more frequent reactivation & dissemination, UV exposure, trauma, fever
- **Risk factors for transmission:** HIV ⊕, <12 mos since 1° infection, symptomatic disease; viral shedding occurs in 10.2% of seropositive **asx** pts (vs. 20% of pts w/ sx disease)

## Evaluation

- **History:** Systemic sx (fever, malaise, LAD) + sudden painful lesions, new or HSV ⊕ sexual partner (1° infection), prodromal mucocutaneous burning/tingling → skin lesions in area previously affected (reactivation), dysuria (genital), triggers (UV exposure, topical retinoids, stress, local trauma), hx immunosuppression
- **Characteristic lesion: Grouped vesicles** on erythematous base that progress to scalloped bordered erosions w/ **hemorrhagic crust**
- **Orofacial:** 1° disease usually in childhood (painful oral lesions + systemic sx) **reactivation:** Typically milder/shorter duration, often same location as prior episodes; *Herpes labialis* ("cold sore"): Crusted papule or erosion w/ hemorrhagic crust on outer vermillion of lip; *Intraoral herpes:* Erosions on keratinized mucosa (hard palate, gingiva, dorsal tongue)
- **Genital:** Vesicles of varying sizes; ♀ : Labia minora, introitus, urethral meatus, reactivation on buttocks of older women; ♂ : Shaft & glans

- **Other subtypes:** Herpetic whitlow (distal phalanx); **eczema herpeticum** in pts w/ atopic dermatitis or burns; "punched out" monomorphic hemorrhagic vesicles & erosions, + fever/malaise → urgent referral to ED
- **Diagnosis:** If dx uncertain, obtain direct fluorescent Ab (result 24–48 h), Tzanck smear (most rapid), viral culture (gold std), skin bx
- **Serologic testing:** Given high seroprevalence, ⊕ test not very useful in dx of specific lesion; **cannot** distinguish between oral & genital HSV-1; Abs can be ⊖ w/ latent infection; **can** help est baseline in HIV ⊕, assist in dx when recurrent ulcers & viral Cx/PCR ⊖

## Management (*JAMA* 2006;296:964; 2011;305:1441; *JAAD* 2007;57:737)

- **Counseling:** Pts can expect recurrence (1–6/y); these episodes are typically milder & shorter duration, often ↓ frequency over time; can ↓ risk of recurrence of orofacial disease w/ regular sunscreen use; prevent autoinoculation w/ hand hygiene
- **Risk of STIs:** Genital HSV infection assoc w/ ↑ risk of HIV infection, likely 2/2 impaired mucosal barrier (*NEJM* 2009;360:1298)
- **Risk of partner transmission:** Risk ↑ when lesions visible; however, majority of infections occur via asx viral shedding; counsel pts to inform partners, use condoms (esp in 12 mos after initial infection) & avoid sexual contact during sx period (*J Infect Dis* 2006;194:420; *BMJ* 2007;334:1048)
- **Pharmacologic tx:** May shorten course; start at 1st signs of cutaneous burning/tingling (consider giving pts w/ recurrent disease Rx they can fill to have available at 1st sign of recurrence)
- **Indications for suppressive treatment:** >6 clinical episodes/y, HSV ⊖ partner, pt at ↑ risk for contracting HIV

**Treatment of HSV in Immunocompetent Patients (*JAAD* 2007;57:737)**

| Treatment of HSV in Immunocompetent Patients (JAAD 2007;57:737) | | |
|---|---|---|
| **Medication** | **Clinical Context** | **Dose*** |
| Acyclovir | Primary genital | 400 mg PO TID × 7–10 d |
| | Recurrent genital | 400 mg PO TID × 5 d |
| | Suppressive therapy (≥6 episodes/y) | 400 mg PO BID |
| | Herpes labialis (*Arch Intern Med* 2008;168:1137) | 400 mg 5×/d × 5 d<br>5% crm—apply 5×/d × 4 d |
| Valacyclovir<br>– ↑ bioavailability<br>– FDA-approved for Rx of HSV in HIV | Primary genital | 1 g PO BID × 7–10 d |
| | Recurrent genital | 500 mg BID × 3–5 d |
| | Herpes labialis | 2 g PO BID q12h × 2 doses |
| | Suppressive therapy | 500 mg PO daily |

*Immunosuppressed → Dose adjustment & consideration of alt agents

# OTHER VIRAL HEPATITIDES

## Hepatitis A (*cdc.gov/hepatitis/HAV*)

- **Background:** Most common cause of **acute** viral hepatitis, ~21,000 cases annually in US (92% ↓ since vaccine 1st available in 1995); ssRNA picornavirus, multiple genotypes; transmitted via fecal–oral or contaminated food/water
- **Risk factors: International travel to endemic areas** (Mexico, central/south America, sub-Saharan Africa) **most common** source of infection in US pop, institution/day care outbreaks, blood, sexual/household contacts
- **Presentation:** 2–6 wk incubation period, then malaise, fever, N/V, RUQ pain, ↓ appetite, jaundice; 70% will be sx
- **Diagnosis:** Acute infection ⊕ **anti-HAV IgM;** immunity is expressed w/ ⊕ anti-HAV IgG; cannot distinguish b/w past exposure or vaccination
- **Screening:** Generally not indicated as no chronic carrier state; only to be considered as efficiency/cost saving in pts w/ ↑ risk of prior infection (Native American/Alaskan, Hispanic, IVDU)
- **Treatment:** Supportive care—usually self-limited infection, rarely fulminant; IG available for high-risk exposure (w/in 2 wks)
- **Prevention:** Counseling of safe travel habits (see *"Travel Medicine"*) & targeted immunization: 2 doses at 6–12 mos apart (see *"Immunizations"*)

## Hepatitis D (*Lancet* 2011;378:73)

- **Background:** ssRNA, **HBV co-infection required** for complete virion assembly & secretion; multiple genotypes; transmitted via blood, sexual contact; 5% of HBV ⊕ co-infected worldwide; worsens severity HBV infection & ↑↑ risk of cirrhosis & death; clears if HBV clears
- **Risk factors:** ↑ Prevalence in E. Europe & Africa; IVDU & multiple transfusions
- **Presentation:** Ranges from fulminant hepatitis to asx carrier state, may present as "flare" of chronic HBV
- **Diagnosis:** Anti-HDV (total & IgM ⊕ in acute + chronic states), HDV RNA ⊕
- **Treatment:** Typically pegylated interferon qwk × ≥48 wks

## Hepatitis E

- **Background:** Small ssRNA of genus *Hepevirus;* transmission primarily fecal–oral, but also zoonotic, seen in travelers to Asia, Africa, Middle East, Central America
- **Natural history:** Usually self-limited, ↑ risk of severe/fulminant in late pregnancy, rarely chronic in immunosuppressed pts
- **Presentation: Acute hepatitis**, no carrier state
- **Diagnosis:** Anti-HEV IgM or HEV RNA ⊕ from blood/feces

## Other Causes of Viral Hepatitis

- Epstein–Barr virus: Young pts, pharyngitis, fatigue, splenomegaly, atypical lymphocytes; up to 90% of mononucleosis cases a/w ↑ transaminases
- Cytomegalovirus: Consider reactivation of latent infection in immunocompromised pt; mononucleosis-like illness (pharyngitis, fatigue, fever)
- Herpes simplex virus: Can be severe, fulminant in neonates, pregnancy, or immunocompromised pt; generally mild in immunocompetent, can be assoc w/ genital or oral vesicles (see *"Herpes Simplex Virus"*)
- Varicella zoster virus: Generally mild transaminitis assoc w/ vesicles, can be severe, disseminated in immunocompromised pt (see *"Herpes*

*Zoster"*)

- Adenovirus: Immunocompromised pt; can p/w respiratory sx, cystitis, or diarrhea

# PNEUMOCYSTIS (PCP) PROPHYLAXIS

## Background (*Emerg Infect Dis* 2002;8:891)

- Pneumocystis pneumonia (PCP) is clinical infection w/ *P. jirovecii;* disease typically limited to those w/ immunodeficiency, although subclinical infection likely widespread
- **Microbiology:** *Pneumocystis jirovecii*, formerly called *pneumocystis carinii* but renamed in attempt to distinguish the strain/species which causes human disease; organism cannot be cultured, therefore diagnosed by induced sputum, tissue bx, or BAL

## Epidemiology (*Guidelines for the Prevention and Tx of Opportunistic Infections in HIV-Infected Adults and Adolescents aidsinfo.nih.gov* 5/7/2013; *BMC Infect Dis* 2004;4:42)

- **Transmission:** Airborne transmission; disease occurs by new acquisition, or possibly by reactivation of latent infection; healthy humans likely reservoir (*NEJM* 2004;350:2487); ~7/8 healthy adults have Abs (*J Immunol* 1988;140:2023)
- **Incidence/prevalence:** Before PCP ppx & ART, ~70–80% prevalence in pts w/ AIDS; now ~0.8% annual incidence among HIV ⊕ pts in US (*AIDS* 2013;27:597)
- **Risk factors for people w/ HIV:** CD4 <200 cells/μL or <14% of T cells; prior PCP; oral thrush; recurrent bacterial PNA; unintentional wt loss; ↑↑ plasma HIV RNA; most pts who develop PCP are unaware of HIV status or not receiving HIV care
- **Non–HIV-infected populations at risk:** Transplant recipients (stem cell & solid organ); pts w/ cancer (esp hematologic malignancies); pts receiving glucocorticoids, chemotherapeutic agents, or other immunosuppressive meds (*Mayo Clin Proc* 1996;71:5)

### Indications for PCP Prophylaxis

| HIV ⊕ | HIV ⊖ |
|---|---|
| CD4 <200<br>CD4 <14% of total T cells<br>Oropharyngeal candidiasis<br>Hx of AIDS-defining illness (TB, crypto, CMV, KS)<br>CD4 200–250 & unable to monitor q1–3mos | >20 mg of prednisone daily (or equivalent) for >1 mo w/ another cause of immunocompromise (e.g., leukemia, 2nd immunosuppressive Rx)<br>1° immunodeficiency (e.g., hyper-IgM, SCID)<br>Allogeneic SCT, solid organ tx, selected auto-SCT<br>*Consider:* In pts receiving immunosuppressive biologic agents (monoclonal Abs, TNF-α inhibitors, etc.); no specific guidelines, but e/o ↑ risk |

## Preventive Treatment (*NEJM* 2004;350:2487; *Eur J Clin Microbiol Infect Dis* 2002;21:523)

- **Prophylaxis effective in target population:** In HIV ⊖, to prevent 1 case, NNT = 15 (*Cochrane Database Syst Rev* 2007;18:CD005590); in HIV ⊕ w/ CD4 <200, to prevent 1 case, NNT ≈ 2 (*BMJ Clinical Evidence* 2010;8:908; *JAMA* 1988;259:1185)

### PCP Prophylaxis Regimens (*aidsinfo.nih.gov guidelines* May 2013)

| Drug | Dosage | Adverse Effects |
|---|---|---|
| **TMP–SMX (1st line)** | **1 ds tab daily** (preferred) or 1 ss tab daily | Fever, rash, neutropenia, GI upset, ↑ LFTs |
| **Alternative Regimens** | | |
| TMP–SMX | 1 DS tab 3×/wk | As above |
| Atovaquone suspension | 1500 mg PO daily | GI distress, rash, high cost |
| Dapsone | 100 mg PO daily **or** 50 mg PO BID | Fever, rash, GI upset, hemolytic anemia (check G6PD), methemoglobinemia |
| Aerosolized pentamidine | 300 mg monthly (via Respirgard II nebulizer) | Cough, wheezing, extrapulmonary PCP |
| IV pentamidine | 4 mg/kg IV monthly | Nephrotoxicity, ↑ Ca, ↓ glu, HoTN, pancreatitis, arrhythmia, ↑ LFTs |

## Discontinuing Prophylaxis (*NEJM* 1999;340:1301)

- **HIV ⊕ :** D/c ppx in pts who respond to ART w/ CD4 counts >200 cells/μL for >3 mos; discontinuation *may* be safe at CD4+ counts 101–200 cells/μL if suppressed VL, but not currently recommended (*CID* 2010;51:1114)
- **HIV⊖ :** CD4 count **not** shown to be reliable marker; decide on a case-by-case basis when to d/c ppx (*JAMA* 2009;301:2578)

# PHARYNGITIS

## Background (*NEJM* 2001;344:205; *Infect Dis Clin North Am* 2007;21:449; *AFP* 2011;83:26)

- Pharyngitis (sore throat, hoarse voice) results in ~2 million ambulatory visits in US annually (*Vital Health Stat* 2011;13:169); most etiologies require supportive care, but important to identify causes which require specific tx and/or referral
- **Etiology:** 50% viral, 20% bacterial, (co-infection w/ GAS + viral may occur), 30% no pathogen isolated (*JAMA* 1967;202:455); STIs, GAS, EBV, fusobacterium more likely in younger pts
- **Complications** rare but can include peritonsillar abscess, parapharyngeal space infection, suppurative jugular thrombophlebitis (Lemierre syndrome 2/2 fusobacterium necrophorum); infection spread to carotid sheath & submandibular space (Ludwig angina)

## Presentation (*NEJM* 2011;364:648; *Ann Intern Med* 2009;151:812)

- **History:** Often no clear distinguishing factor to elicit microbiology; inquire about coryza-like sx (URI, influenza), profound fatigue, wt loss (EBV), fever (GAS, EBV, influenza), new sexual partners (gonorrhea, HIV, HSV)
- **Exam:** OP erythema, soft palate petechiae, swollen uvula (GAS) tonsillar exudate, cervical LAD (GAS, EBV), generalized LAD, splenomegaly, hepatomegaly, or jaundice, rash (EBV, acute HIV), oral ulcers (HSV 1/2)
- **Other etiologies:** HSV (5–10% pharyngitis in college students; minority assoc w/ anterior mouth or lip lesion); *Mycoplasma* & *Chlamydophila* pneumoniae (pharyngitis, acute bronchitis); Influenza (assoc w/ cough, coryza); gonorrhea (young, sexually active); thrush (DM, recent steroids, immunosuppressed); tularemia (tick exposure, oral ulcers)
- **Red flags: Systemic toxicity or respiratory complaints;** severe unilateral pain, inability to swallow, worsening of sx after several days (peritonsillar or retropharyngeal abscess), pseudomembrane, massive tonsillar swelling (diphtheria)

## Testing (*NEJM* 1999;340:969)

- **General approach:** Most cases assoc w/ viral URI & are self-limited,

requiring supportive care; no need for further testing if suspect mild URI; other testing as below

- If suspect **Epstein–Barr virus:** Heterophile Ab: (Se/Sp 85/100%), **25% false ⊖ in 1st wk;** CBC: Lymphocytosis w/ >10% atypical lymphocytes, mild ↓ PLTs, ↑ LFTs; also consider CMV & HIV (~1% of those tested for mono actually have acute HIV)

## Treatment (*CID* 2002;2:113; *Ann Intern Med* 2001;134:506)

- **Symptom management:** Antipyretics, NSAIDs, fluids, gargling w/ warm salt water, lozenges, humidifier
- **Non-GAS infection:** Group G or C β-hemolytic strep: not assoc w/ rheumatic fever, but abx *may* result in earlier sx tx (*BMJ* 2000;320:150); in young adults **w/o** associated viral sx, fusobacterium necrophorum causes similar proportion of pharyngitis to GAS; consider empiric tx (B-lactam, clindamycin, or flagyl, **not** macrolide)
- *N. gonorrhoaea:* Treat as per genital infection (see *"Sexually Transmitted Infections"*)

## When to Refer

- **Red flags:** Refer to ED for persistent fever, trismus, odynophagia, muffled voice, dysphonia, otalgia, unilateral deviation of uvula, swelling of mandible, bulging of pharyngeal wall

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## Group A Strep (*CID* 2012;55:1279)

- **Prevalence:** Causes 5–15% of acute pharyngitis in adults; ↑ risk in those w/ contact w/ school age-children (parents, teachers)
- **Natural history:** Usually self-resolves w/o complications; tx advised to **prevent suppurative complications:** Sinusitis, parapharyngeal abscess; **reduce symptoms:** Sore throat & fever ↓ by 0.5–3 d; prevent rheumatic fever (extremely rare in adults) & ↓ community spread of infection; tx does not ↓ risk of PSGN (*Cochrane Database Syst Rev* 2006;4:CD000023)
- **General approach:** Test if mod–high probability, treat if ⊕; empiric tx can lead to unnecessary abx use (59% appropriate, 32% unnecessary,

9% underuse)

- **Testing:** *Rapid* Ag-*detection test:* (Se 70–90%; Sp 90–100%) recommended if ↑ suspicion (>2 criteria, below); throat culture can be obtained if other causes suspected or to ↑ Se; *Throat cx:* (Se 90%, Sp 95–99%) ⊕ in acute infection & asx carriers; generally not needed given low prevalence of disease in adults but can be used to ↑ Se*; Anti-strep Abs*: Used in dx of post-strep complications; not helpful in acute setting (*JAMA* 2004;291:1587)
- **Treatment: PCN V 500 mg PO BID or TID ¥ 10 d** or benzathine PCN G 1.2 million units IM ×; alternatively amoxicillin 500 mg BID × 10 d, cephalexin 500 mg BID ×10 d, clindamycin 300 mg TID ×10 d; often macrolides resistant; avoid unless confirmed sensitivity
- **Follow-up:** Advise pts to seek care if no sx improvement 3–4 d after abx; failure to improve → reconsider dx or suppurative complication; if repeat tx necessary, repeat w/ amoxicillin–clavulanate or 1st gen cephalosporin

**Centor Clinical Scoring Criteria (*JGIM* 1986;1:1; *NEJM* 2004;344:205)**

| | | |
|---|---|---|
| **Tonsillar exudates** | | 1 pt |
| **Tender anterior cervical LAD** | | 1 pt |
| **Absence** of cough | | 1 pt |
| **Fever** by hx | | 1 pt |
| **Age ≥45** | | –1 pt |
| **Treatment Algorithm** | | |
| **Points** | **Risk of GAS** | **Treatment** |
| –1, 0 | 1–2.5% | No tx or testing |
| 1 | 5–10% | No tx or testing |
| 2 | 11–17% | Test, treat pts w/ a ⊕ rapid test |
| 3 | 28–35% | Consider empiric tx; **testing & treat if ⊕ preferred for most adult pts per IDSA** |
| 4 | 51–53% | |

# PNEUMONIA

## Background (*Natl Vital Stat Rep* 2012;60:1; *Am J Manag Care* 2012;18:380)

- Bacterial pneumonia acquired in community setting; distinguished from health care-associated PNA which is acquired in hospital, SNF, HD facility, or within 90 d of hospitalization; → different resistance patterns & organisms
- **Epidemiology:** >2.5 million annual visits to primary care providers; more pts present to PCP than ED w/ this dx (*Vital Health Stat* 2011;13:1), prevalence of PNA among pts presenting w/ acute cough to 1° care is 5–7% (*Ann Intern Med* 2003;138:109)
- **Microbiology:** *Streptococcus pneumoniae* > *M. pneumoniae, H. influenzae*, & *C. pneumonia* common organisms (*Arch Intern Med* 2001;161:1866)
- **Risk factors:** ≠ **Age,** immunocompromise (HIV, chemotherapy), pulmonary disease (asthma, COPD), smoking (*Arch Intern Med* 1995;155:1649), EtOH (*NEJM* 2000;342:681), medical comorbidities (DM, ESLD, CKD, neoplastic disease)
- Potentially severe (50,000 deaths/y in US), but majority of cases can be treated as outpt

## Evaluation (*NEJM* 2002;347:2039; *AJRCCM* 2001;163:1730)

- **General approach:** Dx requires **clinical features + radiographic infiltrate**
- **History:** Assess for cough (productive/dry), fever, chills, CP, fatigue, SOB, pleurisy, absence of rhinitis
- **Past medical history:** Comorbidities (including cardiac & pulmonary disease, smoking, EtOH, immune suppression); health care, travel, & animal exposures
- **Exam:** Normal vitals & lung exam → ⊖ LR as low as 0.13 (*JAMA* 1997;278:1440)

  *VS:* Fever, tachycardia, hypoxia ($S_aO_2$ <90% assoc w/ ↑ 30 d morbidity/mortality)

  *Pulmonary exam:* Assess work of breathing; listen for rales (common), egophony and/or bronchial breath sounds (*CID* 2011;52:325)

*Volume:* JVP, skin turgor, dry mucus membranes; *Neuro:* Mental status changes

- **Imaging:** All pts in whom PNA is suspected should receive CXR; varied radiographic presentations—lobar/multilobar consolidation, patchy interstitial or reticulonodular pattern, or cavitation; abnormalities may be minimal at <24 h if dehydration, immunocompromise, or older age (*Clin Radiol* 1996;51:689; *J Clin Oncol* 1999;17:796; *Am J Med* 2004;117:305)
- **Labs** (*BMJ* 2013;346:f2450; *Cochrane Database Syst Rev* 2012;9:CD007498)
  *Severity assessment:* Consider CBC w/ diff, lytes, BUN/Cr, glucose, LFTs
  *Dx: Optimal use of labs not yet clear;* CRP shows promise in prediction rules & ↑ procalcitonin may help rule-in bacterial illness; further study needed
- **Microbiologic testing** (sputum culture ± serology, PCR) **optional** in outpts b/c empiric rx usually effective & identifies causative organism only $^{1}/_{2}$ the time (*JAMA* 2000;283:749; *Ann Intern Med* 2005;142:165)
- Seek etiology if ↑ suspicion for epidemiologically important organism (influenza, *Legionella*, TB, CA-MRSA), cavitary lesion, pleural effusion, severe underlying lung disease, failure to respond to tx, or unusual presentation

**CAP Microbiology (*Respir Med* 2005;99:60; *Chest* 2003;123:1512; *Eur J Clin Microb* 1986;5:446)**

| Organism | Associated Features |
|---|---|
| *Streptococcus pneumoniae* | Most common; encapsulated; bacteremia in 1/3 |
| *Haemophilus influenzae* | Encapsulated; ↑ incidence in smokers, COPD |
| *Mycoplasma pneumoniae* | Young adults; ⊕ cold agglutinins, rash; can be self-limited |
| *Chlamydophila pneumoniae* | Young adults; can be self-limited |
| *Moraxella catarrhalis* | Interstitial; usually assoc w/ underlying pulm disease |
| *Legionella* species | Recent travel (2 wks), ⊕ high fevers, GI sxs, ΔMS |
| *Staphylococcus aureus* | Often post-influenza; ↑ risk of abscess, empyema |
| *Klebsiella pneumoniae* | ↑ Incidence in heavy EtOH use, often ⊕ hemoptysis |
| Group A *Streptococcus* | Uncommon; prominent CP, early empyema |

- Other etiologies: **Viral** (influenza, adenovirus, RSV, parainfluenza, SARS, metapneumovirus, Hantavirus), **fungal** (*Histoplasma*,

*Coccidioides*, *Cryptococcus*, *Pneumocystis*), **zoonotic** (psittacosis, Q fever, tularemia)

## When to Hospitalize

- Key management decision: HCAP usually requires inpt tx; in CAP, consider PNA risk scores (PSI/PORT, C[U]RB-65, below), pregnant or immunocompromised status (↓ threshold to hospitalize), & also individual social situation (caregivers available, functional status, likely adherence to meds)

**Pneumonia Severity Index (PSI/PORT Score) (*NEJM* 1997;336:243; *Ann Intern Med* 2005;142:165)**

To calculate score: Age (+age in y), ♀ (–10), Nursing home residence (+10)
Malignancy (+30), liver disease (+20), CHF (+10), stroke (+10), CKD (+10)
ΔMS (+20), RR >30 (+20), SBP <90 (+20), T <35°F or T >40°F (+15), HR >125 (+10)
pH <7.35 (+30), BUN >30 (+20), Na <130 (+20), glucose >250 (+10), Hct <30 (+10), $PaO_2$ <60 (+10), pleural effusion (+10)

| Class | Score | Mortality | Triage |
|---|---|---|---|
| I | Age <50 & healthy | 0.1% | Outpt |
| II | ≤70 | 0.5% | Outp |
| III | 71–90 | 1% | Consider outpt |
| IV | 90–130 | 9% | Hospitalize |
| V | >130 | 27% | Hospitalize |

**C[U]RB-65** (*Thorax* 2003;58:377): Predicts mortality (may use w/ or w/o blood test)
Cumulative score = 1 pt each for Confusion, BUN >20, RR >30, BP <90/60, Age >65 y
→ **0–1 points** may be safe for outpt; **≥2 points** recommend inpt

## Outpatient Treatment

- **General approach:** Empiric regimen based on drug-resistant *S. pneumoniae* risk; treat for minimum 5 d or until afebrile 48–72 h; if ↑ suspicion for unusual organism based on presentation, may alter diagnostics & tx coverage accordingly
- **Risk factors for drug-resistant *S. pneumoniae* (DRSP):**
  Age >65, abx w/in past 3 mos, alcoholism, comorbid illness (chronic heart, lung, liver or renal disease, diabetes, malignancy), asplenia, immunocompromise, exposure to child in daycare (*CID* 2005;40:1288; 2006;43:432; *Inf Dis Clin North Am* 2004;18:993; *CID* 2007;44(Suppl 2):S27)

## Empiric Antibiotic Regimens (*CID* 2007;44(suppl 2):S27)

| Risk | Antibiotic Choice |
|---|---|
| Low DRSP risk | **Azithromycin 500 mg × 1, then 250 mg QD × 4 (preferred)**<br>**Alt:** Azithro 500 mg QD × 3, azithro 2 g × 1, or clarithromycin 1 g QD × 5<br>Assoc w/ ↑ QTc & ↑ CV mortality; use alt or monitor in ↑ risk pts<br>• If adherence concerns, consider short course w/ single dose or 3 d course of azithro (long $t_{1/2}$)<br>(*NEJM* 2012;366:1881; *Eur Respir J* 1995;8:398; *Int J Antimicrob Agents* 2004;24:181) |
| | **Doxycycline 100 mg BID × 7–10 d** (*Diagn Microbiol Infect Dis* 2012;75:107)<br>• Review local resistance patterns; doxycycline preferred if >25% of *S. pneumo* have high-level (MIC ≥16 μg/mL) macrolide resistance |
| High DRSP risk | **Respiratory FQ (preferred)**<br>**Levofloxacin 750 mg QD × 5–7 d, moxifloxacin, or gemifloxacin**<br>• If possible TB, avoid FQ use (2nd-line tx for TB) |
| | (**Macrolide** or doxycycline) & (**amox/clav 2 g BID** or amoxicillin 1 g TID or 2nd-gen ceph)<br>• Amox or amox/clav preferred over cephalosporins; cefpodoxime preferred over cefuroxime (*CID* 2003;37:230) |

- **Follow-up:** Symptoms should improve soon after abx, but some symptoms (cough, fatigue) can linger up to 30 d; repeat CXR usually unnecessary; consider if concerned for malignancy/if smoker
- **Symptomatic treatment:** Cough suppressants or expectorants do not affect outcomes
- **Smoking cessation:** For all pts w/ PNA, screen, advise to quit, & offer assistance
- **Prevention:** Administer pneumococcal vaccine per guidelines (see *"Immunizations"*) to prevent invasive pneumococcal infection (↓ bacteremia & meningitis, but not PNA) (*Cochrane Database Syst Rev* 2013;1:CD000422; *NEJM* 2003;348:1747)

# SEXUALLY TRANSMITTED INFECTIONS

## Background (*CDC: STD Surveillance* 2008 & 2011 2008; *Sex Transm Infect* 2011;87:183)

- Diseases such as chlamydia, gonorrhea, trichomonas, & syphilis represent a significant & mostly "hidden" public health problem; presentation ranges from asx to severe
- **Epidemiology:** >20 million new STIs dx in US annually; $^1/^2$ of these in pts <24 y; most pts are diagnosed/managed by PCP
- **Complications:** *Short-term:* upper genital infections (PID, prostatitis), ↑ **risk acquiring/transmitting HIV;** *Long-term:* **infertility**, chronic pelvic pain, (GC/CT, trichomonas), cervical CA, genital warts (HPV), multiorgan/CNS involvement (syphilis)
- **Microbiology:** HPV most common (~14 million new infections/y); *C. trachomatis* most common bacterial infection (~2.8 million cases/y, majority asx → importance of screening, see below), followed by *N. gonorrhoaea* (~700,000 cases/y)
- **Risk Factors: Young age** (15–24 yo), unmarried, **MSM** (esp ↑ RR of syphilis) African-American ethnicity, new partner in past 60 d, multiple sex partners, hx prior STI, HIV ⊕, illicit drug use, imprisoned, contact w/ sex workers, inconsistent condom use

## Screening

- Routine screening for many STIs not cost-effective, so must target groups w/ risk factors (above), incl those w/ prior STIs (see *"Disease Screening");* sexually active women <25 y, HIV ⊕, prior STIs, MSM should be screened annually for GC/CT
- **Rescreening indications:** If ⊖ , rescreen if high risk; if ⊕, rescreen in 3 mos for new asx infections (*Ann Intern Med* 2006;145:564)
- **Offer HIV testing to all patients,** particularly those being eval for STIs (*CDC* 2010)

## General Approach (*CDC: STD Treatment Guidelines*, 2010)

- **History:** Assess for risk factors (above), ask about partners' STI hx current/prior genital ulcers, intercourse w/ trauma, condom use, pregnancy status

- **Exam:** Genital, pelvic, oropharyngeal, skin, LN exam
- **Management:** In addition to tx of specific STI
  *Testing:* Offer/assess recent HIV testing to all pts being screened for STIs
  *Counseling:* Indicated for risk reduction in all pts in whom assessing STIs
  *Partner Rx:* Recent partners of pts w/ STI should be referred for treatment & testing
  *Reporting:* GC, CT, syphilis, HIV all reportable to local health dept
- **Empiric treatment** is indicated for all women w/ suspected PID (see *"Pelvic Inflammatory Disease"*)

## Chlamydia (*CDC: STD Treatment Guidelines*, 2010; *Annals Int Med* 2013;158:ITC2–1)

- **Microbiology:** Causative organism *C. trachomatis;* specialized intracellular bacteria; can infect genital tract, rectum, oropharynx, & conjunctiva
- **Symptoms:** ♀ : If present, can include dysuria, change/↑ in vaginal d/c, sx of PID (fever, pelvic pain, dyspareunia); ♂ : (2/3 of men sx) urethral d/c, dysuria, testicular pain
- **Exam:** ♀ : Can appear normal or ⊕ cervical friability, purulent d/c, signs of PID (see *"PID"*) ♂ : Mucoid/purulent d/c (can be ↓ if recently urinated); testicular/epididymal pain
- **Diagnosis:** NAAT (nucleic acid amplification test) most sensitive; first-catch urine for men, 1st-catch urine, cervical, or vaginal swabs for women; may perform NAAT (not FDA- approved) for eval of rectal infection; culture also available (but ↓ Se vs. NAAT)
- **Treatment:** Azithromycin 1 g PO × 1; *Alt:* Doxycycline 100 mg BID × 7 d (not if pregnant)
- **Partners:** From past 60 d should be treated (may be done empirically)
- **Complications:** Reactive arthritis (more common in ♂ : Conjunctivitis, urethritis, oligoarthritis); PID & Fitz–Hugh–Curtis syndrome (RUQ pain 2/2 hepatic capsular inflammation)

## Gonorrhea (*MMWR* 2012;61:590; *Annals Int Med* 2013;158:ITC2–1)

- **Microbiology:** *N. gonorrhoeae* causative organism; gram ⊖ diplococcus; can infect genital tract, rectum, & oropharynx

- **Signs and symptoms:** Generally indistinguishable from chlamydia (above); ♀ : Assess for PID S/sx in ♀, 95% of ♂ are sx
- **Diagnosis:** NAAT as above; culture if concern for resistance
- **Treatment:** Dual therapy: Ceftriaxone 250 mg IM × 1 **&** (azithromycin 1 g PO × 1 **or** doxycycline 100 mg PO BID × 7 d if can't take azithro) *Alt:* If ceftriaxone unavailable → PO cefixime (not first-line 2/2 ↑ resistance); azithromycin 2 g PO × 1 if ceph allergy
- **Partners:** From past 60 d should be tested & treated
- **Complications:** Disseminated gonococcal infection (DGI): Rare, more common in ♀ (↑ risk in immediate postmenstrual period); papular rash (<30 lesions on extremities; can → pustular, purpuric/necrotic; oligoarthritis; tenosynovitis; perihepatitis; endocarditis; & meningitis

## Trichomonas (see *"Vaginitis"*) (*cdc.gov*)

- **Microbiology:** *T. vaginalis*, protozoan parasite which can persist w/o sx for mos–y → ↑ prevalence (3 million infected in US), more common in older women
- **Signs and symptoms:** 70% of infections are asx; ♀ : Itching, burning, dysuria, vaginal d/c; ♂ : Penile itching/irritation ± d/c, dysuria or burning after ejaculation
- **Diagnosis***:* Cervical wet prep in ♀, (60–70% Se), cx, urine DNA amp in ♂
- **Treatment:** Metronidazole 2 g PO × 1 or Tinidazole 2 g PO × 1; or metronidazole 500 mg BID × 7 d; reinfection rates high (20% at 3 mos); consider rescreening
- **Partners:** Abstain from sex until both partners are treated

## Syphilis (cdc.gov; *AFP* 2012;86:433)

- **Microbiology:** *T. pallidum;* spirochete which can → chronic, lifelong infection
- **Signs and symptoms:** Vary by stage; incubation avg 21 d (but ranges from 3–90 d)

  **Primary***: Classic:* Firm, painless sore (chancre) on genitals, anus, or mouth; *atypical:* soft, painless, multiple lesions; can last 3–6 wks; only 30–60% of cases dx at this stage as may be subtle or difficult to visualize (vaginal, rectal)

**Secondary:** Occur 2–8 wks after 1° lesion; **rash** (typically red-brown papules on trunk, extremities, & palms/soles, but many forms) **& constitutional sx** (fever, LAD, fatigue, wt loss, myalgia), HA, hair loss

**Latent:** Period after 2° sx resolved early (<1 y) or late (>1 y)

**Tertiary:** Years after initial infection: May include CV, neuro, ophthalmic, granulomatous disease

- **Diagnosis:** Multiple modalities available

  *1°, 2°, or latent:* RPR titer; if ⊕, confirm dx with treponemal test (FTA-ABS, TPPA, ELISA); n.b. some labs screen w/ treponemal test and confirm ⊕ w/ RPR titer; can also perform dark field microscopy on chancre (1°) or condyloma lata (2°)

  *3°:* As above & CSF testing if neuro sx (LP w/ ↑ lymphocytes, TP; 50% ⊕ VDRL)

**Syphilis testing (*AFP* 2012;86:433)**

| Testing Modality | Notes |
|---|---|
| **Indirect:** (measures **ACL**, marker of immune response to infection) **VDRL, RPR** | False ⊕ in other infections, pregnancy<br>False ⊖ early in disease or in immunocompromised<br>Follow titers to track tx response; 4× ↑ in titers can indicate re-infection |
| **Direct** anti-treponemal: **FTA-ABS, TP-EIA, TPPA** | More specific; more costly; false ⊖ early in disease<br>Remains ⊕ for years after tx → cannot be used to dx re-infection |
| Direct visualization of organism: **Darkfield microscopy** (↑Sp) | ⊕ In early disease; requires technical experience |

- **Treatment**

  **1°, 2° or early latent:** Benzathine PCN 2.4 × $10^6$ U IM × 1 (risk of Jarisch–Herxheimer reaction); *Alt:* doxycycline 100 mg PO BID × 14 d or azithromycin 2 g PO × 1 (↓ effective)

  **Late/3°:** Co-mgmt w/ specialist; PCN as above IM weekly × 3 wks, or doxy × 4 wks,

  **Neuro: IV** PCN 4 × $10^6$ q 4 hrs or ceftriaxone 2 g IV QD × 10–14 d; monitor RPR titer and repeat LP over 12–24 mos

## Other

- **Chancroid (*H. ducreyi*):** multiple, painful ulcers & tender LAD; *Dx:* Often clinical, order gram-stain + special culture; *Tx:* Azithromycin 1

gm PO × 1 or ceftriaxone 250 mg × 1, or cipro 500 mg PO BID × 3 d; partners from past 10 d should be tx; test pt for syphilis
- **HSV, HIV, HBV, HCV**—see respective chapters

## When to Refer

- Diagnosis uncertain, treatment-resistant disease, 3° syphilis, co-mgmt in HIV ⊕, multiple STIs → infectious disease specialist and/or STI clinic

## Prevention (*CDC: STD Treatment Guidelines*, 2010)

- Consistent, correct condom use is an effective method of risk reduction for STIs; abstinence from oral/vaginal/genital sex is only way to assure 0% risk of STI
- **Immunization:** HPV vaccine (Gardasil) for ♀ & ♂ ages 9–26; HAV & HBV vaccines for MSM, injection drug users, & HIV-infected pts; HBV vaccine all pts being eval for an STI (see *"Immunization"*)
- **Other considerations:** Pre- or postexposure HIV ppx; circumcision (↓ transmission of HIV & some STIs for heterosexual men in Africa); tx of partners
- Education and counseling about risk behaviors should be implemented in all pts at ↑ risk (*Ann Intern Med* 2008;149:497)

# SKIN & SOFT TISSUE INFECTIONS

## Background (*NEJM* 2004;350:904; *BMJ* 2012;345:e4955; *Arch Intern Med* 2008;168:1585)

- **Definition:** Acute, pyogenic inflammation of the dermis & subcutaneous tissue 2/2 bacterial infection; comprises cellulitis, abscesses, & erysipelas
- **Presentation:** May occur on any part of epidermis, but legs common, followed by face, feet, hands, torso, neck, & buttocks (*AFP* 2002;66:119)
- Most patients w/ cellulitis present in outpt setting; can be recurrent or isolated; most cases mild, but can → severe/complicated infection (NSTI, osteomyelitis); prompt recognition & tx important; however, misdiagnosis can → unnecessary use of abx & inefficient care; always consider appropriate Ddx (including noninfectious)

- **Epidemiology:** Incidence estimated as ~4%/y; >14 million outpt visits/y in US (↑ >50% in past 10 y), in large part 2/2 ↑ in CA-MRSA infection
- **Risk Factors:** Disruption of skin barrier (tinea, AD, trauma); disruption of vascular/lymphatic system (PAD, venous stasis, prior surgery/trauma), or disruption of immune system (DM, HIV)
- **Microbiology:** Nearly all cases 2/2 *S. aureus* or pyogenic Strep spp (GAS >> GCS, GGS); hospital or community-acquired MRSA (CA-MRSA) → 20–50% of SSTIs
  *S. aureus more common:* Abscess, furuncle/carbuncle, impetigo, folliculitis
  *S. pyogenes more common:* Erysipelas, cellulitis
  *Polymicrobial:* Abscess 2/2 IVDU, trauma; deep/subacute DM foot infection (see below)

**Classification**

| Diagnosis | Definition | Typical Presentation |
|---|---|---|
| Impetigo | Superficial infection of epidermis | Discrete vesicular or crusted lesions on face/extremities, children >> adults |
| Erysipelas | Infection of upper dermis/ lymphatics | Raised erythematous, well-demarcated lesions on face or extremities |
| Cellulitis | Infection of the deeper dermis, sub-cutaneous tissue | Painful, erythematous, poorly demarcated lesions on lower extremities |
| Abscess | Pus collection in dermis & deep tissue | Painful, fluctuant nodule, often w/ pustule or surrounding erythema, ± surrounding cellulitis |
| Folliculitis | Superficial infection of hair follicle | Erythematous papules in follicular distribution, often a/w shaving site |
| Furuncle/ Carbuncle | Abscess involving hair follicle; carbuncle = coalescing infection of multiple furuncles | Consistent with abscess in hair-bearing area, often assoc w/ folliculitis |
| Necrotizing soft tissue infection (NSTI) | Aggressive infection propagates along subdermal fascia, includes muscle & neurovascular bundle | See *"Red Flags"* below → 50–70% mortality if not managed early & aggressively ↑ suspicion for pain out of proportion to exam |
| Diabetic foot infection (DFI) | Any infection caudal to the malleolus in a person w/ DM | Various; see below |

## Evaluation

- **History:** Inquire re: onset, duration, prior hx of similar presentations, tx (incl topical) risk factors (above) including prior injury to area, prior episodes of infection, shaving (folliculitis), presence/absence of

systemic symptoms

- **Features suggestive of specific pathogen:** Hot tub (*P. aeruginosa* folliculitis), animal bites (*Pasteurella multocida, Capnocytophaga canimorsus;* see *"Bites & Stings"*), freshwater exposure (Aeromonas, Pseudomonas), salt water (Vibrio, Erysipelothrix), unseen "spider bite" (MRSA), immunocompromised (GNR, *P. aeruginosa*, rarely nontuberculous Mycobacteria, Cryptococcus, other fungi)
- **Methicillin-resistant *S. aureus* risk factors:** Hx MRSA colonization, ⊕ MRSA household contacts, IVDU, recurrent infection, failure to respond to MSSA/*Strep* tx, recent health care facility exposure, indwelling line, immunocompromised; contact sports, crowded or unsanitary living conditions, MSM; n.b. many pts w/ MRSA have no "risk factors"; should consider local endemic rates when deciding on empiric coverage
- **Exam:** *Gen:* Vital signs, ill-appearing or not; *LN:* assess for proximal LAD, look for proximal streaking (lymphangitic involvement); *CV:* Check distal pulses (PAD), *Lesion:* Assess for purulence, well- vs. poorly demarcated (superficial vs. deep), indurated, fluctuant (abscess), bright red (infectious) vs. darker (hemosiderin, dependent rubor); if lesion on LE, elevate leg (if redness ↓↓, consider Ddx), temperature of affected skin relative to surrounding areas; distribution (bilateral suggests other causes), ulceronodular lesions w/ surrounding erythema (Sporothrix, other fungi [soil], mycobacteria, tularemia)
- **Red flags:** Rapid spread, woody feel w/ loss of palpable landmarks, edema & hyper/hypesthesia extending beyond cellulitic border, skin ecchymosis, SC emphysema, necrosis, or e/o sepsis → **suspect NSTI** → immediate referral to ED
- **Diagnostics:** imaging/labs typically not needed; obtain if suspect sev/systemic infection
- **Culture:** Indications vary by SSTI; *Cellulitis:* Tissue/blood cx if suspicion for atypical pathogen, e/o systemic infection; *Abscess:* If large/multiple abscesses, planned abx use
- **Differential diagnosis:** Up to 1/3 of LE "cellulitis" cases are actually due to another cause; **venous stasis** > lipodermatosclerosis, irritant dermatitis, lymphedema, gout, dermatophytosis; many of these

causes are also RF for cellulitis which independently require mgmt (*JAAD* 2012;67:186) (see *"Lower Extremity Edema"* for dx & mgmt of venous insufficiency)

## Treatment

- **Impetigo:** Topical generally equivalent to systemic abxs; *1st-line:* Topical **mupirocin TID;** preferred to bacitracin/neomycin 2/2 ↑ activity vs. staph; *many lesions or failing topical tx:* Oral abx against strep/staph
- **Erysipelas:** May cause sepsis or deeper infection if not treated early, esp in elderly: → hospital if febrile as may progress quickly; *1st-line:* PO PCN/amoxicillin
- **Cellulitis:** PO abx against *S. pyogenes* 1st-line; no e/o improvement w/ empiric MRSA coverage in pts w/o MRSA risk factors or purulence (*CID* 2013;56:1754); treat underlying conditions (maceration, edema, venous stasis, tinea, dermatitis) as able to prevent recurrence
  *1st-line:* Cephalexin 500 mg q6h × 5–10 d
  *Alt:* Amoxicillin, dicloxacillin, clindamycin (avoid macrolides 2/2 resistance); empiric MRSA coverage if ⊕ RF or purulent cellulitis
  *If failing to improve:* Consider switch to IV, adding MRSA coverage, skin bx, alternate organisms & diagnoses (above) and/or drain abscess if present, consider ID consult
  *Other:* See *"Bites and Stings"* for animal, human bite pathogens & tx
- **Folliculitis:** Usually spontaneously resolves; warm compresses, avoid shaving affected area; consider mupirocin (*AFP* 2002;66:119)
- **Furuncles/carbuncles:** No evidence abx significantly improve outcomes
  *1st-line:* Moist heat → auto-drainage
  *Alt:* I&D if large; systemic abx if significant cellulitis or pt clinically ill
  *Recurrent/interpersonal transmission:* Consider staph eradication w/ antibacterial soaps/washes & mupirocin nasal carriage eradication
- **Abscess:** I&D considered 1st-line (**no abx**) for most cases
  *Indications for abx:* **Location** (digits, face, genitals, or multiple sites), **severity** (systemic sx, inability to fully drain), significant **surrounding cellulitis**/phlebitis, ↑ **risk complications** (immunosuppressed, elderly), **tx failure** w/ I&D alone

*Abx choice:* **All pts who receive abx should have culture obtained from abscess site to help guide tx**; empiric coverage for MRSA generally recommended—susceptibilities vary by region & even by hospital

**Select Oral Antibiotics with Activity Against MRSA (*CID* 2011;52:285)**

| Antibiotic | Dosage | Notes/Precautions |
|---|---|---|
| Doxycycline | 100 mg BID | Caution resistance w/ tetracyclines; photosensitivity |
| Minocycline | 100 mg BID | Less resistance than doxy; less well tolerated than doxy |
| TMP–SMX | 1 DS tab BID | Limited strep coverage: Caution in cellulitis; little resistance in MRSA; caution in CKD |
| Clindamycin | 600 mg TID | Up to 50% inducible resistance in MRSA<br>Use only if test for inducibility done |
| Linezolid | 600 mg BID | $$$, use for tx failure; risk cytopenias<br>Reserve for antimicrobial stewardship |

Caution w/ FQs for MRSA even if reported susceptible; do not use as monotherapy.

- **Necrotizing soft tissue infection:** If suspected, broad-spectrum β-lactam, vancomycin & clindamycin (*in vitro* toxin suppression), admit to hospital & seek immediate surgical opinion; early debridement more important than abx (*CID* 2005;41:1383)

## When to Refer (*BMJ* 2012;345:e4955)

- **Emergency department:** Periorbital cellulitis (ENT eval), abscess requiring extensive I&D, in cosmetic/sensitive area, suspect extension near/into deeper structures (surgical eval), **concern for NSTI,** meets sepsis criteria or e/o systemic infection; **Infectious disease specialist:** Failure to improve w/ tx, complex DFI, immunocompromised pt; **Dermatology or ID:** Dx uncertain

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# Diabetic Foot Infection (*CID* 2012;54:e132)

## Background

- **Pathophysiology:** Trauma (often minor) or loss of skin integrity → neuropathic wound → impaired healing 2/2 vasculopathy, neuropathy → superinfection
- **General approach:** Infection (vs. colonized ulcer) determined by

purulence ± inflammation; Ddx includes trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis

- **Risk factors:** ⊕ Probe-to-bone test, ulcer present >30 d, ⊕ PAD or ↓ sensation in affected limb, prior LE amputation, CKD, hx walking barefoot
- **Classification:** Acute (<2 wks); chronic (>3 wks); mild (limited to SC tissue), mod (extending to deeper structures), severe (infection + SIRS)
- **Microbiology:**
  Superficial/acute infections → staph & strep spp
  Deep/chronic infections → polymicrobial, incl *P. aeruginosa*, enteric GNRs, anaerobes

## Evaluation

- **History:** Prior DFI, neuropathy, CKD; lesion characteristics (onset, duration), systemic sx
- **Exam:** Assess for ulcer, local inflammation, vascular exam, neuropathy, tinea; for ulcers, probe for communication to bone
- **Diagnostics:** Obtain deep cx if possible; if probes to bone or chronic deep ulcer, eval for osteomyelitis; Plain radiograph insensitive in early infection → if ⊖, serial radiograph vs. MRI; no imaging needed if clinical bone infection
- **Culture:** Recommended, given ubiquitous wound colonization, 1st cleanse + debride, then culture wound w/ sterile instruments; if pt stable/minimal inflammation, complete biopsy/debridement *prior to abx;* no role for superficial wound swab

## Management

- **All patients:** *Behavioral*: Offload wt bearing, wound care, glycemic control, proper footwear; osteomyelitis not curable if unable to heal overlying skin defect; *Referral*: Co-mgmt w/ ID, orthopedics, wound specialists, vascular services optimal
- **Indications for hospitalization**: Severe disease; mod disease & complicating factors (e.g., severe PAD) or unable to adhere to tx regimen as outpt; failing to improve w/ outpt tx

## Oral Antibiotics for Selected DFI

| Classification | Antibiotic | Notes/Precautions |
|---|---|---|
| **Mild** | Cephalexin | Consider MRSA coverage if ulcer; treat 1–3 wks based on clinical improvement |
| | Amoxicillin/Clavulanate | |
| **Mild + RF for MRSA** | Doxycycline | |
| | TMP–SMX | |
| **Moderate** | Amox/clav & ciprofloxacin | Adding *Pseudomonas* & anaerobe coverage<br>Treat 2–4 wks w/o osteo, 4–6 wks w/ osteo |
| **Moderate + RF for MRSA** | (TMP–SMX or doxycycline) & (cipro/flagyl or moxi) | |

- If not improving at 3–5 d follow-up, re-eval abx, consider surgical mgmt (amputation generally indicated if incapable of wound healing, esp w/ osteomyelitis)

# TICK-BORNE ILLNESSES

## Background (http://www.cdc.gov/niosh/topics/tick-borne; http://www.niaid.nih.gov/topics/tickborne)

- Tick-borne disease can be caused by bacteria, viruses, or parasites; found throughout US, most common in Northeast; incidence is ↑, in part 2/2 ↑ settlement in rural areas
- **Presentation:** Ranges from mild flu-like illness to fulminant infection; common sx include fever, myalgias, arthralgias, rash, HA, & fatigue
- **Epidemiology:** >25,000 cases/y; most common in summer months; outdoor workers & others w/ outdoor activity at ↑ risk; most diseases w/ geographic restriction
- **Prevention:** Counsel those at ↑ risk to **reduce exposure** by wearing light-colored long-sleeved shirts & pants, socks & hat when possible; use of **insect repellent** prior to outdoor activity, & **daily tick checks** during periods of exposure, including axillae, groin, & scalp; size of adult ticks ≈ sesame seed, nymphal ticks ≈ poppy seed
- **Counseling:** If tick is found, **prompt removal** w/ gentle grip of fine-tipped tweezer; grasp very near skin & pull steadily to extract completely; wash area w/ soap & water

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## LYME DISEASE

### Background (*CDC* 2012; *CID* 2006;43:1089)

- **Microbiology:** Pathogen *B. burgdorferi*, a spirochete bacterium; vector is nymphal *L. scapularis* ("black-legged tick"/"deer tick", East/Midwest US) or *I. pacificus* (West coast); infection typically requires tick to be attached >24 h; animal hosts include white-tailed deer & rodents
- **Epidemiology:** *When*: Can occur year-round, most cases in Jun/July; *Where:* NE, Midwest; 96% of cases in CT, DE, MA, ME, MI, NH, NJ, NY, PA, VT, & WI; *Who:* Common in children, adult distribution peaks ~40–50 y; re-infection can occur

### Presentation (*NEJM* 2001;345:115)

- **Erythema migrans:** Occurs in 70% of pts w/ Lyme disease: classical appearance is warm, nonpruritic/nonpainful erythematous expanding (>5 cm) "bull's eye" lesion at site of tick bite; appearance may also include confluent erythema, vesicles, pustules, purpura; distinct from local bite reaction: self-resolving small papule occurring 1–2 d after tick removal
- **Natural history:** Untreated disease progresses through 3 stages, w/ varying individual presentations; often 1 stage or more is absent; 10% of pts are totally asx

**Stages of Untreated Lyme Disease** (*NEJM* 2001;345:115; *cdc.gov/lyme*)

| Stage | Manifestations |
|---|---|
| Early localized (3–30 d after tick bite) | Erythema migrans (EM) (70–80%), constitutional sx (as above), LAD |
| Early disseminated (d–wks) | *CNS sx* (15%): Bell palsy (8%), meningitis, ataxia, radiculopathy; *Derm:* Additional/multiple EM lesions; *CV* (1–5%): AV block, myocarditis; *Arthritis:* Large joints, esp knee, can be TMJ |
| Late disseminated (wks–mos) | *CNS sx* (5%): Polyneuropathy, subtle cognitive deficits (5%); *Arthritis* (60%): Recurrent, inflammatory |

## Diagnosis

- **Serology: ELISA & confirmatory Western blot only approved diagnostic tests per IDSA & CDC** (<30% serologically ⊕ at presentation by IgM; >80% ⊕ by IgG at 1 mo)
- **Early localized disease:** Diagnosed clinically by exam & hx potential/actual tick exposure; often timing uncertain: If suspect early disease, treat; if ELISA ⊖, consider altdx & consider repeating test during convalescence
- **Disseminated disease:** Serology: ELISA → if ⊕, confirmatory Western blot; can remain ⊕ after tx (even IgM, in some cases)

## Treatment (*CID* 2006;43:1089)

- **Treatment:** Determined by site/severity of manifestations—CNS dx → IV abx × 2–4 wks

**Treatment of Lyme Disease** (*CID* 2006;43:1089)

| Manifestation/Indication | Antibiotics (alternates) | Course |
|---|---|---|
| Erythema Migrans<br>Bell palsy<br>1st-degree heart block | **Doxycycline 100 mg PO BID**<br>(amoxicillin 500 mg PO TID, cefuroxime 500 mg PO BID) | 14–21 d |
| Arthritis (w/o CNS disease) | **Doxycycline 100 mg PO BID**<br>(amoxicillin 500 mg PO TID, cefuroxime 500 mg PO BID) | 28 d |
| Meningitis<br>Radiculopathy<br>2nd-/3rd-degree AV block | **Ceftriaxone 2 g IV QD**<br>(PCN G 4 million U IV q4h, cefotaxime 2 g IV q8h)<br>Meningitis sx warrant LP; arrhythmia mgmt | 14–28 d |

- Persistent arthritis after PO tx → 4 wks of PO abx or 2–4 wks of IV abx
- **Post-treatment Lyme disease syndrome:** 10–20% of pts c/o persistent sx after tx, including cognitive deficits, fatigue, & arthralgias; potentially autoimmune but **not 2/2 persistent** infection; RCTs have shown no improvement in outcomes w/ prolonged abx (*NEJM* 2001;345:85; *Neurology* 2008;70:992)
- **Prophylaxis:** May Rx doxycycline 200 mg PO × 1 **if** (1) endemic area, (2) confirmed ixodes tick, (3) attached ≥36 h before removal, & (4) ppx can start w/in 72 h of removal

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## Other Tickborne Illnesses

### Anaplasmosis/Ehrlichiosis (*CID* 2006;43:1089)

- **Microbiology:** Intracellular bacteria, infect WBCs; *Anaplasma phagocytophilum* transmitted by *Ixodes* ticks (often w/ Lyme); in Southeast, *Ehrlichia chaffeensis* spread by *Amblyomma/Dermacentor* ticks
- **Geography:** Throughout Eastern US, most in DE, ME, MI, NH, NJ, NY, RI, VT, WI
- **Presentation:** *S/sx:* Fever, systemic sxs, HA; ± rash (30%); 1–4 wks after exposure
  *Labs:* Leucopenia, thrombocytopenia, elevated LFTs
- **Diagnosis:** Peripheral blood smear showing inclusions, ELISA for Abs
- **Treatment:** Doxycycline 100 mg PO BID × 10 d; *Alt:* Rifampin 300 mg PO BID × 10 d

### Babesiosis (*CID* 2006;43:1089; *NEJM* 366:2397)

- **Microbiology:** Intracellular protozoan *Babesia microti;* transmitted by *I. scapularis* ticks; **often co-transmitted w/ Lyme**
- **Geography:** Northeast/Midwest US (similar to Lyme), coastal & inland
- **Presentation:** *S/sx*: Fever, systemic symptoms, arthralgias, N/V, rash (rarely)
  *Labs:* Hemolytic anemia ± thrombocytopenia, incl LDH, elevated LFTs
  *Complications:* **Severe infection possible**, w/ hemolysis, renal failure, hepatic failure, ARDS, DIC; ↑ risk if immunocompromised, asplenic, elderly
- **Diagnosis:** Thin smear showing parasites, or *Babesia* PCR (if low-level parasitemia)
- **Treatment:** Atovaquone 750 mg PO q12h + azithromycin 500 mg PO × 1, then 250 mg PO daily, × 10 d; for severe infection (>5% parasitemia) → admission

## Rocky Mountain Spotted Fever (*cdc.gov/rmsf*)

- **Microbiology and epidemiology:** Intracellular bacterial pathogen *Rickettsia rickettsii;* transmitted by *Dermatocentor* "American dog tick" in eastern US
- **Geography: Occurs throughout US,** highest incidence in MO, AK, OK, TN, NC
- **Presentation:** Fever, then rash: erythematous, maculopapular, nonpruritic, centripetally distributed, can involve palms & soles, present in 90%; petechial = more severe
- **Diagnosis:** Often made clinically; can also see rise in Ab (*2* titers 2–4 wks apart)
- **Treatment:** Doxycycline 100 mg PO BID × 7–14 d

## Other

- **Tularemia:** Gram ⊖ coccobacillus *Francisella tularensis* transmitted throughout US; sx can include ulcers, PNA, ocular, pharyngeal involvement; Dx by serology (notify lab if suspect)
- **Southern Tick-Associated Rash Illness (STARI):** Organism unknown, thought to be 2/2 *Borrelia lonestari;* transmitted in SE, lower Midwest; sx similar to Lyme; suspect if in area w/o endemic Lyme

- **Tick-borne relapsing fever:** *Borrelia hermsii* in western US, *Borrelia turicatae* in SW & central US; sx include high fever lasting ~3 d after days-weeks of convalescence; can → HoTN, ARDS; dx by blood smear/culture
- **Viral tick-borne illnesses:** Incl Colorado tick fever 2/2 reovirus in Western US: Powassan encephalitis 2/2 flavivirus in NE, N-central US: Clinical dx w/ supported care

## When to Refer *(CDC)*

- If patient has clinical signs of serious medical complications (high-degree heart block, meningitis sx, metabolic derangements, clinically ill) → **ED**; if dx uncertain, tx-refractory, unclear interpretation of results, or other concerns → **ID specialist**
- **Reporting:** All of the above diseases reportable to local health dept

# TRAVEL MEDICINE

## Background (*http://tinet.ita.doc.gov,* 2011 *data; J Travel Med Infect Dis* 2010;17:38)

- >60 million international visits by US citizens in 2012; 37 million of these beyond N. America; most have decided on travel plans >60 d in advance, yet few seek travel-related health advice; those who do are most likely to present to PCP
- Travelers can be exposed to ↑ risk of infectious disease, accidents (incl MVCs), & potential complications from medical problems occurring in resource-poor or remote settings; however, these risks can be ↓ w/ behavioral & prevention strategies
- **Visiting Friends and Relatives (VFR):** Often used to refer to immigrants from developing countries returning home; broader definitions exist but this focuses on those at ↑ infectious risk during travel; in 2011, >40% of US-based travelers outside N. America listed VFR as purpose of visit

## General Approach (*Ann Intern Med* 2012;156:ITC6–1; *AFP* 2009;80:583)

- **Assess traveler:** Immune status, pregnancy, PMHx, medications, mental health, behavioral risk factors

- **Assess travel:** Time until departure, destination, duration, season, food sources, planned activities, transportation (incl cruise ships), altitude
- **"Universal precautions": Pre-travel counseling for risk reduction**
- **Immunizations:** Routine & area-appropriate; **referral** to travel clinic as appropriate

## General Advice

- **Hydration/activity:** Caution w/ EtOH (hemoconcentration → ↑ intoxication/hangover effect)
- **Medications:** Bring as **carry-on**, original containers if going through customs; hard copy of Rx/provider note for needles, sharps, or meds problematic w/ airport security
- **Emergency supply:** Carry-on snacks/insulin (DM), rescue inhalers, migraine meds, NTG
- **Medication timing:** If time-critical meds, keep dosing at "home" times or for longer trips gradually shift to "local" times; for other meds, ok to dose at "local" times right away; **DM:** Eastbound travel = shorter day = less insulin, vice versa
- **Past medical history:** Pts w/ complex or significant hx should carry summary incl meds, allergies, ± ECG; assess for CV/pulm risk factors (see *"Preflight Assessment"*)
- **Jet lag:** Usually develops if time difference >5 h; manifests as insomnia/daytime fatigue (*NEJM* 2010;362:440); adjustment typically worst eastbound due to "shorter" day, harder to shorten Circadian cycle; natural adjustment takes ~1 d/time zone; melatonin can be helpful: 0.5–3 mg taken 30 mins before local bedtime, helpful to try "test dose" in advance

## Safety Counseling (*Ann Intern Med* 2012;156:ITC6–1; *AFP* 2009;80:583; cdc.gov/travel)

- Indicated for all patients; wt of each topic will vary based on pt & nature of travel
- **Transportation: MVC the leading cause of preventable death of US international travelers**; appropriate levels of caution & attention to rules of the road; use licensed drivers & larger/newer vehicles when possible; **seatbelt when in vehicle, helmet when bicycling**
- **Security:** Be aware of surroundings, esp in unfamiliar areas; avoid

displaying expensive items which may make you a target (e.g., jewelry, mobile phone)

- **Sexual behavior:** Pts may have ↑ risk of sexual behavior abroad; contacts may have ↑ prevalence of STIs; always use barrier protection (may need to pack)
- **Food and water:** In less-developed regions or countries; adherence often poor among hotel tourists (although still at risk); *Water:* Boiled, chemically purified, commercially bottled or carbonated, including for tooth brushing; avoid ice in beverages; *Foods:* Hot, freshly cooked; avoid foods which cannot be boiled or peeled (*Lancet* 2000;356:133)
- **Hygiene:** Frequent hand washing, use of EtOH-based gel if soap & water unavailable
- **Water safety:** Swim in designated areas; caution re: fresh water in developing countries (schistosomiasis), wear shoes on soil/sand w/ potential animal waste (hookworm, strongyloides)
- **Environmental exposure:** Appropriate sunblock, layers, protection to manage heat/cold
- **Animal avoidance:** Steer clear of animals unknown to traveler; seek urgent care for any bites
- **Altitude sickness:** For rapid ascents to >9000 ft, acetazolamide 125 mg BID, starting 1 d before ascent; S/e: paresthesias, urinary frequency (*NEJM* 2001;345:107)
- **Emergency preparedness:** Know where to find health care (ASTMH, State Dept, embassies have lists); consider evacuation insurance & medical alert tag if indicated

## Immunizations (*CID* 2006;43;1499; *CDC "Yellow Book" for Int'l Travel 2012, www.cdc.gov/travel*)

- Routine vaccines esp advisable before int'l travel (see *"Immunizations"*):
  **Tetanus, diphtheria:** q10y Tdap **Measles, mumps, rubella:** ⊕ titers or 2 lifetime MMR doses for int'l travelers born after 1957
  **Influenza:** year-round if available b/c flu season varies regionally
- **Required for some travel**
  **Yellow fever:** Endemic in parts of equatorial Africa + South America (not Asia); vaccine requirements vary by country; severe adverse events ~1/100,000 vaccines; benefit >risk for most travelers to

high-risk areas; caution if pregnant or elderly; q10y booster not needed per WHO; CDC still recommends (*MMWR* 2002;51:1)

**Meningococcus:** Advised for sub-Saharan "belt" in dry season; required for Hajj

- **Recommended for some travel**

**Hepatitis A:** All travelers to developing countries; 1 dose → short-term protection in 94–100% of adults; 2nd dose at 6–12 mos for long-term protection; If older/ill/immunocompromised, consider Ig (administer at separate anatomic site)

**Typhoid:** Vaccinate if ↑ risk country or if expect prolonged unsanitary food/water; IM (booster q2y) or oral (1 tablet QOD × 4, not while on abx; booster q5y)

**Polio:** Previously vaccinated adults need single lifetime IPV booster before travel to countries w/ ongoing transmission (incl Afghanistan, India, Pakistan, Nigeria)

**Hepatitis B:** For endemic areas (much of Africa/Asia/S.Am./E.Eur./Iberia/Arctic) or if likely medical/sexual/etc. contact w/ blood/body fluids; see *"Immunizations"*

**Japanese encephalitis:** Consider for travel to S & E Asia or Western Pacific during transmission season (summer-fall, rainy season in tropics) if staying ≥1 mo or visiting rural/agricultural areas (*MMWR* 2010;59:1)

**Rabies:** Consider if caves, rural work or camping, or staying >1 mo in endemic area (India, SE Asia, Africa) w/o available postexposure Ig (*CMAJ* 2008;178:567)

- **No indication** for vaccination against **cholera, plague, typhus,** or **anthrax**
- **Schedule:** Multiple vaccines at same visit OK, but space live-virus vaccines 1 mo apart

## GI Infection (travelers' diarrhea) (*NEJM* 1993;328:1821; *IDCNA* 2012;26:691; *CID* 2006;43:1499)

- 20–90% incidence during first 2 wks in much of S. Asia, Africa, Middle East, Mexico, Central/S. America; nearly all benign, self-limited (3–5 d); most common etiology is ETEC
- **Prevention: Sources mostly fecal–oral,** include tap water (+ ice),

uncooked & unpasteurized foods, condiments, street vendors, food handlers, nonsterile dishes

Consider bismuth subsalicylate (525 mg QID) as short-term ppx in healthy pts; up to 65% effective, but s/e may be intolerable (*CID* 2002;34:628)

Consider **prophylactic abx** (quinolones or rifaximin) for **high-risk** pts (IBD, severe comorbidities, immunocompromise, on PPIs) or high-stakes trips

- **Self-treatment** (*J Trav Med* 2009;16:161): **If unresolved at 72 h, seek medical attention**

**Treatment of Traveler's Diarrhea**

| Severity | Treatment |
|---|---|
| Mild | **Fluid replacement:** Ample broth, juice, etc. often sufficient for traveler's diarrhea; oral rehydration if ↑ watery diarrhea (*NEJM* 1990;323:891) |
| Moderate (3–5 stools/d, no fever) | **Fluids + antimotility agents:** Loperamide for up to 48 h, fluid replacement, ± abx (*CID* 2008;47:1007) |
| Severe (fever, blood, mucous, >5 stools/d) | **Antibiotics + fluid replacement**<br>Cipro 500 mg BID × 1–3 d (resistance in SE Asia; avoid in pregnancy)<br>*Alt:* Azithro 1000 mg ×1 (s/e: Nausea) or 500 mg QD × 3 d |

## Malaria Prevention (*NEJM* 2008;359:603; *IDCNA* 2005;19:185; *CDC Yellow Book* 2012)

- **Risk:** Regional endemicity info available from WHO (http://www.who.int/malaria/travellers) or CDC (http://www.cdc.gov/malaria/map/); risk also depends on type of accommodation, season, elevation, & duration of exposure; especially increased risk among pregnant women, military personnel, or immigrants visiting region of origin
- **Self-protection** (also ↓ other vector-borne diseases): Insect repellent (DEET 20–50% or picaridin >20%), long sleeves, pants; screens + permethrin-treated net if sleeping w/o A/C

**Antimalarials for Prophylaxis in Travelers (*CID* 2006;43;1499)**

| | Atovaquone/ Proguanil (Malarone) | Chloro-quine | Doxy-cycline | Mefloquine (Lariam) | Prima-quine |
|---|---|---|---|---|---|
| **Dose** | 1 tab daily | 300 mg base weekly | 100 mg daily | 228 mg base weekly | 30 mg base daily |
| **Before trip** | 1–2 d | 1–2 wks | 1–2 d | 2 wks | 1–2 d |
| **After return** | 1 wk | 4 wks | 4 wks | 4 wks | 1 wk |
| **Resistance** | — | Widespread | — | SE Asia | Use for *P. vivax* **only** |
| **Side effects** | GI, HA | GI, HA, visual, insomnia, pruritus | Photo-sensitivity, GI, Candida | Neuropsych (incl severe), GI, cardiac | GI |
| **Contra-indications** | Coumadin, ±pregnancy (relative) | ±Psoriasis | Pregnancy | Ψ disease, Conduction disease | G6PD def, Pregnancy |
| **Cost** | $$$-$$$$ | $$ | $ | $$$ | $$$ |

## Returning Travelers (*J Travel Med* 2000;7:259; *CID* 2007;44:1560; *BMC Infect Dis* 2012;12:386)

- **Common complaints:** Persistent GI illness (10%), skin lesions (8%), respiratory infections (5–13%, depending on season), fever (up to 3%) (cdc.gov)
- **Exposure history:** Insect bites, animal bites, fresh water swimming, bites, sexual contacts, raw meat, seafood, or unpasteurized dairy consumption
- **Fever:** Requires urgent medical attention during & after travel;

**malaria** is most common etiology (~20%); *P. falciparum* potentially fatal, often missed; *P. vivax* or *ovale* can relapse mos later (dormant hypnozoites), even w/ ppx; **also consider dengue, typhoid**, viral **hepatitis**, acute **HIV**, leptospirosis, rickettsia, schistosomiasis

- **Gastrointestinal illness:** If fever & colitis, send stool culture; if upper GI-predominant sxs, consider *Giardia lamblia*, *Cyclospora;* if immunocompromised or diarrhea >10–14 d, O&P
- **Respiratory illness:** If persistent/LRI sxs, consider legionella, influenza, TB

## Online References/Resources for Further Info

- **CDC Travelers' Health web page and "Yellow Book":** cdc.gov/travel
- **WHO International Travel and Health:** www.who.int/ith/en/
- **Global TravEpiNet:** Tools for clinical decision-making: www.gten.travel

## When to Refer (*AFP* 2009;15:583)

- **When traveler or destination are w/ risk or complexity:** Travel medicine specialist
- **Post-travel illness** → travel/ID specialist if significantly ill or any uncertainty in dx/mgmt

# TUBERCULOSIS

## Background (*cdc.gov/tb; who.int*; *MMWR* 2012;61:11; *NEJM* 2013;368:745)

- Tuberculosis (TB) infection occurs in >1/3 of the world's population; range of disease from lifelong asx infection (90%) to pulmonary or extrapulmonary disease
- **Microbiology:** Causative organism *Mycobacterium tuberculosis;* aerobic, slow-growing
- **Transmission:** Acquired via aerosolized transmission of infected **droplets**, often from close contacts of infected pts (household members, etc.); casual contacts at low risk for infection
- **Latent TB:** Infection present but no clinical illness, no evidence of active disease, **not infectious**

- **Active TB** (10% of infected persons): Illness present, infectious (degree varies by site)
  *1° disease:* Illness occurs <24 mos after infection
  *2° disease:* Occurs >24 mos after infection
- **Natural history:** 90% of infected persons have lifelong asx infection (LTBI); 5% develop 1° disease; 5% develop 2° disease ("reactivation")
- **Frequency of extrapulmonary TB sites:** Pleural > lymphatic > bone + joint disease > GU tract > miliary disease, meningitis, peritonitis

## Epidemiology (*CDC; MMWR* 2012;61:11; *Am J of Resp and Crit Care Med* 2000;161:S221)

- **Incidence/Prevalence:** Estimated 4% US population (11 million) has latent TB infection; 10,521 new cases active TB reported in 2011, annual incidence of 3.4/100,000 persons
- **Demographics:** 62.5% active TB cases in US are among foreign-born people (12× ↑ rate than US-born population; particularly ↑ among emigrants from Asia); Mexico, Philippines, India, Vietnam & China most common; within US-born persons racial disparities exist (↑ risk in African-American, Hispanic, Native Hawaiian populations)
- **Risk factors for acquisition:** Employees at long-term care facility, hospital, clinic, lab, high prevalence of TB in country of origin, residents & employees of prisons, jails, SNFs, homeless shelters, known close contact w/ person w/ active TB
- **Risk factors for developing active TB:**
  *Immunodeficiency:* **HIV**, organ transplant, long-term corticosteroids
  *Medical hx:* DM, ESRD, gastrectomy/bypass, CA, silicosis, >10% underwt
  *Recent acquisition:* Within last 2 y; rate ↓ w/ time
  *Other:* EtOH abuse, IVDU; ↓ BMI; healed TB on CXR, inadequate/incomplete prior tx
- **HIV:** 7.9% of TB cases in 2011 w/ known HIV test result were coinfected w/ HIV

## Screening (*CDC; MMWR* 2000;49(RR06):1)

- **Who to screen:** High-risk groups of acquisition (above), annually, or more frequently according to exposure & specific risk of infection; **health care providers annually**

- **Tuberculin skin test:** Uses Mantoux intracutaneous tuberculin (PPD); dependent on cell-mediated immunity; can be ⊖ in up to 25% of active disease (usually pts w/ immunosuppression)
- **Administration/interpretation:** Should be performed by trained personnel; 0.1 mL (5 tuberculin units) injected intradermally on volar surface of forearm; reaction size determined at 48–72 h (may remain ⊕ for 1 wk; if at >72 h, cannot interpret; (details in *MMWR Recomm Rep* 2005;54:1)
- Tuberculin skin test interpretation: Based on **induration (not redness)**; depends on pre-test probability

**"Positive" TST (indicates active or latent TB) (*MMWR* 2000;49(RR06):1)**

| TST Cutoff | Population |
|---|---|
| ≥5 mm | HIV+, close contact of active TB case, fibrotic changes on CXR c/w prior TB, organ transplant recipients, immunosuppressed |
| ≥10 mm | Recent immigrants, IVDU, occupational or residential risk exposure (prison, nursing home, homeless shelter, health care worker), medical conditions listed above |
| ≥15 mm | No known risk factors (therefore no clear indication for test) |

- **Prior BCG vaccination:** (Given to young children in endemic countries) can → false ⊕ but wanes w/ time; hx of BCG should not alter interpretation of TST, but consider IGRA instead
- **Interferon-gamma release assays (IGRA):** E.g., QuantiFERON, T-SPOT; blood test w/ Se/Sp ~92%/97%; Preferred if hx BCG vaccine, or if unlikely to return for PPD read (http://www.cdc.gov/tb/factsheets/testing/IGRA.pdf)

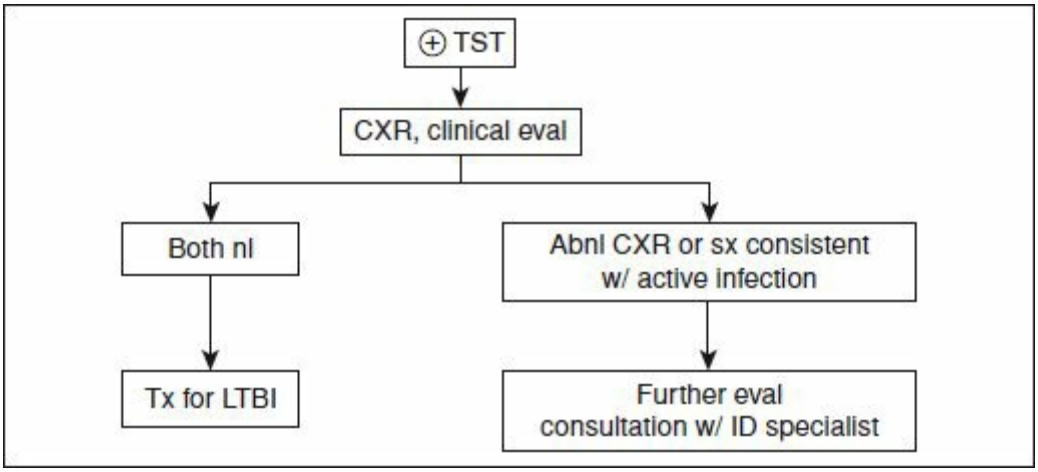

Figure 7-2 Evaluation following positive TST

## LATENT TB INFECTION (LTBI) MANAGEMENT

- **Reporting:** Public health dept must be notified of all new dx of TB (latent or active)
- **HIV ⊕ or pregnant patients:** Best managed w/ assistance of ID specialists
- **General approach**
  1. **Exclude active TB**
  2. **Whom to treat?** Determine risks/benefits of tx for individual pt
  3. **Feasibility?** Assess pt's level of commitment to completing tx
  4. **Regimen?** Decide on appropriate regimen
  5. **Labs?** Baseline labs, if appropriate
  6. **Monitoring?** Monthly evals

### Exclusion of Active TB (*AFP* 2000;61:2667,2681)

- **General approach:** Critical to distinguish between latent & active disease before beginning tx; determined by hx, exam, & diagnostics
- **History:** *Systemic sx:* Wt loss, anorexia, fever, chills, night sweats, fatigue
  *Pulmonary sx:* Cough >3 wks, pleuritic chest pain, hemoptysis
  *Extrapulmonary sx:* Altered mental status, back pain, abdominal pain,
- **Physical exam:** Full PE, including careful pulmonary exam, LN exam
- **Chest radiograph:** In all cases w/ suspicion for LTBI or active TB
  *1° TB:* Typically, pleural effusion, hilar LAD most common, LL lesions
  *Reactivation/2° TB:* UL lesions more common, may show atelectasis, consolidation, pleural effusion, cavitation, or miliary pattern
- If any of above workup ⊕ → TB precautions (N-95 mask, ⊖ pressure room, resp. isolation) → further eval to r/o active TB (e.g., induced sputum for AFB, cultures) in consultation w/ ID specialist or clinician experienced in TB mgmt; initial tx of active TB tx consists of 4-drug regimen (INH, rifampin, PZA, EMB) + $B_6$; see *NEJM* 2013;368:745 & cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm for details
- If any of the above w/u equivocal, high suspicion, or pt immunocompromised → consider further w/u, involvement of ID

specialist

## Whom to Treat

- **Treatment recommended:** All groups w/ ↑ likelihood of reactivation (determined by risk factors, above; model available at http://www.tstin3d.com/en/calc.html)
- Given duration of most regimens & level of adherence required to eradicate, frank conversation re: risks/benefits, pt & provider assessment of potential barriers to adherence, & assessment of pt commitment should be initiated prior to starting tx
- **Factors which may Ø adherence:** ↓ Perceived personal risk of progressing to active TB (incl questions re: LTBI dx), concerns re: frequent venipuncture, cultural, language, or logistical barriers (*AJRCCM* 2006;174:717)

## Treatment (*MMWR* 2000;49:1; *NEJM* 2013;368:745)

- Isoniazid (INH) monotherapy (300 mg QD × 9 mos) considered 1st-line
  *S/e:* GI upset (common), hepatotoxicity (avoid EtOH), neuropathy
  *Labs:* Baseline + monthly LFTs in pts w/ HIV, liver disease, chemotherapy, pregnancy, or regular EtOH use; for everyone else, only as per sx
  *Monitoring:* Monthly eval for hepatitis or neuropathy sx; labs per symptoms
  *Vit $B_6$:* **50 mg QD pyridoxine** recommended for pts w/ at risk for neuropathy (DM, EtOH, malnutrition, HIV)
- **Monthly visits:** Recommended for assessing s/e, monitoring adherence

**LTBI Therapy**

| Drug | Duration | Notes |
|---|---|---|
| **INH**<br>300 mg QD<br>(± 50 mg Vit $B_6$ QD) | 9 mos<br>(6 mos) | **1st-line**<br>6 mos ↓ efficacy, but ↓ cost & may ↑ adherence |
| Rifampin<br>600 mg QD | 4 mos | *S/e:* Orange urine/sweat/tears GI upset, hepatoxicity, drug interactions (incl warfarin & HIV meds), rash |
| INH 900 mg qwk &<br>Rifapentine 900 mg qwk | 12 wks | Recommended only as DOT (Directly-observed therapy) |

- **Completion of treatment:** Give pt copy of TST/IGRA, CXR results, regimen used & duration; they should present this if TB testing required in the future

# URI AND INFLUENZA

## Background (*Ann Intern Med* 2009;151:ITC-5-1; *NEJM* 2003;348:1256; 2009;360:2245)

- Adults have 2–3 viral upper respiratory infections/y → 25 million PCP visits/y in US (*AFP* 2012;86:817); rhinovirus most common, also adeno, metapneumo, RSV, influenza
- **Differential diagnosis:** Bacterial pharyngitis, bacterial sinusitis, infectious mononucleosis, pertussis, PNA, bronchitis, otitis media, & allergic rhinitis (see *"Sinusitis," "Pharyngitis," "Allergic Rhinitis," "Otitis Media," "Pneumonia"*)

## Evaluation

- **History:** Typically, onset of symptoms 24–72 h after exposure, including rhinorrhea, low-grade fever, conjunctivitis, nonproductive cough, coryza, sneezing, pharyngitis, HA, & malaise; symptoms may last up to 2 wks; consider bronchitis (cough >5 d), mononucleosis (adenopathy, splenomegaly), pertussis (paroxysmal cough, ask re: TDaP); see *"Sinusitis"* & *"Pharyngitis";* **high fever** + sudden onset + profound fatigue **should prompt consideration of influenza** (below)
- **Exam:** *HEENT:* nasal discharge, middle ear effusion, tonsillar exudates, post nasal d/c; *Pulmonary:* consolidation, wheezing; *Lymph nodes:* cervical, periauricular
- **Diagnostics:** None needed in simple URI, if influenza suspected, see below

## Treatment

- **Supportive care** (*AFP* 2012;86:153)
  **Decongestants:** Intranasal oxymetazoline (limit to 3 d to avoid rebound congestion), phenylephrine, pseudoephedrine; use cautiously in pts w/ arrhythmias, HTN
  **Antihistamines:** Diphenhydramine, chlorpheniramine effective if combined w/ a decongestant; monotherapy no more effective than placebo; s/e include altered mental status in the elderly, exacerbation of BPH/glaucoma, & drowsiness; nonsedating

antihistamines unlikely to be beneficial

**Analgesics:** ASA, APAP, ibuprofen, naproxen

**Ipratropium:** Inhaler (to control cough) or intranasal (to control rhinorrhea)

**Cough suppressants:** Dextromethorphan (avoid in pts on MAOIs), benzonatate

**Other:** Mentholatum, intranasal cromolyn, ice chips for sore throat, lozenges, hydration, humidifiers, guaifenesin

**Zinc:** Controversial; some trials suggest ↓ in duration of illness; s/e include nausea, abnl taste; avoid intranasal zinc due to risk of permanent anosmia

- **Patient education:** (1) Validate concerns; (2) Acknowledge discomfort; (3) Recommend specific sx relief (consider sx relief prescription); (4) Advise f/u if sx do not improve

  **Abx misuse:** Risks include disruption of nl flora (i.e., *C. diff*), resistance, & allergic reactions; abx do not alter the course of viral diseases (*JAMA* 2003;289:2750)

  **Combination OTC remedies:** May interact w/ other medications, inadvertent overuse

  **Prevention:** Wash hands, cover cough, avoid immunocompromised pts, stay at home

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## INFLUENZA

### Background

- **Natural history:** 33% of pts asx; usually resolves after 3–7 d but can → complications
- **Persons at ≠ risk of complications:** *Pulmonary* disease (incl asthma, COPD, CF), *cardiac* disease (hemodynamically significant), *immunosuppressed* (HIV ⊕, cancer, DM, CKD), Pts >65, SNF or long-term care residents, BMI >40, Native American (cause unknown)
- **Microbiology:** ⊖ ssRNA Orthomyxoviridae; 2 viruses (A & B); A virus undergoes frequent antigenic drift → responsible for most cases; *Antigenic drift:* Minor mutations in hemagglutinin or neuraminidase → seasonal epidemics; *Antigenic shift:* Major antigenic Δ → most of population is susceptible → pandemics (occur every few decades)

- **Bacterial co-infection:** Complicates influenza in 0.5% of healthy pts, 2.5% of pts >65 y, obese, or w/ pre-existing medical comorbidities (*JAMA* 2013;309:275)

## Evaluation (*CID* 2009;48:1003)

- **Presentation:** Distinguishing features vs. URI include **high fever & cough**, severe myalgia, exhaustion, sudden-onset; ask about vaccination, known/suspected flu exposure
- **Testing strategy** varies by clinical scenario (below)
- **During flu season**, testing of pts p/w influenza-like illness (ILI): Fever, respiratory symptoms (incl exacerbation of underlying lung disease)
  *Immunocompetent pts at ↑ risk of complications:* Test if <5 d after sx (virus sheds ~5 d)
  *Immunocompromised pts:* Regardless of time since sx onset (sheds for wks–mos)
- **During institutional outbreak**, test residents, health care personnel, & visitors who present w/ ILI; during larger outbreak (e.g., regional), test those w/ epidemiological link (household contacts of cases, travelers from epidemic region) presenting w/ ILI
- **Testing modality:** Multiple options available
  *Rapid* Ag *testing:* Can detect A vs. B or identify presence of either in <20 mins but ↓ Se; consider PCR testing in pts likely to have influenza on clinical grounds but test negative
  *PCR:* Can identify type A or B, H1N1, H5N1; most sensitive
  *Immunofluorescence:* Can distinguish between type A & Bl
  *Viral culture & serology* (rarely used)

## Treatment

- Determined by timing and whether pt is at ↑ risk for complications; do *not* delay tx while awaiting test results
- **Indications for treatment in outpatient population**
  1. Pts at ↑ risk of complications w/ ⊕ test or highly suspected
  2. Pts of average risk <48 h from disease onset w/ ⊕ test or highly suspected (goal to ↓ illness duration, avoid transmission to ↑ -risk contacts)
  3. Pts w/ persistent mod–severe illness >48 h from onset w/ ⊕ test

(data relatively lacking)

- **Indications for prophylaxis**
  1. Pts at ↑ risk pts of complications or health care workers <48 h after contact w/ infectious individual
  2. SNF residents where an outbreak occurs (>2 lab confirmed cases in <72 h), regardless of pt vaccination status
  3. Consider in exposed unvaccinated pregnant women
- **Treatment agents: Zanamivir** (inh, avoid in COPD/asthma/pregnancy) & **oseltamivir** inhibit viral neuraminidase & ↓ duration of illness 1–3d if given <48 h of sx onset; due to resistance, tx w/ rimantadine or amantadine not recommended
- **Treatment regimen:** (May change w/ seasons; refer to cdc.gov/flu)

**Antiviral Dosage and Schedule**

| Agent | Treatment | Prophylaxis |
|---|---|---|
| Oseltamivir | 75 mg BID × 5 d | 75 mg QD × 7 d* |
| Zanamivir | 10 mg (2 inh) BID | 10 mg (2 inh) QD × 7 d* |

## Prevention

- **General measures:** Hand washing, avoid touching mucous membranes, masks; smoking cessation (*NEJM* 2003;348:1256); **influenza vaccination:** CDC recommends in all individuals >6 mos age; see *"Immunizations"* (*MMWR* 2010;59:1)
- **Patient education:** *Ann Intern Med* 2009;151:ITC-15-15

# HERPES ZOSTER

## Background (*Arch Int Med* 1997;157:1217; *JAAD* 2007;57:S136; *Ann Intern Med* 1995;155:1605)

- **Definition:** VZV causes 2 forms of disease: varicella ("chickenpox") & zoster ("shingles")
- **Risk factors: Age >50 yo, immunosuppression** (s/p transplant, autoimmune disease, immunosuppressive medications esp MMF, malignancy, HIV ⊕), ♀ gender, trauma, stress
- **Complications:** Postherpetic neuralgia (5% in pts <60 yo, 20% in pts

>80 yo) that may last mos–years; bacterial superinfection of the skin (2.3%); meningitis/encephalitis (0.5%); ocular complications (1–2%); motor neuropathy (1–3%); GBS (0.03%); stroke syndromes due to infection of cerebral arteries (1.5–4.4% of HIV ⊕ pts) (*J Pain Symptom Manage* 1996;12:290; *CID* 2010;51:525; *Neurology* 2008;70:853; *Brain* 1994;117:987)

- **Recurrence:** 1–4% of individuals will have a 2nd episode of zoster; ↑ in immunocompromised pts (*Mayo Clin Proc* 2007;82:1341; *Ann Intern Med* 1988;108:221)

## Evaluation (*JAMA* 2009;302:73)

- **History: Prodromal HA & fatigue; skin pain, burning, itching** often in dermatome where the eruption later develops; assess for risk factors as above
- **Physical:** Cutaneous findings of **grouped ("herpetiform") erythematous to violaceous edematous papules** → vesicles on an erythematous base, which can appear umbilicated or pustular if long-standing → hemorrhagic crusting (usually w/in 1 wk, no longer infectious); usually affects only **one dermatome** but can affect 2–3 consecutive dermatomes
- **Diagnosis:** Determined by morphology & distribution; confirmatory tests are best done in vesicular phase: direct fluorescent Ab testing (quickest to result, usually within 24–48 h), viral culture, skin bx

## Management

- **Acute neuritis:** NSAIDs, APAP, ice for mild pain; opioids may be necessary for mod–severe pain; neither glucocorticoids nor TCAs have been shown to help in the mgmt of acute neuritis or in preventing postherpetic neuralgia (*JAMA* 2009;302:73)
- **Antivirals in immunocompetent hosts: Valacyclovir 1000 mg PO TID,** famciclovir 500 mg PO TID, or acyclovir 800 mg PO 5×/d × 7 d; ↓ time to resolution of lesions if given **within the first 72 h**, lessens acute neuritis & helps prevent postherpetic neuralgia (*JAMA* 2009;302:73; *CID* 1996;22:341; *Arch Intern Med* 1997;157:909; *Scand J Infect Dis Suppl* 1991;80:62)
- **Antivirals in immunocompromised hosts:** Treat all pts even if they

present after 72 h; if disseminated, will need urgent ED referral for admission & acyclovir 10 mg/kg IV q8h (w/ IV fluid to prevent crystalluria)

- **Postherpetic Neuralgia**

**Treatment of Postherpetic Neuralgia**

| Medication Class | Examples | Considerations |
|---|---|---|
| Anticonvulsants | Gabapentin, pregabalin, divalproex sodium | Dizziness, somnolence, dry mouth, edema, wt gain reported<br>Abrupt d/c may → withdrawal sx |
| TCAs | Nortriptyline, amitriptyline, desipramine | Anticholinergic effects & lag time, (up to 3 wks), can ↑ QTc |
| Opioids | Codeine, tramadol | Potential for addiction & diversion |
| Topical Agents | Capsaicin, lidocaine patch | Intolerable in up to 1/3 of pts |

## When to Refer (*NEJM* 2005;353:e14)

- **Herpes zoster ophthalmicus:** Reactivation of VZV in CN V1 dermatome; accounts for 10–25% of all zoster cases; presents w/ **vesicles & erosions on nasal tip** (Hutchinson sign); 71% have ocular complications including conjunctivitis, episcleritis, keratitis, corneal scarring, iritis, vision loss in 15% → **urgent ophthalmologic eval** (*JAAD* 2007;57:S136)
- **Herpes zoster oticus (Ramsay Hunt syndrome):** Reactivation of VZV in CN VII dermatome, geniculate ganglion; p/w ipsilateral facial paralysis, ear pain, occipital HA, vesicles in the auditory canal & auricle; ± numbness over jaw, ↓ taste, vestibular symptoms → ENT referral (*Ann Neurol* 1994;35:S62; *JAMA* 2009;302:73)
- **Disseminated zoster:** Prevalence in immunosuppressed pts; defined by >20 vesicles outside of 1 dermatome; consider derm referral

## Prevention

- **Persons w/ no hx prior varicella infection:** Avoid contact w/ pts w/ zoster until lesions are crusted as they may acquire 1° varicella (chickenpox)
- **Pregnant women w/ no hx varicella infection:** Avoid contact w/ pts w/ zoster as *1°* varicella infection may occur & put the fetus at risk of congenital varicella (no evidence recurrent VZV can → congenital

varicella)

- **Varicella zoster virus vaccine:** Live-attenuated vaccine administered as a 1-time SC injection; see *"Immunizations"* for details

# URINARY TRACT INFECTIONS

## Background (*NEJM* 1996;335:468; 2012;366:1028; *J Urol* 1993;149:1046; *Ann Epidemiol* 2000;10:509)

- **Acute uncomplicated cystitis:** Acute (< 14 d) infection of the lower urinary tract in an o/w healthy, nonpregnant woman—the classic UTI seen in 1° care
- **Complicated cystitis/UTI:** Acute UTI in anyone else (see "Red Flags" below)
- **Pyelonephritis:** Infection of the kidneys
- **Epidemiology:** Lifetime incidence in ♀ ≥ 50%; 11% of ♀ report at least 1 UTI/y; much rarer in young ♂, although after age 65, incidence equal between ♀ & ♂
- **Microbiology:** *E. coli* cause 80% of uncomplicated UTIs; other pathogens: *Proteus mirabilis, Staph saprophyticus*, & *Klebsiella pneumoniae* (*CID* 1999;29:113); complicated UTIs may be caused by broad variety of organisms
- **Risk factors:** Previous UTIs, sex, spermicide use (alters vaginal flora), BPH, DM2

## Evaluation (*AFP* 2002;65:1589; *Ann Intern Med* 2012;156:ITC3-1; *JAMA* 2002;287:2701)

- **History:** Dysuria, frequency, suprapubic pain, malodorous urine, & urgency in the absence of vaginal sx argue strongly for UTI; may present as altered mental status or incontinence in the elderly; elicit sexual hx (i.e., new partners) to evaluate for STIs
  **Red flags (complicated UTIs):** ♂, childhood UTIs, urinary tract abnormality (incl indwelling catheter or recent instrumentation), DM, hx pyelonephritis, nephrolithiasis, elderly, recurrent UTIs, recent abx, hx multidrug resistant UTIs
  **Telephone diagnosis** of acute uncomplicated UTIs using established protocols is safe & effective (*Wisc Med J* 2007;106:326; *Am J Med* 1999;106:636; *Arch Intern Med* 2004;164:1026)
- **Differential diagnosis:**
  **Gonococcal or Chlamydial urethritis:** H/o STIs, new sex partners (see *"STI"*)
  **Interstitial cystitis:** Bladder pain related to filling/emptying w/

frequent voids occurring over mos; accompanied by abdominal, hip, pelvic, or buttock tenderness

**Irritants:** Reaction to tampons, condoms, detergents, etc.

**Pyelonephritis:** Fevers, flank pain, rigors, CVA tenderness, N/V

**Vaginal infections (i.e., trichomonas, candidiasis) or PID:** Vaginal odor, d/c, pruritus, dyspareunia, pelvic pain (see *"Vaginitis"*)

**Prostatitis, BPH, or epididymitis** in ♂

- **Exam:** Assess for suprapubic or CVA tenderness; consider pelvic exam
- **Diagnostics:** Uncomplicated UTI may be diagnosed based on sx alone (i.e., clinical dx); routine U/A or UCx not needed; midstream U/A & UCx if dx unclear or concern for sev infection/pyelonephritis

  **Urine dipstick:** Leukocyte esterase, Se 75–96%/Sp 94–98% for WBC; nitrite detects *Enterobacteriaceae* only (*Med Clin North Am* 1991;75:313)

  **Urinalysis: Pyuria** (> 10 neutrophils/HPF [95% Se, 71% Sp]) + **bacteriuria** ± hematuria (> 5 RBC/hpf); pH > 6.5 suggests urea-splitting organism such as *Proteus*

  **Urine culture:** > $10^5$ cfu/mL used to be the gold standard for dx, but if hx strongly suggests UTI then a lower cut-off ($10^2$ cfu/mL) reasonable

## Treatment (*AFP* 2000;61:713; *AFP* 2010;82:638; *CID* 2011;52:e103; *NEJM* 2003; 349:259)

- **Urinary analgesic:** Phenazopyridine 200 mg PO TID × 2 d; avoid in pts w/ G6PD deficiency
- **Uncomplicated UTI:** Cx not required but can be very helpful if tx failure; obtain if possible

  **Nitrofurantoin** monohydrate macrocrystals 100 mg PO BID × 5 d is preferred for 1st-line treatment

  **Trimethoprim–sulfamethoxazole** 160/800 mg (DS) one PO BID × 3 d if no abx use in past 3 mos, no recent hospitalization, & local resistance is < 20%

  **Fosfomycin** 3 g PO × 1

  **Amoxicillin–clavulanic acid** 500/125 mg PO BID × 7 d (2nd-line agent)

  **Fluoroquinolones** should *not* be used routinely; save for complicated illness

- **Complicated UTI:** Preferred regimen varies by case; review prior culture data; may use broad-spectrum abx initially then narrow based on culture results
  **Empiric therapy:** Ciprofloxacin 500 mg PO BID or levofloxacin 500–750 mg PO QD × 7–14 d in pts who have not recently received FQs & not from long-term care facility; do not use moxifloxacin (GU drug concentration too low)
  **Healthy young men:** Ciprofloxacin 500 mg PO BID × 7–14 d, or TMP-SMX 160/800 mg (DS) one PO BID × 7 d; avoid nitrofurantoin or b -lactams in ♂, as they do not treat occult prostatitis
- **Recurrent UTI:** > 2 UTI in 12 m
  **Prevention:** Consider cranberry juice, avoid spermicides; unclear whether hydration, postcoital voids, methenamine hippurate, probiotic vaginal suppositories, wiping urethra front-to-back are effective
  **Prophylaxis:** See below
  **Self-treatment:** TMP-SMX or FQ; call if sx > 48 h
  **Postmenopausal:** Consider intravaginal estrogen cream
- **Pyelonephritis, uncomplicated:** Pts who are o/w healthy, nonpregnant, tolerating POs, have close f/u, & who lack s/sx of systemic toxicity may be considered for outpt Rx; *always* get UCx prior to tx; consider imaging if pt is ♂, diabetic, has no response to abx after 72 h, or has renal colic
  **Empiric treatment:** Ciprofloxacin 500 mg PO BID **or** levofloxacin 500 mg PO QD **or** TMP-SMX 160/800 mg (DS) one PO BID × 14 d; consider an initial IV dose × 1 (cipro 400 mg IV, Cftx 1 g IV); always give 1 IV dose of Cftx or ciprofloxacin if community FQ resistance > 10%; tailor Rx to UCx results once available; consider renal abscess if failure to respond to appropriate abx; nitrofurantoin ineffective in upper urinary tract
- **Asymptomatic bacteriuria:** Defined as > $10^5$ cfu/mL of a single organism; found in 5% of women; treat if pt is pregnant, undergoing hip arthroplasty or a urologic procedure; pts w/ DM do not need to be screened or treated for asx bacteriuria (*NEJM* 2002;347:1576)
- **Symptomatic candiduria:** Fluconazole 200 mg PO QD × 14 d; consider U/S or CT for persistent candiduria in DM pts to assess for

hydronephrosis, fungal balls, or abscesses

## Prophylaxis

- Considered in cases of recurrent UTI; NNT to prevent 1 UTI/y = 2.2; NNH to cause 1 side effect (nausea, rash, candidiasis) = 13.5 (*AFP* 2005;71:1301)
- **Initiation:** 6 mos trial w/ observation for infection; start after latest infection resolved (confirmed w/ negative UCx); > 12 mos' duration not evaluated; not recommended in pts at risk for complicated UTIs
- **Regimens:** TMP-SMX $^{1}/^{2}$ ss tab (40/200 mg) PO QHS if local *E. coli* resistance < 20%, **or** nitrofurantoin 100 mg PO QHS; may also use ciprofloxacin, norfloxacin, cefaclor, cephalexin; FQs & TMP-SMX **contraindicated** in pts who could become pregnant
- Chronic nitrofurantoin associated w/ hepatitis, neuropathy, pulm complications—counsel pt; advise risk & sx of *C. diff* infection
- **Postcoital ppx:** Nitrofurantoin 50–100 mg PO **or** cephalexin 250 mg PO × 1 postcoitally; TMP-SMX $^{1}/^{2}$ SS tab (40/200 mg) PO **or** FQ (e.g., ciprofloxacin 125 mg PO) **if** pt has high-efficacy birth control regimen

# BACK PAIN

## Background (*JAMA* 2008;299:2067; *NEJM* 2001;344:363)

- **Epidemiology:** 2nd most common complaint in primary care, 66% lifetime risk in adults; 60–70% of cases resolve in 6 wks, 80–90% by 12 wks

### Etiologies of Back Pain and Common Presenting Symptoms

| |
|---|
| **Muscle or ligament injury (70%):** Sudden onset of pain, often w/ precipitating movement, may radiate to buttock, upper thigh; feeling of "something giving way" |
| **Degenerative joint disease (10%):** Chronic, subacute pain often assoc w/ other OA |
| **Disk herniation (4%):** L5–S1 most common; ⊕ straight leg test; worse w/ coughing, straining; Sciatic pain (sharp/burning, radiating down buttock, thigh, or leg) in dermatomal distribution |
| **Compression fracture (4%):** Sudden onset of pain in pt w/ risk factors for fracture (i.e., osteoporosis, steroid use, malignancy, elderly) after coughing, bending, lifting, or minor trauma; loss of height, point tenderness; may be presenting sign of osteoporosis |
| **Spinal stenosis (3%):** Pain in lower back, buttocks (pseudoclaudication), wide gait, paresthesias (often bilateral), worsened by standing, walking (downhill > uphill, in contrast to claudication) and ↓ by sitting/bending/leaning forward (*JAMA* 2010;304:2628; *NEJM* 2008;358:818) |
| **Spondylolisthesis (2%):** Forward subluxation of vertebrae causes chronic ligamentous pain worse w/ activity, relieved by rest |
| **Malignancy (<1%):** Gradual onset of pain w/ activity, unrelieved/worsened by supine position; may be accompanied by incontinence/urinary retention, saddle anesthesia, muscle weakness, wt loss; breast, gastrointestinal, lung, lymphoma/leukemia, myeloma, & prostate most common malignancies |
| **Epidural abscess, vertebral osteomyelitis, discitis (0.01%):** Fever, back pain, neuro deficit in minority of pts; risk factors include instrumentation, HIV, IVDU or TB, & hematogenous seeding from a UTI, catheter, or abscess (*NEJM* 2006;355:2012; 2010;362:1022) |
| **Spondyloarthropathies (<1%):** Skeletal manifestations of psoriatic arthritis, IBD; Ankylosing spondylitis: onset of pain insidious, improves w/ motion, worse in the morning/better at night, & typically occurs in ♂ pts 20–40 y |
| **Extraspinal (2%):** Referred pain from hip, SI joint; AAA/TAA, endometriosis, fibroids, nephrolithiasis, pancreatitis, cholecystitis, pyelonephritis, neuropathy, claudication |

### Anatomic Localization of Sciatic-type Back Pain

| Nerve | Sensory | Motor |
|---|---|---|
| L4 | Pain radiating to anterior thigh; sensory abnormalities anterior–lateral thigh, medial calf | Difficulty rising from chair, extending leg at knee, heel walk; ↓ patellar reflex |
| L5 | Pain to buttock, down lateral thigh & calf to foot; sensory abnormalities lateral calf, great toe | Difficulty w/ heel walk, dorsiflexion of great toe; normal reflexes |
| S1 | Pain to buttock, down posterior thigh/ calf to lateral foot; ↓ sensation plantar/lateral foot, posterior leg | Difficulty w/ toe walk; ↓ plantarflexion of toe & foot; ↓ ankle reflex |

## Evaluation (*Ann Intern Med* 2007;147:478; *AFP* 2007;75:1181)

- **History:** Location, provocative/palliative factors, quality, radiation, severity, timing, hx trauma/back pain; *Assoc sx:* fever, bowel/bladder incontinence, neuro deficits, saddle anesthesia; *Risk factors:* steroid use, malignancy, infection, depression, avoidance behaviors, ergonomics

  **Occupational injury:** Documentation of injury history, functional limitation; risk factors for chronic disabling back pain include pre-existing psychological problems/chronic pain, job dissatisfaction, see *"Chronic Pain"* (*NEJM* 2005;352:1891)
- **Exam:** Flexibility of spine; palpation of spine; toe/heel walk, rising from chair; neuro exam (strength, sensation, reflexes); pedal pulses; observation of walking, spontaneous activity (i.e., getting on & off exam table, getting dressed) helpful; exam of hip joint

  **Straight-leg test:** Somewhat useful for detecting herniated discs (91% sensitive, 26% specific) (*Spine* 2000;25:1140); with pt supine & leg extended, examiner lifts leg at heel → considered ⊕ if sciatica reproduced between 30–70 degrees; **Crossed straight-leg test:** elevation of opposite leg reproduces sx (↑ Sp)
- **Workup:** Hx/PE suggestive in most cases; imaging in absence of red flags does not improve clinical outcomes (*Lancet* 2009;373:463); abnl findings common in asx pts (i.e., degenerative changes, herniation, stenosis) (*NEJM* 2001;344:363)

  **Labs:** Guided by clinical scenario: consider ESR/CRP, CBC, BCx, Aφ, HLA-B27 (in pts w/ idiopathic back pain >3 mos & <45 y w/ possible spondyloarthritis); for pts on chronic opioids, random drug testing to assess for presence of opioids (prevent diversion) and detect substance use d/o (*JAMA* 2013;309:919)

  **Radiographs:** Useful in diagnosing compression fractures, ankylosing spondylitis

  **MRI:** Cauda equina syndrome, epidural abscess, malignancy; ~2/3rds of healthy adults without back pain have abnl findings on spine MRI & sx may not relate to imaging findings (*NEJM* 1994;331:69; 2013;368:999,1056)

  **Electromyography and nerve conduction studies:** Useful in pts w/ subacute radiculopathy & an unrevealing MRI

### Red Flags to Prompt Imaging (American College of Radiology Criteria www.acr.org)

| | |
|---|---|
| Unexplained fevers or wt loss | Trauma/heavy lifting & age >50 y |
| Immunosuppression | Hx malignancy or IVDU |
| Age >70 y | Prolonged steroid use |
| Osteoporosis | Focal neuro deficit |
| Duration >6 wks | New back pain in pt >50 y |
| Indwelling catheter, recent UTI or cellulitis | Pain at night |
| Bowel/bladder incontinence | Urinary retention |

## Treatment

### Acute/Subacute (<12 wks)

| |
|---|
| **Urgent surgical eval:** Indicated for cauda equina, motor weakness, cord compression |
| **Medications:**<br>**APAP +/– NSAIDs:** 1st-line, scheduled for short course<br>**Topicals:** Lidocaine, capscaicin<br>**Muscle Relaxants:** Cyclobenzaprine, baclofen, tizanaidine, methocarbamol may be combined w/ NSAIDs for short course; caution re: sedation, drug interactions; avoid cyclobenzaprine in pts w/arrhythmia, CHF, hyperthyroid; low-dose diazepam may also be used (2nd-line 2/2 abuse potential)<br>**Opioids:** Should be used sparingly and only for a short course if needed<br>**Bisphosphonates:** Pts w/ osteoporotic compression fractures & pain unrelieved by PO meds |
| **Nonpharmacologic Therapy:**<br>**Physical activity as tolerated:** Pain relief/function improved in pts advised to stay active compared to bed rest (*Cochrane Database Syst Rev* 2010;16:CD007612)<br>**Reassurance:** 90% of pts w/ acute, nonspecific back pain improve in <2 wks w/o intervention (*BMJ* 1994;308:577)<br>**CAM:** Physical therapy, yoga (chronic low back pain), acupuncture, chiropractic, aquatherapy, massage tx; Heat; cold compresses (acute back pain)<br>**Self-care:** Education books (e.g., *The Back Book*); back braces or abdominal binders<br>**Lifestyle modification:** Good lifting techniques (bend knees, not back); lay flat w/ pillow under knees to straighten spine; firm/tempurpedic mattress; workplace ergonomic eval; padded mats if pt must stand for long periods; evidence low quality, but may be helpful |

### Chronic (>12 wks)

| |
|---|
| **Epidural steroid injections:** Consider for chronic radicular pain from disk herniation; Cochrane review found "insufficient evidence to support use in subacute & chronic low back pain … it cannot be r/o that specific subgroups of pts may respond" (*Spine* 2009;34:49) Contaminated steroids assoc w/ 2012 fungal meningitis outbreak (*MMWR* 2012;61:1) |
| **Medications:** SNRIs (i.e., duloxetine), TCAs (see *"Chronic Pain"*) |
| **Behavioral modification:** Wt loss, cognitive behavioral Rx, smoking cessation |
| **Herniated discs & spinal stenosis:** Surgical correction for herniated discs (i.e., discectomy or microdiscectomy) or sx spinal stenosis (laminectomy or intraspinous spacer implantation) assoc w/ short-term benefits compared to conservative mgmt that diminish over time (*Spine* 2009;34:1094); pts treated w/ nonoperative mgmt for herniated discs improve substantially over 2 y (*JAMA* 2006;296:2441) |
| **Vertebral fusion:** Degenerative spondylolisthesis w/ laminectomy; consider for pts w/ >1 y disabling nonspecific back pain refractory to behavioral modification/intensive interdisciplinary rehabilitation (*Spine* 2009;34:1066) |
| **Osteoporotic compression fractures:** Vertebroplasty provided no benefit compared to sham procedures (*NEJM* 2009;361:557,569) |

| |
|---|
| **Other (multidisciplinary specialist consultation recommended):** Best evidence for multidisciplinary rehab/chronic pain clinic & CBT; other options include ablation, intrathecal analgesic pumps; chronic pain clinic referral; pts who fail back surgery for disc herniation may benefit from spinal cord stimulation; facet joint injections |

- **Patient information:** *JAMA* 2000;284:21; 2013;309:1738 (general back pain); *JAMA* 2009;302:216 (sciatica); *JAMA* 2008;299:980 (spinal stenosis); *JAMA* 2010;304:114 (OA of spine); *JAMA* 2006;296:2512 (herniated discs); *JAMA* 2012;308:2047 (epidural steroid injections)

# FIBROMYALGIA

## Background (*Arthritis Care Res* 2010;62:600; *J Rheumatol* 2007;34:1415)

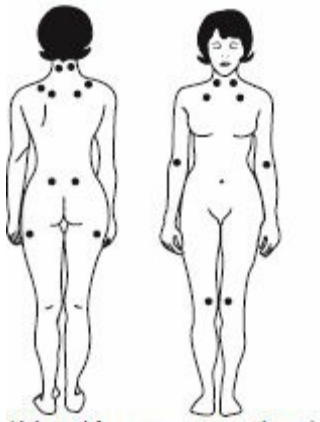
- **Definition:** Generalized pain amplification w/ widespread musculoskeletal pain & fatigue, thought due in part to aberrant central pain processing, sleep disturbance, anxiety, & depression may contribute/exacerbate sx
  **Fibromyalgia synonyms:** Myofascial pain syndrome, fibromyositis, fibrositis
- **1990 ACR criteria:** 85–90% sensitive, ~80% specific, must have both:
  1. Hx widespread pain present for ≥3 mos; pain must be in both sides of body (above & below waist); axial skeletal pain needs to be present (spine or anterior chest)

2. Pain in 11 of 18 tender points upon applying 4 kg pressure (enough to blanch nail bed)

- **Epidemiology:** Affects 2–5% US adults, ♂:♀ , 7:1; average time to diagnosis 5 y
- **Risk factors:** Depression, anxiety, sleep disturbance, FHx, life stressors, trauma/injury
- **Differential diagnosis:** Autoimmune disease (SLE, RA, myositis, PMR), malignancy, drug toxicity (i.e., statins), OSA, hypothyroidism, depression, chronic fatigue, Lyme

## Evaluation and prognosis (*Arthritis Rheum* 2010;62:3101; *Mayo Clin Proc* 2011;86:457)

- **History:** Triad of diffuse pain for >3 mos; hx fatigue, sleep disturbance, anxiety, depression; other sx include cognitive difficulties, stiffness, HA, pelvic, abdominal wall & chest wall pain; screen for depression, anxeity, sleep apnea, restless leg
- **Exam:** Only finding should be pain in at least 11 of 18 anatomic points; additional findings suggest separate processes; **Findings *inconsistent* w/ fibromyalgia:** joint swelling, muscle atrophy, rash, alopecia, abnl labs, focal neuro findings (numbness, weakness)
- **Workup:** Labs not necessary to confirm dx, but useful to r/o other disease; **Recommended:** ESR, CRP, Chem-12, TFTs, CBC, vit D; consider iron studies, $B1_2$ (based on hx & PE); **Not recommended:** ANA, RF, CCP unless H&P suggestive or if ↑ ESR/CRP
- **Prognosis:** 10–30% of pts are disabled; fibromyalgia does not ↑ mortality but may be assoc w/ ↑ risk of suicide



(Adapted from www.niams.nih.gov/Health_Info/Fibromyalgia/)

## Treatment (*AFP* 2007;76:247; *JAMA* 2004;292:2388; 2009;301:198)

- **General principles:** Mainstay is to address contributing sleep disturbance/insomnia see *"Insomnia"*), anxiety (see *"Anxiety"*), depression (see *"Depression"*); Nonpharmacologic approaches should be tried first; fibromyalgia should never be treated w/ opioids, which can amplify pain; APAP may be helpful for pain control during flares
- **Pharmacologic:** Indicated if persistent/severe sx despite conservative Rx; no clear guidance for one agent over another, but can consider starting w/ amitriptyline or cyclobenzaprine; duloxetine/milnacipran in AM may help if fatigue is predominant; Pregabalin at night helpful for severe sleep disturbances + pain; combination Rx in pts refractory to monotherapy w/ rheum guidance
- **Nonpharmacologic:** Educate about dx, tx, prognosis, sleep hygiene, manage expectations, reassure about benign nature, validate that this is a "real disease"

  **Physical activity:** Improves function, pain, mood, fatigue; Tai Chi more effective than wellness education + stretching (*NEJM* 2010;363:743)

  **Cognitive behavioral therapy:** Improves coping, pain, fatigue, mood, anxiety

  **Acupuncture, massage, yoga:** Along w/ mind–body center referral may ↓ pain

### Fibromyalgia Treatments

| Drug | Dosing | Outcome | Adverse Reactions |
|---|---|---|---|
| **Amitriptyline** (TCA) | Start 5–10 mg QHS, ↑ to 25–50 mg QHS | ↓ Pain, sleep disturbance, fatigue | Constipation, dry mouth, ↑ wt ↓ concentration |
| **Cyclobenzaprine** | Start 10 mg QHS, ↑ to 10 mg QAM & 20–30 mg QHS | ↓ Pain & fatigue, less antidepressant effect | Sedation, dry mouth, dizziness, GI upset |
| **Pregabalin** | Start 75 mg BID, ↑ to 150–225 mg BID | ↓ Pain, ↑ in fibromyalgia ratings vs. placebo | Dizziness, dry mouth, ↑ wt, somnolence |
| **Duloxetine** (SNRI) | Start 30 mg/d, ↑ to 60 mg/d | | Nausea, dry mouth, somnolence, fatigue |
| **Milnacipran** (SNRI) | Start 12.5 mg/d, ↑ to 50 mg BID | | Nausea, HA, dizziness, palpitations |
| **Gabapentin** | Start 100 mg QHS, ↑ to 600 mg TID | ↓ Pain, less evidence vs. pregabalin | Sedation, dizziness, lightheadedness, ↑ wt |

- **When to refer:** Uncertain Dx, unusual/refractory sx, abnl labs, refractory anxiety/depression
- **Patient information:** cfidsselfhelp.org; treatcfsfm.org

# FOOT & ANKLE DISORDERS

## Evaluation (*BMJ* 2003;326:1)

- **History:** Inciting injuries, specific location of pain, functional impairment, chronicity of sx, exacerbating conditions; medical hx including DM, arthropathies, vascular disease, neuropathy
- **Exam:** Assess gait, ability to toe rise; look at ankle alignment from behind; assess hindfoot alignment & arch (cavus vs. neutral vs. planus); visually inspect pedal skin & nails for soft tissue breakdown or asymmetry in color, temp, texture; palpate foot for areas of tenderness, masses or swelling; assess active ROM, including tibialis anterior (ankle dorsiflexion), gastrocsoleus (plantarflexion), inversion w/ the foot plantar-flexed (posterior tibialis), eversion w/ the foot dorsiflexed (peroneals); gentle passive ROM of ankle (tibiotalar joint), subtalar joint, transverse tarsal joint, Lisfranc joint (plantarflexion of 1st metatarsal & adduction), & MTP joints; palpate pulses (dorsalis pedis & posterior tibial) & capillary refill; test reflexes & sensation to light touch & pinprick
- **Imaging:** Radiograph of ankle should include AP, lateral, mortise; Radiograph of feet should include AP, lateral, oblique, & wt-bearing views (default unless assessing for fracture or pt unable to bear weight); stress fracture may take 2–6 wks to be apparent on radiographs; MRI more sensitive

  **Ottawa rules: Ankle radiograph for ankle injury if:** Pain near malleoli + either (1) Inability to bear wt (4 steps) immediately after injury & at eval **or** (2) Bone tenderness at posterior edge/tip of either malleolus; **Foot radiograph for foot injury if:** Pain at midfoot + either (1) Inability to bear wt (4 steps) immediately after injury & at eval **or** (2) Bone tenderness at navicular bone or base of 5th metatarsal (Se nearly 100%, Sp 30–50%)

## ATRAUMATIC FOOT PAIN (*AFP* 2007;76:975; 2011;84:676; *NEJM* 2004;350:2159)

- **Calcaneal bursitis:** Infra- or retrocalcaneal pain in SC or subtendinous bursa; **Dx:** Tenderness & swelling, pain w/ supracalcaneal squeeze; **Ddx:** Achilles tendinopathy; **Tx:** Time, NSAIDs, ice
- **Hallux rigidus:** OA of the 1st MTP joint; **Dx:** Sx include ↓ motion, crepitation, tenderness, ✔ radiographs; **Tx:** Nonspecific; stiff sole or rocker sole shoe
- **Morton (interdigital) neuroma:** Irritation of digital nerve usually in 3rd or 4th web space; burning pain in webspace ± numbness of digits; **Dx:** Reproduction of sx w/ pressure in the web space; Mulder click—palpable click between metatarsal heads elicited by compressing forefoot; **Ddx:** Stress fracture; **Tx:** Podiatry referral for orthotics & steroid injection in refractory cases
- **Plantar fasciitis:** Medial/plantar heel/arch pain ↑ in AM & w/ standing after prolonged sitting (*Ann Intern Med* 2012;156:ITC-1) appears to be a self-limiting enthesopathy
  **Risk factors:** Pts often middle-aged; specific risk factors include ♀ gender, obesity, tight gastrocnemius, & prolonged wt bearing at work
  **Dx:** Tenderness of plantar fascia originates from calcaneus; **Ddx:** Tibial nerve compression (Tinel sign behind medial malleolus), bursitis at Achilles insertion, calcaneal stress fracture (squeeze test), heel pad pain (pain more posteriorly at center of heel pad), posterior tibial tendinitis (palpate tendon behind medial malleolus)
  **Tx:** NSAIDs, ice, heel cord stretching & plantar fascia stretches, silicone gel heel cups; steroid injection in refractory cases may be considered; wt loss
- **Cysts/ganglions:** Pain w/ weight bearing, friction; **Dx:** Clinical, U/S, MRI; **Tx:** Surgery for off-loading, aspiration, excision if painful
- **Bunions:** 1st MTP joint w/ medial prominence; pain onset gradual, progressive, ↑ w/ ROM, weight-bearing, shoe pressure; a/w RA, OA, DM, neuropathy, ↑ age, FHx, footwear, running; **Tx:** Footwear modification, bunion shield, surgical correction only for refractory pain or deformity severe enough to prevent nl shoewear (i.e., not for cosmesis); APAP for pain relief

- **Pes planus (flat foot) or Pes cavus (high arch): Dx:** Clinical, plain films; varied adult presentations; Cavus often assoc w/ neuromuscular disease; planus assoc w/ medial ankle pain → suspect adult-acquired flat foot 2/2 posterior tibialis pathology; **Tx:** Off-the-shelf orthotic w/ medial arch support; otherwise, referral for footwear modification, orthoses, bracing, surgical correction
- **Plantar fibromatosis:** Foot manifestation of Dupuytren disease; genetic (autosomal dominant; British Isles & Scandinavia); firm, palpable SC plantar nodules, continuous w/ plantar fascia; pts often p/w pain, but lesions not typically painful; most pts do not bring this problem to the attention of a doctor; **Tx:** Nonspecific palliative

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## SKIN AND NAIL DISORDERS (*AFP* 2001;63:677; 2002;65:2095; 2009;79:303; 2012;85:779)

- **Hyperkeratotic:** Pressure induced (corns) vs. shear-induced (calluses); assoc w/ neuropathy, deformity, activity, middle to advanced age; **Ddx:** Verruca plantaris, dermatofibroma, hypertrophic scar, porokeratosis; **Tx:** Topical keratolytics (lactic acid 12% lotion, urea 20–40% cream, footwear modification)
- **Verruca:** Virally-induced (HPV) hyperkeratotic lesions w/ punctate bleeding, disrupted skin lines, pain w/ compression; ↑ in youth, immunosuppressed, skin trauma, gym/pool use; **Tx:** Topical acids/vesicants, see (*"Benign Skin Lesions"*)
- **Blisters:** Serous/blood filled vesicles/bullae; ↑ w/ friction, shear, deformity, activity, tight shoes, hyperhidrosis, neuropathy; **Tx:** Neoprene insoles, acrylic socks, off-loading, aspiration (do not de-roof); if de-roofed, hydrocolloid dressing (*Sports Med* 1995;20:3)
- **Tinea pedis (Athlete's foot):** Rubor, scaling, desiccated vesicles, moccasin distribution, maceration fissuring, pustules, malodor; **Dx:** +KOH; **Ddx:** Eczema, xerosis, dermatitis; **Tx:** Topical antifungal (see *"Tinea"*)
- **Xerosis cutis:** Skin dry, rough, pruritic, fissuring; ↑ w/ age, DM, autonomic dysregulation; **Tx:** Topical emollients, barrier creams; discourage prolonged, frequent or hot foot soaks
- **Ingrown nail (Onychocryptosis):** Nail plate encroaching upon nail fold w/ pain, swelling, bleeding/drainage, hypertrophy of nail

fold ± paronychia (see below); assoc w/HAV, tight footwear, improper trimming; **Tx:** Foot soaks, wide shoe, Podiatry referral

- **Onychodystrophy:** Δ in nail plate morphology ± pain; ↑ w/ age, DM, runners; **Hutchinson sign:** Brown/black pigmentation of nail asssoc w/ melanoma
- **Onychomycosis:** Fungal nail infection; onychodystrophy + nail erosion; ↑ w/ DM, immunocompromised, ↑ age, nail salon use, trauma, tinea pedis; **Dx:** +KOH, +PAS; **Tx:** Podiatry referral, antifungal tincture (ciclopirox), PO terbinafine ( ✔ LFTs); see *"Tinea"*
- **Paronychia:** Nail fold infection a/w onychocryptosis; erythema, warmth, edema, purulent d/c, pain; **Tx:** Saline soaks BID, topical antiseptic, consider oral abx, prompt podiatry referral
- **Nail contusion:** Subungual hematoma/seroma s/p stubbing or crush injury; if pain in toe, obtain plain film; **Ddx:** Glomus tumor (benign subungual vascular lesion); **Tx:** If no fracture, Podiatry referral; if fracture + nail bed laceration, podiatry/ortho referral

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## FOOT & ANKLE TRAUMA (*AFP* 1999;59:2156; 2003;68:2413; 2007;76:817)

- **Achilles tendon rupture:** "Popping" & sudden onset of pain → instability

  **Dx:** Ecchymosis & palpable deficit posterior ankle, Thompson test ⊕ (no plantarflexion of foot w/ calf squeeze), MRI, U/S

  **Tx:** Referral to ortho, in the interim splint in 20° of plantar flexion (not neutral): Brief cast immobilization followed by Achilles rehab protocols; surgery
- **Fractures:** High index of suspicion if pain onset acute, pt w/ DM, ↑ age, osteopenia, neuropathy, hx Fx, smoking, ± trauma; **Dx:** Tenderness, edema, ecchymosis, pain, plain films (if ⊖ , presume stress Fx)

  **Metatarsal:** 5th metatarsal tuberosity avulsion Fx occur w/ inversion of foot/ankle while in plantar flexion or inversion → pt may report sprained ankle; acute & stress diaphyseal Fx also occur, w/ stress Fx frequently only visible on radiograph once healing creates bony callus; Ortho referral for 1st metatarsal, multiple, displaced, stress Fx of proximal diaphysis of 5th metatarsal, or intraarticular

Fx; O/w, splint, progressive wt bearing (often in hardsole shoe), ice, elevation

**Sesamoid:** Pain under 1st MTP joint

**Calcaneus:** Pain s/p fall/jump; pain w/ lateral squeeze, Mondor sign (ecchymosis extending to sole); stress Fx may present like plantar fasciitis, however unlike plantar fasciitis, tenderness on sides of calcaneus present

**Toes:** Ortho/podiatry referral for great toe Fx, circulatory compromise, displaced intraarticular or irreducible Fx

**Tx:** Cast or boot; buddy toe taping × 4–6 wks for lesser toe fractures; if intra-articular, comminuted, displaced >3 mm, urgent Podiatry/Ortho eval

- **Lisfranc dislocation:** High energy insult → damage to Lisfranc ligaments (maintain relationship between forefoot & midfoot) → midfoot pain/swelling; must have a high index of suspicion & cannot r/o unless have wt-bearing radiographs (may only displace w/wt bearing); if pt unable to wt bear, repeat radiographs in 2 wks when pt able to wt bear; **Dx:** Midfoot diastasis, 2nd metatarsal step off, fleck sign (bony fragment at base of 2nd metatarsal), ± metatarsal fracture on plain films, CT, MRI; **Tx:** Jones dressing, posterior splint, emergent Orthopedic eval
- **Plantar plate injury (Turf toe):** Dorsiflexion injury causing attenuation of 1st MTP joint plantar plate w/ pain, swelling, ecchymosis; **Ddx:** Gout, sesamoid injury, cellulitis; **Dx:** Clinical, arthrogram, MRI; **Tx:** Cast or boot, Podiatry/Orthopedic referral (*Am J Sports Med* 2011;29:1)

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## ANKLE PAIN (*AFP* 2009;80:1107; 2012;85:1170)

- **Achilles tendinitis:** Pain w/ exercise, relieved by rest, morning stiffness; Pain w/ passive rotation of ankle; MRI may aid dx; **Tx:** Rest, ice, APAP, orthotics, PT
- **Ankle sprain:** Limited wt bearing, early mobilization, range-of-motion exercises, ice, compression (ACE wrap), elevation, NSAIDs
- **Ankle fracture:** Fx that are stable & can be managed nonoperatively w/ splinting, ice, elevation, analgesics include completely nondisplaced fractures where the talus remains perfectly seated

within the ankle mortise

- **Patient information:** *AFP* 2011;84:686; *JAMA* 2003;290:1542 (plantar fasciitis); *JAMA* 2010;303:188 (Achilles tendinopathy)

# GOUT AND PSEUDOGOUT

## GOUT

### Background (*AFP* 2007;76:801; *Arthritis Care Res* 2012;64:1431)

- **Pathophysiology:** Uric acid (UA) produced by purine metabolism; ↑ UA assoc w/ gout attacks, kidney damage, kidney stones; sx of gout due to deposition of monosodium urate (MSU) crystals in joints, bones, & soft tissue; usual joints include 1st MTP ("podagra"), tarsal joint, ankle, knee, & sometimes fingers, but may be anywhere; Tophi (urate MSU deposits w/ granulomatous inflammation) are a pathognomonic feature of gout & can occur in many different tissues; presence of tophi indicative of chronic tophaceous gout
  **Asymptomatic hyperuricemia:** Pts should be assessed for gouty arthritis, urolithiasis (see *"Kidney Stones"*), & kidney damage (see *"Chronic Kidney Disease"*); most pts w/ asx hyperuricemia require no tx; indications for consideration of tx include **(1)** UA >13 in ♂, 10 in ♀; **(2)** Urinary UA excretion >1.1 g/d (↑ risk of kidney stones); **(3)** Planned XRT or chemo; causes of ↑ UA include $B12$ deficiency, lymphoproliferative d/o, psoriasis, hemolysis, obesity, diet/EtOH, **CKD,** hypothyroidism, ↑ PTH, hypothyroidism, CHF, volume depletion, diuretics
- **Risk factors:** ↑ age, M > F (7–9:1); consumption of red meat, shellfish, EtOH; meds (ASA, thiazide & loop diuretics), trauma/surgery, infection, HTN; iatrogenic flare can be caused by IV contrast
- **Epidemiology:** Affects 8 million pts in US; ~10% of pts w/ hyperuricemia develop gout

### Evaluation (*JAMA* 2003;289:2857; 2012;308:2133; *NEJM* 2003;349:1647)

- **History:** Sudden onset of painful, erythematous, warm, swollen joint;

can be polyarticular later in course; w/o active Rx, tends to resolve in days to weeks; presence of fevers should prompt w/u of septic arthritis (see *"Joint Pain"*)

- **Exam:** Monoarticular inflammation, inspect for tophi (accumulations of urate in connective tissues ± calcification) (*NEJM* 2012;366:e6)
- **Workup:** Joint fluid w/ *3 C's: C*ell count (WBCs often 2K–60K/μL, but can be >100K), *Cx* (⊖), & crystal analysis; fluid will often be cloudy & demonstrate strongly *negatively* birefringent needle-shaped crystals; ideally, Dx will be made based on joint aspirate, however clinical criteria exist (*JAMA* 2012;308:2133); consider BUN/Cr for renal function, CBC for neutrophilia, serum UA

  **Serum UA:** ↑ UA is supportive but not diagnostic; during acute flares, UA can be nl or even low; UA crystallizes >6.8 mg/dL, but only 22% of pts w/ UA >9 have sx so not specific (*Am J Med* 1987;82:4210); all pts w/ gout at some point have ↑ UA, however not all pts w/ ↑ UA develop gout

## Treatment (*Ann Intern Med* 2010;152:*ITC-1; Arthritis Rheum* 2012;64:1447)

- **Acute flare:** Treat ASAP to ↓ duration of Sx; urate-lowering Rx & low-dose ASA (81 mg) should be continued in pts already on these meds; severe attacks may be treated w/ colchicine + NSAIDs or PO steroids + colchicine

  **NSAIDS:** Typically 1st-line; naproxen, indomethacin, or celecoxib; continue 1–2 d after attack; use cautiously in pts w/ CKD, hx GIB, CVD, CHF, anticoagulant Rx

  **Colchicine:** If pt cannot tolerate NSAIDs, then consider colchicine; 1.2 mg at onset, → 0.6 mg an h later → 0.6 mg QD-BID (various regimens exist); continue for 2–3 d after attack ends; low dose (1.8 mg/1 h & high dose 4.8 mg/6 h equally effective, but low dose less toxic, & preferred)

  **Steroid injection (if monoarticular):** first aspirate to verify crystals & r/o infection; use methylprednisolone or triamcinolone (10–80 mg, depending on joint size) after numbing SC (2% lidocaine or 1% xylocaine); can inject up to 3×/year

  **Prednisone:** Consider if multiple joints involved; many options for dosing, but can consider 20 mg BID × 1 wk, then 10 mg QD × 1 wk; pts can reflare if prednisone tapered too quickly

- **Prevention:** Start during acute flare if pt has had multiple attacks; encourage hydration to prevent kidney stones; indications include ≥2 attacks/y, erosive disease on radiograph, nephrolithiasis, CKD ≥ stage 2, tophi, or urinary UA >1.1 g/d; Goal serum UA <6 & often <5 mg/dL; generally, initiate UA lowering Rx 2 wks after attack, although this is debated (*Am J Med* 2012;125:1126)
  **Diet/Lifestyle:** ↓ meat, seafood, high-purine vegetables, **EtOH**, high-fructose corn syrup; avoid HCTZ & loop diuretics; ASA may exacerbate; cherry juice may prevent or ↓ attacks
- **Prophylactic medications:** Administer during initiation of urate-lowering Rx to ↓ risk of triggering a flare when allopurinol, febuxostat, or probenecid are prescribed; colchicine (0.6 mg QD-BID, ↓ frequency in CKD); Low-dose NSAIDs (naproxen/ibuprofen/indomethacin) or prednisone (≤10 mg/d) are alternatives (albeit w/ less supporting data); Ppx should be continued at least 6 mos **or** 3 mos after achieving target serum UA (no tophi) **or** 6 mos after achieving target serum UA (tophi present); Pts unable to reach goal UA levels w/ xanthine oxidase inhibitor alone may benefit from combination Rx w/ uricosuric agent
  **Allopurinol: 1st-line agent**; xanthine oxidase inhibitor; start 100 mg QD × 2 wks (↓ dose in CKD), then 200 mg QD × 2 wks; titrate to lower UA by 1 mg/dL/wk; Typical dose 300–800 mg/d; ✔ LFTs at 1 mo & watch for toxicities (i.e., acute gouty attack, rash, diarrhea, cytopenias, fever); pts of Han Chinese, Thai, & Korean pts w/ stage 3 CKD ancestry are at ↑↑↑ risk of hypersensitivity reaction (consider PCR-based HLA-B*5801 screening) (*Pharmacogenomics* 2011;12:1741); warfarin interaction
  **Febuxostat:** Xanthine oxidase inhibitor; 40 mg/d starting dose, up to 80 mg/d; s/e include abnl LFTs, nausea, rash, arthralgias; use prophylactic colchicine/NSAIDs; useful in CKD
  **Probenecid:** Promotes UA secretion (uricosuric); appropriate for pts w/ ↓ renal UA secretion (verified by 24 h urine UA); contraindications include CKD, nephrolithiasis, tophi; titrate to goal serum UA; losartan has a mild uricosuric effect
  **Refractory gout:** Pegloticase (converts UA to allantoin, which is more soluble) indicated in pts who have contraindications to or who are refractory to above agents

- **Patient information:** *AFP* 2007;76:811; *JAMA* 2012;308:2161

## PSEUDOGOUT (CALCIUM PYROPHOSPHATE DEPOSITION DISEASE)

### Background

- **Pathophysiology:** Mono- or oligoarthritis typically of knee (>50%), & also wrist, ankle; possibly caused by excess pyrophosphate → crystal formation
- **Risk factors:** ↑ age, hyperthyroidism, hemochromatosis (see *"Hemochromatosis"*), epiphyseal dysplasias.; assoc w/ hyperparathyroidism, Mg/phosphate abnormalities, hypothyroidism, GH-secreting adenomas

### Evaluation

- **History:** Presentation similar to gout—acute pain, inflammation of one to several joints; may be provoked by illness, trauma, surgery, or rapid ↓ Ca
- **Workup:** Synovial fluid shows crystals are rectangular/rod/rhomboid shaped w/ weak, ⊕ birefringence; radiograph can show chondrocalcinosis (calcifications within the joint space/cartilage) & aid dx; chem-12, Mg, ferritin, iron, transferrin, TSH, PTH, IGF-1

### Treatment

- **Acute flare:** Similar to gout; joint aspiration & injection (for dx & tx); NSAIDs or colchicine; oral & intraarticular steroids may be helpful; ice & immobilize joint
- **Prophylaxis:** Treat underlying condition & low-dose colchicine (0.6 mg PO BID-QOD)
- **Patient information:** mayoclinic.com/health/pseudogout/DS00717; arthritis.org

# HAND DISORDERS

### Common Nontraumatic Hand Disorders

| Disorder | Description | Clinical Presentation |
|---|---|---|
| **Osteoarthritis** (*Arthritis Rheum* 1990;33:1601) (see *"Osteo-arthritis"*) | Hand pain + ≥3 of: (1) Enlargement of ≥2 of 10 joints: 2nd & 3rd DIP/PIP, or any MCP joint from both hands; (2) Firm enlargement of ≥2 DIP joints; (3) ≤3 swollen MCP joints; (4) Deformity of ≥1 of the 10 joints<br>Heberden nodes (bumps created by bone spurs); PIP 2nd & more variable (Bouchard nodes) | Pain worsened w/ activity (opening jar, writing), relieved by rest; gelling/stiffness w/ inactivity; morning stiffness <30 min |
| **Dupuytren Contracture** | Genetic fibroproliferative disease (autosomal dominant, incomplete penetrance); collagen within palmar fascia proliferates, thickens, & contracts | Painless palmar skin nodules or cords, which sometimes cause flexion contracture (inability to straighten finger) |
| **Trigger finger** (Stenosing tenosynovitis) | Thickening of the flexor tendon & A1 pulley of the flexor sheath | Sometimes painful snapping (triggering) at PIP joint w/ active motion; reluctance to form fist; tender A1 pulley nodule & triggering open from tight fist |
| **De Quervain tendinopathy** | Thickening & swelling of the tendons of the 1st extensor compartment | Tenderness, pain, & swelling at radial aspect of wrist; ⊕ Finkelstein test (pain w/ radial deviation w/ thumb in fist) |
| **Ganglion cyst** | Mucin-filled synovial cyst | Painless mass, Δ in size, characteristic locations: dorsal & volar-radial wrist; dorsal DIP (a/w OA); over A1 pulley (retinacular ganglion cyst) |
| **Carpal tunnel syndrome** (idiopathic median neuropathy in carpal tunnel) | Genetic compression of median nerve → sensory & motor neuropathy | Transient numbness in median nerve distribution w/ wrist flexion (sleeping, driving) → eventual constant numbness, thenar atrophy, & weakness |
| **Cubital tunnel syndrome** (idiopathic ulnar neuropathy in cubital tunnel) | Compression of ulnar nerve at elbow → neuropathy | Initially transient then constant numbness of the small & ulnar half of ring finger; weakness & atrophy of 1st dorsal interosseous muscle |

## Evaluation

- **History:** Characteristic of given condition (above); hx injuries; systemic disease
- **Exam:** Examine skin, muscle mass, joints, nails, & overall posture of the digits & wrist, then compare to the contralateral side; grip

strength; joint palpation; *Range of motion:* Test finger & thumb ROM by asking pt to actively extend all digits & then forming a composite fist; general alignment of fingernails & overlap of fingertips in fist

- **Imaging:** Radiographs after trauma; imaging rarely useful for common dx above

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## CARPAL TUNNEL SYNDROME (*AFP* 2011;83:952; *BMJ* 2007;335:343; *JAMA* 2000;283:3110)

- **Anatomy:** The carpal tunnel, made up of the carpal bones & the transverse carpal ligament, keeps the flexor tendons & the median nerve in position when the wrist is flexed; median nerve divides within carpal tunnel into (1) *recurrent motor branch* to thenar eminence (→ thumb weakness) & (2) *digital sensory cutaneous branches* to thumb, index, middle, & radial half of ring finger (→ hand tingling/numbness)
- **Epidemiology:** Estimated 1–5% of entire population (*JAMA* 1999;282:153); very common disease, ↑ risk w/ age; many pts don't seek medical attention
- **Risk factors:** Genetics explain 50% of the risk; there are no proven epigenetic factors to date; the evidence that it is related to environmental factors is low quality & inconsistent
- **Differential diagnosis:** Cubital tunnel syndrome (see below), neuropathy, cervical radiculopathy
- **History:** Intermittent numbness & tingling of the thumb, index, middle, ring finger (pt may describe as the "entire hand"); *Classic:* Awakens pt from sleep or present on waking; not typically a painful condition except that the numbness can be very intense & experienced as pain; pts may report aching in the forearm & arm
  **Provocative factors:** Wrist flexion/extension; nocturnal worsening since wrist often flexed during sleep
  **Palliative factors:** Shaking or wringing hands, placing hand dependent at side of bed
  **Hand Sx diagram:** Pts mark specific location of sx on self-administered diagram depicting dorsal & palmar aspect of hands/arm
- **Exam:** (*J Am Acad Orthop Surg* 2009;17:389)

**Sensory:** Affects threshold sensibility initially (light touch measured) then discriminatory sensibility later (measure w/ 2-point discrimination)

**Motor:** In severe disease only: weakness of thumb palmar abduction against resistance; atrophy (or concavity) of thenar muscles

**Provocative maneuvers:** Test is ⊕ if paresthesias (not pain) occur in median nerve distribution; combining results from >1 test can ↑ Se/sp

**Provocative Tests for Carpal Tunnel Syndrome (*J Hand Ther* 2004;17:309)**

| Test | Maneuver | Se (%) | Sp (%) |
|---|---|---|---|
| Phalen | Wrists flexed for 30 seconds | 68 | 73 |
| Tinel | Tap on median nerve proximal to carpal tunnel to elicit paresthesias | 50 | 77 |
| Durkan | Press both thumbs over transverse carpal ligament for 30 s | 64 | 83 |

- **Diagnosis:** Clinical dx is suspected w/ report of classic sx
- **Workup:** Indications for electrodiagnostic testing debated: Used to (1) R/o CTS in reports of paresthesias where it is a possible but less likely dx, (2) Provide objective data to manage postoperative expectations in pts w/ severe disease; Imaging generally not useful in dx

  **Nerve conduction studies (NCS):** Document location & severity of median neuropathy; standard tests include median sensory NCS across the wrist w/ distal latency compared to ulnar & radial nerve, & median motor NCS from abductor pollicis brevis (*Neurology* 1993;43:2404)

  **Electromyography (EMG):** Excludes other peripheral neuropathies

**Preferred Nonsurgical Treatment Modalities**

| Modality | Description |
|---|---|
| Splinting | Brace holds wrist neutral to prevent waking w/ numbness |
| Steroid injection | Single injection into carpal tunnel |

*J Bone Joint Surg Am* 2009;91:2478

**Modalities w/ insufficient evidence:** Carpal bone mobilization; nerve gliding; yoga; ergonomic keyboard; oral steroids, U/S

**Modalities w/o significant benefit:** Diuretics, NSAIDs, Vit $B_6$,

magnet Rx, laser acupuncture, exercise (*Neurology* 1998;51:390)

- **Surgery:** Indicated if failure of nonoperative Rx or median nerve denervation demonstrated on clinical or electrodiagnostic testing (*JAAOS* 2009;17:389)
  **Carpal tunnel release:** Decompression of the carpal tunnel through open or endoscopic complete division of the transverse carpal ligament
  **Postoperative care:** No indications for wrist immobilization or rehabilitation
  **Complications:** Nerve injury is rare but problematic
  **Prognosis:** Severe disease w/ constant numbness & atrophy is permanent; the sx from mod disease usually disappear, but the NCS/EMG don't normalize
- **Patient information:** *AFP* 2011;83:965; *JAMA* 2011;306:2283

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## CUBITAL TUNNEL SYNDROME (*AFP* 2013;87:568)

- **Anatomy:** Ulnar nerve formed by C7/8/T1, passes near medial epicondyle of humerus (at elbow) & between pisiform/hamate bone in wrist
- **History:** Ulnar neuropathy at elbow → paresthesias in 4th & 5th fingers, worsened by elbow flexion
- **Exam:** Tinel test at elbow (percuss elbow → sx); Neck motion to r/o C8/T1 radiculopathy
- **Workup:** NCS or EMG to confirm dx & localize lesion
- **Nonoperative treatment:** Brace or pillow to limit elbow flexion at night
- **Surgery:** Generally indicated to avoid; constant numbness, weakness, atrophy

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## DUPUYTREN DISEASE (*AFP* 2007;76:89; *JAAOS* 2011;9:746; *NEJM* 2007;356:e11; 2009;361:968)

- **Epidemiology:** ♂ > ♀, age >40 y; **Risk factors:** genetics: (Autosomal dominant, variable penetrance); pts w/ ancestry from British Isles & Scandinavia

- **History:** Begins as a nodule or cord → can progress to finger contracture
- **Exam:** Nodules in the palmar fascia and/or digits w/ occasional pitting of skin; variable PIP & MCP joint contractures
  **Table top test:** ⊕ if pt unable to place palm of affected hand flat on a table (usually if MCP contracture is >30°)
- **Differential diagnosis:** Soft tissue tumors, stenosing tenosynovitis (note triggering)
- **Nonoperative treatment:** Observation of isolated nodules; percutaneous needle fasciotomy, or injectable collagenase for substantial contractures
- **Surgery:** Excision of diseased palmar fascia (fasciectomy)
- **Patient information:** *AFP* 2007;76:90

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## TRIGGER FINGER (STENOSING TENOSYNOVITIS) ( *JAAOS* 2001;9:246)

- **Epidemiology:** Idiopathic; may be assoc w/ DM; Ring >> thumb > long > index > small finger
- **Exam:** Pain at palmar base of involved digit w/ nodule, "catching" and/or locking of digit in flexion as pt tries to extend fingers from fist
- **Differential diagnosis:** Sagittal band insufficiency
- **Nonoperative treatment:** *Palliative:* NSAIDs, splinting; *Disease-modifying:* corticosteroid injection into the tendon sheath (works ~50% of the time, can take 2 mos to show efficacy)
- **Surgery:** Release of digital A1 pulley

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## DE QUERVAIN TENDINOPATHY (*JAAOS* 2007;15:757)

- **Epidemiology:** Seen in both sexes in adults of all ages; often seen 6 wks postpartum
- **Exam:** Focal tenderness over the 1st dorsal compartment of the wrist
  **Finkelstein test:** ⊕ pain w/ ulnar deviation of the wrist w/ the thumb in fist
- **Differential diagnosis:** Trapeziometacarpal arthritis of the thumb (no crepitus & stiffness)

- **Nonoperative treatment:** NSAIDS, thumb spica wrist splint, corticosteroid injection in the 1st dorsal compartment
- **Surgery:** Release of 1st extensor compartment

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### GANGLION CYST (*JAAOS* 1999;7:231)

- **Epidemiology:** Idiopathic; most common hand/wrist tumor
- **Exam:** Well-circumscribed, smooth mass usually located adjacent to joints & tendons (i.e., dorsal or volar wrist); can be intratendinous or intraosseous; transilluminates
- **Differential diagnosis:** Lipomas, neuromas, hamartoma, sarcoma, vascular aneurysms
- **Nonoperative treatment:** Observation, as many spontaneously resolve; avoid aspiration (clear, gelatinous fluid) on volar surface as often abuts radial artery
- **Surgery:** Excision (5–10% recurrence rate)

# HIP PAIN

## Background

- **Anatomy:** Hip joint comprises femoral head articulated w/ acetabulum; blood supply to head & neck of femur from the *medial femoral circumflex artery;* total of 18 bursae; innervated by *obturator nerve*, *femoral nerve*, & *sciatic nerve*

**Causes of Hip Pain**

| Diagnosis | Symptoms | Demographics |
|---|---|---|
| **Osteoarthritis** (*NEJM* 2007;357:1413) | Pain in groin w/ movement, better with rest, ↓ ROM; dx criteria: hip pain + ≥2 of: (1) ESR <20, (2) osteophytes, (3) Joint space narrowing | Common in the elderly |
| **Trochanteric bursitis** | Lateral hip pain w/ point tenderness over trochanteric bursa, exacerbated by gait impairment/walking & direct pressure (i.e., lying on side), ⊕ Ober test, ± iliotibial band tightness | Middle-aged women, younger pts, runners |
| **Meralgia paresthetica** (lateral femoral cutaneous nerve entrapment) | Paresthesias, occasionally burning, over upper outer thigh (due to lateral femoral cutaneous nerve entrapment by inguinal ligament near the ASIS) | Obese or pregnant pts; DM patients; tight clothing |
| **Occult hip fracture** (*AFP* 2003;67:537) | Severe pain w/ partial wt bearing, pain w/ passive rotation | Elderly, osteoporosis, steroid use |
| **Osteonecrosis** (*NEJM* 2011;365:62) | Groin or nonspecific "hip area" pain often followed by thigh & buttock pain; rest & night pain common | Steroid users, EtOH, hx hip injury, sickle cell, SLE, trauma |
| **Leriche syndrome** | Claudication, buttock & hip pain, ↓ pulses (2° iliofemoral atherosclerosis) | Severe PAD |
| **Referred pain & spinal stenosis** | Back, hip & buttock pain 2° to lumbosacral disc & facet joint disease | Middle-aged & elderly |
| **Septic arthritis** | Fever, HoTN, anterior hip pain | Immunocompromised; IVDU; systemic infection |
| **Gluteus medius tendinopathy** | Pain w/ hip abduction & rotation, pain above the greater trochanter, ⊕ Trendelenburg sign | More common in women (wider pelvis) |
| **Piriformis syndrome** | Sciatic pain at SI joint or sciatic notch → foot, w/o numbness/weakness; worse sitting on hard surface, ↓ w/ walking (2° to compression of sciatic nerve by the piriformis muscle) | Anatomic variation in sciatic nerve or piriformis muscle (i.e., fibrosis after trauma) |
| **Labral tear** | Anterior hip or groin pain, clicking/ locking of the hip | Pts w/ OA, athletes |
| **Femoroacetabular impingement** (*AFP* 2009;80:1429) | Chronic groin antero/lateral pain worse w/ turning, ↓ ROM, early onset OA (form of DJD of the hip joint) | Athletes (hockey > golf > dance > football > soccer) |
| **Malignancy** | ↓ wt, blood in stool, or constant pain | Personal or FHx of CA |
| **Hernia** | Groin pain radiating to hip | Wt lifters, elderly |
| **Muscle strain** | New onset pain after ↑ activity | Athletes, elderly |

## Evaluation (*Clin J Sport Med* 2003;13:152; *Orthop Relat Res* 2009;467:638)

- **History:** Location & character of pain (68% of pts w/ intra-articular pathology c/o groin pain), provocative/palliative factors, timing (constant pain suggests infectious, inflammatory, or neoplastic etiology), trauma, medications (steroids, EtOH → osteonecrosis),

back pain, claudication, paresthesias, ortho hx, impact on function

- **Exam:** Natural gait & heel-to-toe; look for Trendelenburg/antalgic gait, & short leg limp
  **Squatting:** Will be limited by mod-to-severe OA, bursitis, or muscle weakness
  **FABER:** Hip is **F**lexed, **AB**ducted, And **E**xternally **R**otated; ⊕ in 88% of pts w/ hip pathology
  **Internal & external rotation:** ↓ rotation in pts w/ severe OA or septic arthritis
  **Palpation of trochanteric bursa:** Hip must be flexed to 90°, assess for tenderness
  **Sensory exam:** Anterolateral exam w/ ↓ or ↑ sensation in meralgia paresthetica
  **Straight leg raise:** ⊕ test elicits pain at 60° elevation → S1/L5 nerve root irritation
  **Lasegue sign:** Thigh is flexed & internally rotated; resisted abduction or adduction reproduces sx (stretches sciatic nerve)
  **Vascular:** LE pulses ↓ in Leriche syndrome
  **Ober Test:** Pt lies laterally on unaffected side w/ hip extended, affected knee flexed to 90°, & abducted (w/ hand on iliac crest for stability); examiner lowers affected knee; if unable to adduct to neutral position, ⊕ test
- **Diagnostics:** Radiograph to assess for fracture in pt w/ acute hip pain (typically wt-bearing AP pelvis & hip & axial cross-table film of the proximal femur)
  **MRI:** When radiographs inconclusive, for suspected fracture, osteonecrosis, infection, & tumor; radionuclide bone scan if MRI contraindicated
  **Ultrasound:** Useful to guide aspirations; hip aspiration indicated if infection is suspected (should be image-guided) (*Eur J Radiol* 2012;81:3737)

## Treatment

- **Bursitis:** Avoid pressure over hip, bending & stairs; stretching, heat, APAP, NSAIDs, PT (for orthotic & gait eval); consider steroid injections if conservative measures fail
- **Femoroacetabular impingement:** Rest, PT, NSAIDs/APAP, ortho

referral for arthroscopy in refractory cases

- **Labral tear:** PT; may require arthroscopic surgery (*Curr Rev Musculoskelet Med* 2009;2:105)
- **Meralgia paresthetica:** Self-limited, benign condition w/ spontaneous remission; reassurance, avoid tight garments, wt loss; If persistent consider gabapentin, carbamazepine, or phenytoin
- **Osteoarthritis:** Limit high impact activities, rest, heat, stretching (see *"Osteoarthritis"*); Hip arthroplasty if failure of conservative Rx or significant disability
- **Osteonecrosis:** Rest, weight-bearing as tolerated, pain control; referral to ortho for surgical mgmt of progressive disease, failure of conservative mgmt
- **Piriformis syndrome:** PT, stretching, NSAIDs, gabapentin, nortriptyline; steroid/botulinum toxin injection if conservative measures fail (*Muscle Nerve* 2009;40:10)
- **Patient information:** *AFP* 2009;80:1439; *JAMA* 2007;298:2442 (hip fx)

# KNEE PAIN

## Background (*AFP* 2003;68:917; *JAMA* 2001;286:1610; *NE JM* 2006;354:841)

### Differential Diagnosis of Knee Pain by Location

| |
|---|
| **Anterior:** Injury to quadriceps, patella, or patellar tendon, plica syndrome, patellofemoral pain syndrome, severe OA, prepatellar bursitis, RA, gout, pseudogout, septic joint |
| **Lateral:** Lateral meniscal tear, lateral collateral ligament injury, iliotibial band syndrome |
| **Medial:** OA, anserine bursitis, medial collateral ligament injury, medial meniscal tear, tibial plateau fractures, plica syndrome |
| **Popliteal:** Effusion, popliteal/Baker cyst, DVT |

## Evaluation and Treatment (*AFP* 2003;68:917)

- **History:** Trauma or constitutional sx, location of pain, acute/chronic, provocative/palliative factors, orthopedic hx, swelling, stiffness, instability, catching, popping, snapping sensation, sensory/motor changes; have pt point to area of pain w/ one finger
  **Red flags:** Pain after trauma, constitutional sx, disabling pain
- **Exam:** Examine both knees (uninjured knee as a control), hip, & ankle; observe gait, squat, duck waddle (pt squats & moves forward); test quadriceps, hamstring strength
  **Inspection:** Joint architecture, erythema, swelling, effusions
  **Palpation:** Warmth (nl knee is cooler than anterior shin), vascular exam, tenderness to palpation (patella, tendons, lateral & medial joint lines, anserine bursa), pain w/ lateral displacement of patella (patellofemoral syndrome)
  **Range of motion:** Active & passive extension, (0–135° nl), varus & valgus instability at 0° for LCL & 30° for MCL; Crepitus
- **Workup:** Start w/ radiograph; MRI to evaluate meniscal or ligament tear if dx unclear; if constitutional Sx present consider CBC, ESR, CRP; U/S if popliteal cyst suspected
  **Ottawa knee rule:** Plain films after acute injury to r/o fracture if any of the following: ≥55 y, isolated patellar tenderness, tenderness at head of fibula, cannot flex to 90°, cannot bear wt for 4 steps immediately after injury & in ED; Se 98.5%, Sp 48.6% (*Ann Intern Med* 2003;139:575; 2004;140:121)
  **Communication w/ radiologist:** Interpretation of imaging may be

improved when PCPs communicate where the pain is when requesting imaging

**Useful Exam Maneuvers (Described for R Knee)**

| Name | Description |
|---|---|
| **Lachman test** (ACL injury) 87% sensitive, 93% specific | L hand on femur grasped just above the knee, R hand on the tibia, apply slight flexion; pull sharply toward your abdomen w/ R hand while stabilizing w/ the L hand; muscles must be relaxed; ⊕ for ACL injury if tibia feels unrestrained during sharp pull |
| **Posterior drawer test** (PCL injury) 51–86% Se | Pt supine w/ knee flex to 90°, stabilize foot by sitting on it, place hands around tibia w/ thumbs meeting along front; apply pressure backward in plane parallel to the femur; ⊕ for PCL injury w/ unrestrained backward motion |
| **McMurray test** 53–97% Sp | Tests for meniscal injury; place left hand on medial joint line w/ knee fully flexed; w/ right hand evert foot, apply valgus stress & gently flex & extend knee; ⊕ test w/ clicking around medial joint line |

(*JAMA* 2001;286:1610; *Ann Intern Med* 2003;139:575)

- **Patellofemoral syndrome ("Runner's knee"):** Most common cause of knee pain in primary care, Pts typically ♀, <45 y, p/w pain, popping/clicking/snapping going up/down stairs, rising from seated position, while running, or after prolonged sitting; exam: Tenderness over patellofemoral joint or behind patella, reproduced on compression of patella against femur; dx of exclusion
  **Treatment:** Rest, ice, NSAIDs, PT, stretching, wt loss; quadriceps strengthening (i.e., stationary cycling); consider foot orthoses; orthopedic referral if refractory
- **Osteoarthritis** (see *"Osteoarthritis"*): Pain w/ activity & relieved by rest, ↓ ROM, gelling/stiffness w/ inactivity, slowly progressive; crepitus; medial pain prominent
  **Diagnostic criteria:** Knee pain + 3 of the following: age >50 y, morning stiffness <30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth
  **Treatment:** Wt loss (if overweight), physical therapy, APAP
- **Anterior cruciate ligament injury:** Trauma → "pop," immediate pain, swelling, mechanical sx; ⊕ Lachman test, tear visible on MRI; pt cannot squat/duck waddle; ♀ at ↑ risk; ACL injury ↑ risk of OA (*NEJM* 2008;359:2135)

**Treatment:** Rest, ice, elevation, APAP, compression, PT; ortho referral if pt young, has significant instability, wishes to return to vigorous activity, or s/sx of other joint damage; rehabilitation + early ACL reconstruction = rehabilitation ± delayed ACL reconstruction (*NEJM* 2010;363:331)

- **Bursitis:** Local pain on rest & motion; anserine bursa is medial & 6 cm below joint line; pain typically at night; prepatellar bursa is anterior & between patella & skin; inflammation caused by trauma/repetitive kneeling
  **Treatment:** Compression dressing/braces/knee pads, NSAIDs, ice, PT; chronic bursitis may respond to steroid injections, aspiration
- **Iliotibial band syndrome:** Lateral aching/burning/stinging where the iliotibial band traverses the knee, esp over lateral femoral condyle, often seen in runners, cyclists; pain may radiate to hip; Ober test assesses strength of iliotibial band
  **Treatment:** Ice, NSAIDs, stretching, temporary avoidance of activities that ↑ pain; Steroid injections or surgery for cases refractory to conservative Rx
- **Gout/pseudogout:** Other joints affected, joint swollen/tender; often w/ effusion; crystals in joint aspirate; (see *"Gout and Pseudogout"*)
- **Medial collateral ligament injury:** Medial knee pain, pain w/ walking, twisting, pivoting; typically injured after twisting or hyperextension of leg;
  **Treatment:** Rest, ice, compression, elevation, joint protection; ASA/NSAIDs, early mobilization as tolerated; pt ortho referral if knee unstable or pain/disability persists
- **Meniscal injury:** Often asx, but can p/w mechanical sx (buckling, locking), tenderness over joint line, pain w/ twisting, ⊕ McMurray test; commonly occurs when knee twists w/ foot locked on ground; pt cannot duck waddle, tear visible on MRI (*JAMA* 2001;286:1610; *NEJM* 2008;359:1108)
  **Treatment:** Rest, avoid activities that cause pain, ice, crutches, patellar brace, PT; persistent pain may require open/arthroscopic repair
- **Plica syndrome:** Irritation/injury of the plica, a component of synovial tissue → medial knee pain & popping sensation w/ flexion in runners/athletes or after trauma; pain ↑ w/ flexion of knee or

sitting; (*Curr Rev Musculoskeletal Med* 2008;1:53)
**Treatment:** Rest, ice, stretching, NSAIDs, PT; arthroscopic surgery may be curative

- **Popliteal cyst:** Cyst in popliteal fossa due to ↑ pressure in joint 2° to joint disease (OA, RA, meniscal injury); mass in popliteal fossa ↓ w/ flexion at 45°
- **Stress fracture:** Pain after an ↑ in activity; activity worsens pain, relieved by rest; may not be visible on plain film in 1st 2 wks, but may be seen on MRI (*AFP* 2011;83:39)
  **Treatment:** Avoid activities causing pain, APAP, bracing, shoe inserts for cushioning, calcium/vitamin D supplementation, PT; high-risk fractures (i.e., patella, anterior tibia) should be referred to ortho
- **Tendinitis:** Pain going up/down the stairs, commonly seen in runners
- **Patient information:** *AFP* 2007;75:204; *JAMA* 2007;297:1740

# MONOARTICULAR ARTHRITIS

## Background (*AFP* 2003;68:83; 2011;84:653; *JAMA* 2007;297:1478)

- **Differential diagnosis:** Trauma (i.e., hemarthrosis, Fx), infection (Lyme, Staph > Strep > GNR, fungal mycobacterial), avascular necrosis; also consider causes of oligo- or polyarticular arthritis (crystal-induced, OA, RA, seronegative spondyloarthropathies, sarcoid, etc.); causes of monoarthritis can coexist, infection must always be r/o before treating other causes
  **Bursitis:** Inflammation/injury of bursa (protect bony prominences) 2° to degeneration, infection, injury, crystals, RA; p/w pain on motion/rest, swelling, focal tenderness ± ↓ ROM; EtOH, DM, immunosuppression are risk factors for septic bursitis
  **Septic arthritis:** Hip & knee > > wrist, ankle; risk factors include immunosuppression, IVDU, malignancy, prosthetic joints, RA, renal failure, ↑ age, skin infection, steroid inj; early diagnosis and treatment key due to mortality (7–15%) & risk of joint destruction
  **Gonococcal:** Acute onset in sexually active young adult w/o hx trauma; may p/w polyarthralgias, skin lesions, tenosynovitis or

purulent arthritis w/o skin lesions

## Evaluation

- **History:** Chronicity, hx trauma or prior joint pain/swelling; sexual hx (gonococcal); EtOH/red meat/shellfish intake (crystals); travel (Lyme, infectious); comorbidities (↑ risk for septic arthritis in pts w/ RA, prosthetic joints, DM); anticoagulant use, bleeding d/o (↑ risk of hemarthrosis); IVDU (septic)
  **Extra-articular manifestations:** Fevers/chills (septic arthritis), GI illness (reactive arthritis, IBD-assoc arthritis), genital pain/lesions (gonococcal), rash (psoriasis, lupus, viral exanthems, Lyme erythema migrans), oral ulcers (SLE), inflammatory eye disease (seronegative spondyloarthropathies, RA)
- **Exam:** Warmth, redness, effusion, joint line tenderness, bony crepitation w/ flexion, rash or break in skin, soft tissue swelling, tophi; assess for extrarticular disease (above)
  **Range of motion:** ↓ active ROM w/ preserved passive ROM suggests soft tissue cause; limited active & passive ROM more likely joint involvement; significant pain w/ minimal ROM concerning for septic arthritis
- **Workup:** Arthrocentesis most important test (cell count w/ diff, gram stain, crystals, Cx); radiograph can be useful to assess for fracture (hx trauma) or chondrocalcinosis (seen in CPDD), erosions (seen in RA, gout, osteomyelitis); BCx if septic arthritis suspected; ESR, CRP, uric acid
  **Bursitis:** Aspiration of fluid for Cx, cell count, crystals; deep bursal infections may be imaged w/ MRI or u/s

**Synovial Fluid Analysis**

| Measure | NI | Noninflammatory | Inflammatory | Septic |
|---|---|---|---|---|
| Color | Clear | Yellow | Yellow | Yellow/green |
| Clarity | Clear | Clear | Clear-opaque | Opaque |
| WBC/mm$^3$ | <200 | 0–1000 | 1K–100K | 15K–100K |
| PMNs (%) | <25 | <25 | >50 | >75 |
| Cx | ⊖ | ⊖ | ⊖ | Often ⊕ |

**Predictive Value of Synovial Fluid WBC for Septic Arthritis**

| Measure | Se (%) | Sp (%) | ⊕ Likelihood Ratio (95% CI) |
|---|---|---|---|
| WBC >100K | 29 | 99 | 28 (12–66) |
| WBC >50K | 62 | 92 | 7.7 (5.7–11) |
| WBC >25K | 77 | 73 | 2.9 (2.5–3.4) |
| PMNs >90% | 73 | 79 | 3.4 (2.8–4.2) |

(Adapted from *JAMA* 2007;297:1478)

## Treatment

- **Septic arthritis:** ED/admission for empiric abx & orthopedics eval
- **Hemarthrosis:** Analgesics, aspiration/injection, compression sleeve to prevent reaccumulation, assessment for bleeding d/o
- **Bursitis:** Avoid activities that ↑ pain, joint protection, NSAIDs, ice, heat, PT; intrabursal steroid injection in refractory cases
- **Patient information:** *JAMA* 2007;297:1510

# MUSCLE PAIN

## Background (*AFP* 2001;64:1565; *Am J Med* 2004;117:420; *JAMA* 2011;305:183; *Lancet* 2003;362:971; *NEJM* 2005;352:1448)

- **Definitions:** *Myalgia:* muscle pain; *myopathy:* muscle disease; *myositis:* muscle inflammation; *cramps:* painful, involuntary muscle contraction; *contractures:* failure of muscles to relax, assoc w/ glycolytic & neurologic disease
- **Etiologies:** Range from benign to life-threatening
- **Dermatomyositis (DM) & polymyositis (PM):** Immune-mediated inflammatory myopathy; insidious onset of mild myalgias in 25–50% of pts + symmetric, proximal weakness (deltoids, neck, hips → difficulty climbing stairs, carrying heavy loads); may p/w dysphagia, ILD, polyarthritis; skin changes seen in DM (see *"Rheumatologic Skin Disease"*) but not PM
- **Pyomyositis:** Skeletal muscle infection, typically from hematogenous source assoc w/ trauma, HIV, IVDU, malnutrition, most frequently caused by *S. aureus*

### Differential Diagnosis of Myalgias

| Category | Examples |
|---|---|
| Infectious | Viral (enterovirus, hepatitis B/C, influenza, dengue, HIV), Bacterial (*S. aureus*, *S. viridans*), Spirochetal (see *"Tick-Borne Illness"*), necrotizing fasciitis |
| Pain syndromes | Fibromyalgia (see *"Fibromyalgia"*), chronic fatigue syndrome |
| Rheumatologic | PMR, polymyositis/dermatomyositis, RA, SLE, spondyloarthropathy, vasculitis |
| Metabolic | Scurvy, metabolic myopathy, vit D deficiency |
| Endocrine | Adrenal insufficiency, hypothyroidism, neuropathy |
| Medications | Statins, antipsychotics, fibrates, colchicine, AZT, cocaine, methadone, labetalol, cimetidine, CsA, ciprofloxacin, bisphosphonates, aromatase inhibitors, withdrawal from antidepressants, EtOH |
| Localized | Exercise/overuse, trauma, pyomyositis, infarction, compartment syndrome, bursitis, necrotizing fasciitis, muscle strain/sprain |
| Nocturnal leg cramps (*AFP* 2012;86:350) | Foot d/o (flat feet), prolonged sitting/standing, diuretics, HD, pregnancy, spinal stenosis, PD, radiculopathy, exercise, meds, claudication, ↓Mg, ↓Ca, neuropathy, DVT |

## Evaluation (*AFP* 2002;65:907; *NEJM* 2010;363:e17)

### Distinguishing Features of Myalgias

| Presenting Features | Potential Diagnosis |
|---|---|
| Pain out of proportion to exam | Necrotizing fasciitis/cellulitis/myositis, compartment synd |
| Sudden onset | Acute bacterial or viral illness |
| Gradual onset | Statins, Hep C, endocrinopathy, pain syndrome, PM/DM |
| Joint involvement | PMR, RA |
| Fever, HA, malaise | Viral infection (i.e., influenza), pyomyositis |
| Weakness (see *"Weakness"*) | PM/DM, hypothyroidism, statin-induced |
| Dysphagia, dyspnea | Dermatomyositis, polymyositis |
| Red/brown urine + weakness | Rhabdomyolysis (↑ serum CK, ↑ urine myoglobin) |
| Redness, swelling, asymmetry | Pyomyositis, compartment syndrome |
| Delayed reflexes | Hypothyroidism |
| Rash: Hyperpigmentation → Adrenal insuff; Malar rash → SLE; Erythema migrans → Lyme, Mechanic's hands → Polymyositis, Gottron's papules (occur on dorsal MCP & IP joints), Gottron sign (papules/patches/macules on elbows, knees, ankles), facial erythema, heliotrope eruption on upper eyelids → Dermatomyositis | |

- **Workup:** CBC, U/A, Cr, LFTs; consider Ca, albumin, phos, TSH, CK, 25OH Vit D, BCx, ESR, CRP, ANA, RF, Anti-CCP, ACTH stimulation test; imaging generally reserved for eval of inflammatory muscle disease, pyomyositis, muscle infarction; EMG used to dx myopathy (along w/ nerve conduction studies); bx occasionally necessary
  **Dermatomyositis/polymyositis:** ↑ CK, LDH; ⊕ ANA, ⊕ anti-Jo-1; CXR to evaluate for ILD; consider muscle or skin bx, EMG, MRI
  **Pyomyositis:** CT or MRI, BCx; high index of suspicion (& r/o necrotizing fasciitis)

## Management

- **Medication-induced:** D/c medication, may take wks to mos for sx to resolve
- **Chronic fatigue syndrome:** Cognitive behavioral therapy & graded exercise Rx (no evidence for medications or dietary changes)
- **Dermatomyositis/polymyositis:** Glucocorticoids (1 mg/kg [max dose = 80 mg] → taper after 4–6 wks); comanagement w/ rheum ± derm; physical therapy; SLP eval if dysphagia present; PCP Ppx if long-term high-dose steroids used (see *"PCP prophylaxis"*)
- **Pyomyositis:** Abx (assess risk of MRSA infection) and/or drainage

# OSTEOARTHRITIS

## Background (*Osteoarthritis Cartilage* 2013;1; *Best Pract Res Clin Rheumatol* 2006;20:3)

- **Epidemiology:** Most common joint d/o (21 million pts in US); prevalence ↑↑ > 40 y
- **Risk factors:** Age, obesity, trauma, repetitive use, ♀, genetics/FHx, neuropathy, pseudogout, bleeding dyscrasias (→ hemarthrosis) (*Nat Rev Rheumatol* 2011;7:23)
- **Pathophysiology:** Slow, progressive loss of articular cartilage assoc w/ hypertrophy (osteophytes) & sclerosis of nearby bone; usually 1° (idiopathic) but may also be 2/2 trauma, deformity, inflammatory process; thought to represent a heterogeneous group of diseases
  **Affected joints:** Typically hands (DIP, thumb base, 1st MTP), feet, knees, hips, spine (C5, T8, L3), shoulders; ankles, elbows, wrists less commonly involved
- **Differential diagnosis:** RA, gout/pseudogout, septic joints (acute onset, fevers, leukocytosis, severely ↓ ROM), bursitis, referred back/hip pain, avascular necrosis, spondyloarthropathies (typically assoc w/ other systemic sx, i.e., IBD)

## Evaluation and Prognosis (*AFP* 2011;84:2012;85:49; *JAMA* 2003;289:1016; *NEJM* 2007;357:1413)

- **General principles:** Clinical dx; see specific chapters for hand, knee, hip OA

- **History:** Highly variable & depends on affected joint(s); pain worsened by activity, relieved by rest; gelling/stiffness w/ inactivity; slowly progressive; morning stiffness that resolves in <30 min; joint locking, popping, or instability; may report trauma/repetitive injury
  **Noninflammatory OA:** Pain/disability is 1° Sx as compared to joint swelling; prolonged morning pain, effusion, night pain seen in **inflammatory OA**
  **Patterns of presentation:** Monoarticular (young adults), pauciarticular/large joint, polyarticular, rapidly progressive, trauma-related
- **Exam:** Depends on joint; generally, swelling ( ± tenderness) around joint line; crepitus; ↓ ROM w/ pain at end of range, typically w/o warmth; periarticular muscle weakness/wasting or bursitis/tendinitis that may explain sx
- **Workup:** Imaging (esp CT or MRI) is rarely necessary unless suspicion for alt dx (e.g., meniscal injury in the knee); plain radiography may confirm dx (e.g., joint space narrowing w/ osteophytes & sclerosis) but late finding
  **Lab investigation** (e.g., ANA, RF, anti-CCP, Lyme serology) should not be initiated unless suspicion for alt dx exists; CRP may be slightly ↑
- **Prognosis:** Slowly progressive, cases may stabilize, w/ risk factor reduction, exercise

## Management (*AFP* 2011;83:1287; 2012;85:49; *NEJM* 2006;354:841; *Osteoarthritis Cartilage* 2008;16:137)

- **Nonpharmacologic:** Pt education, exercise (esp non wt-bearing like swimming), resting affected joint for brief periods (<12 h), wt loss, PT/OT, joint braces/splints, stretching, massage, heat, paraffin wax; unloading of joint wt w/ a cane/walker; soft shoes/insoles; TENS controversial (*Br J Rheum* 1994;33:455); acupuncture (*JAMA* 2007;297:1697)
- **Pharmacologic:** Nonpharmacologic therapies should be tried 1st; **Noninflammatory OA:** APAP prn → standing → NSAIDs (if persistent pain); **Inflammatory OA:** NSAIDs prn → standing (if persistent pain)
  **Opioids:** Use cautiously; may be indicated for acute ↑ in pain;

tramadol may be synergistic w/ APAP (*Cochrane Database Syst Rev* 2006;CD005522); other opioid use not recommended by American College of Rheumatology

**NSAIDs:** Start at lowest dose & uptitrate; may take 2–4 wks for maximal pain control; do not combine NSAIDs; contraindicated in PUD & pts w/ ASA sensitivity; May ↑ risk of bleeding w/ warfarin; use cautiously in pts w/ CKD, CHF, cirrhosis, on diuretics due to risk of AKI; may worsen HTN; NSAIDs + PPI/misoprostol may ↓ PUD risk; Ibuprofen, naproxen inhibit PLT function; **Nabumetone:** ↓ renal toxicity, ↓ antiplatelet activity; **Sulindac:** ↓ renal toxicity; contraindicated in cirrhosis/liver disease (hepatic metabolism); **Diflunisal:** ↓ risk of PUD, ↓ antiplatelet activity; **COX-2 inhibitors** (celecoxib) may ↑ CV risk as much as ibuprofen, no effect on PLT function

**Intraarticular injections:** Short-term pain relief w/ glucocorticoids (1–2 mos) or hyaluronans (~4 mos); consider in pts w/ pain refractory to NSAIDs

**Glucosamine & chondroitin:** ↓ pain in some studies (*AFP* 2008;77:177); consider in mod–severe knee OA but should be discontinued if no improvement by 3–6 mos (*NEJM* 2006;354:795); glucosamine contraindicated in pts w/ shellfish allergy

**Topicals:** Capsaicin & NSAIDs (i.e., diclofenac)

**Colchicine:** Consider in pts w/ inflammatory OA unresponsive to NSAIDs

- **Surgical:** Consider joint replacement in pts w/ severe hip/knee OA who fail medical Rx; timing of surgery balanced btw limited hardware lifespan (15–20 y) & functional loss, muscle atrophy; improved outcomes for surgeons w/ ↑ volume; no benefit for arthroscopic debridement/irrigation of knee (*Lancet* 2012;379:1331; *NEJM* 2008;359:1097)
- **Patient information:** *AFP* 2011;83:1294; 2012;85:57; *JAMA* 2010;304:114

# POLYMYALGIA RHEUMATICA

## Background (*AFP* 2006;74:1557; *BMJ* 2008;336:765)

- **Definition:** Various criteria published, but diagnostic features: age >50 y, ↑ ESR/CRP, bilateral aching or pain, tenderness, & AM stiffness (>30–45 min) of proximal muscles groups (shoulder/upper arm >> neck and/or pelvic girdle) for >2 wks, rapid response to steroids, & exclusion of other conditions (*Arthritis Rheum* 2012;64:943)
  **Other symptoms:** Fatigue, low-grade fever, mild synovitis (MCPs/knees/wrists), anorexia, wt loss, distal extremity swelling (usually unilateral)
  **Muscle weakness: not** characteristic of the disease (may be limited by pain)
- **Epidemiology:** Most common inflammatory rheumatic disease in elderly white pts; typically occurs in M:F 1:2–3; incidence in pts >50 y ~50/100,000; average age of dx >70 y
- **Differential diagnosis:** RA, spondyloarthropathy, pseudogout, dermatomyositis/polymyositis, infection (e.g., viral syndrome, SBE), SLE, endocrinopathy (e.g., hypo- or hyperthyroidism), OA, rotator cuff d/o, fibromyalgia, malignancy (MM)
- **Association with giant cell arteritis:** GCA is a large- to medium-sized arteritis that involves branches of the proximal aorta; p/w jaw claudication, scalp tenderness, blurred vision, new HA; may occur w/ PMR or in isolation; PMR & GCA hypothesized to be different manifestations of one disease process; 16–30% of pts w/ PMR have GCA; 40–60% of pts w/ GCA have PMR (see *"Vision Complaints"* for GCA dx/tx)

## Evaluation

- **Exam:** ↓ active & passive ROM in affected joints; proximal joint swelling; swelling of hands and/or feet; nonerosive peripheral arthritis; assess tenderness in scalp & temporal artery
- **Workup:** ✓ESR & CRP; IL-6, if available; ✓TFTs, Chem-12, CBC w/ diff, UA; RF & anti-CCP typically ⊖ ; ANA in elevated titer not assoc w/ PMR; PMR assoc w/ anemia of chronic disease; CPK should be nl; nl ESR does **not** exclude PMR (ESR <50 mm/h seen in 10%) (*BMJ* 2012;344:e1408)
  **Radiographs:** Not routinely ordered & rarely helpful; may aid dx if nl ESR; MRI or U/S can demonstrate synovitis; joint erosions are

not assoc w/ PMR

- **Giant cell arteritis:** Screen by H&P; no role for temporal artery bx w/o sx or suspicion for GCA (e.g., very high ESR or significant systemic manifestations)

### Management (*Best Pract Res Clin Rheumatol* 2012;26:91; *Lancet* 2007;372:234)

- **Steroids:** Mainstay of Rx w/ initial dose of 15 mg/d (maximum 20–30 mg/d) of prednisone or equivalent (*Ann Intern Med* 2009;169:1839); anticipate initial improvement within 24–48 h & continued improvement over subsequent wks; failure to respond to steroids should raise suspicion for alt dx (e.g., vasculitis); higher doses of steroids may be used to treat flares; ✓BMD, A1c, lipids, PPD (if risk factors present) for pts on long-term steroids to screen for glucocorticoid-related osteoporosis, DM2
  **Duration:** Steroid Rx often continues for 2–3 y w/ slow dose ↓ guided by inflammatory markers (ESR, CRP, ± IL-6) & sx; maintenance dose typically 2.5–5 mg/d prednisone; 50% of pts relapse
- **Steroid-sparing agents:** Trials, case-series, & reports describe successful use of MTX, leflunomide, tocilizumab (*Arthritis Care Res* 2012), & TNF-α blockade
- **Patient information:** *AFP* 2006;74:1557

## POLYARTICULAR ARTHRITIS

### Background (*AFP* 2003;68:1151)

- **History:** Sx acute vs. chronic (>2 mos), inflammatory vs. noninflammatory, type of joint involved (peripheral vs. axial, native vs. prosthetic, small vs. large), symmetric vs. asymmetric, episodic vs. continuous vs. migratory; # of joints involved: Mono- (1); oligo- (2–4); poly- (>4); presence of other systemic disease or symptoms (e.g., IBD)
- **Workup:** RF, CCP (for RA, below), ESR, CRP; Acute-onset (<6 wks), consider parvovirus $B1_9$, HBV, HCV, Lyme serologies
- **Differential diagnosis:** In addition to specific disease below: OA;

gout/pseudogout; Lupus, PMR, paraneoplastic polyarthritis; sarcoidosis (assoc w/ hilar adenopathy, erythema nodosum); adult-onset Still disease (assoc w/ high fevers, rash, ↑ ferritin); systemic vasculitides (e.g., granulomatosis with polyangiitis, Churg-Strauss syndrome); hemochromatosis (esp w/ MCP and/or wrist involvement); PM & DM, fibromyalgia, reactive arthritis (Reiter syndrome), serum sickness

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## RHEUMATOID ARTHRITIS (*AFP* 2011;84:1245; *Ann Intern Med* 2010;153:ITC1; *Lancet* 2010;376:1094)

- **Definition:** Symmetric, inflammatory arthritis affecting multiple peripheral joints
  **Extraarticular manifestations:** Seen in 30–50% of pts; include Sjögren syndrome (dry eyes/mouth, most common), pulmonary (ILD), vasculitis, cardiac (pericarditis/CAD), cutaneous (rheumatoid nodules), anemia of chronic disease, ↓ BMD, Felty syndrome (RA + neutropenia + splenomegaly + recurrent infections)
  **Complications:** ↑ risk of infection, cervical subluxation → pain, neuro deficit, instability
- **Epidemiology:** 0.5–1% of Caucasian adults; peak incidence 50–60 y
- **Pathophysiology:** Loss of immune tolerance → symmetric synovial inflammation, cartilage & bone destruction, joint deformity (*NEJM* 2011;365:2205)
- **Risk factors:** ↑ age, ♀ > ♂, FHx; HLA-DRB1 loci; smoking

### ACR/EULAR 2010 Criteria for Diagnosis of RA (*Lancet* 2010;376:1094; *Arthritis Rheum* 2010;62:2569)

| Category | Criteria (points) |
|---|---|
| **Joint Involvement** (any *swollen* or *tender* joint on exam, excluding DIP, 1st MTP, 1st CMC) | • One medium to large joint (0)<br>• 2–10 medium/large joints (shoulder, elbows, hips, knees) (1)<br>• 1–3 small joints (i.e., MCP, PIP) (2)<br>• 4–10 small joints (3)<br>• >10 joints (including ≥1 small joint) (5) |
| **Serology** | • ⊖ RF & ⊖ anti-CCP (0)<br>• Low-⊕ RF or low-⊕ anti-CCP (2)<br>• High-⊕ RF or high-⊕ anti-CCP (3) |
| **Acute-phase reactants** | • Nl CRP & nl ESR (0)<br>• Abnl CRP or abnl ESR (1) |
| **Duration of symptoms** | • <6 wks (0), ≥6 wks (1) |
| **Scoring:** ≥6 pts consistent with dx of RA; pts may meet more criteria w/ time & should be followed serially if ↑ suspicion | |
| ≥2 typical erosions or long-standing disease meeting ACR 1987 criteria also c/w dx of RA | |

- **History:** Typically polyarticular arthritis (common joints involved: PIPs, MCPs, wrists, cervical spine); Subacute onset of sx (healthy → undifferentiated arthritis → early RA → RA); prolonged (>45 min) AM stiffness; extra-articular manifestations; impact of sx on daily activities
- **Exam:** Rheumatoid nodules (SC nodules commonly on pressure points), grip strength
- **Workup:** CBC, Chem-12, UA, uric acid, ANA (r/o lupus), uric acid; plain films of hands/feet show juxta-articular erosions & symmetric joint space narrowing (contrast w/ asymmetry in OA) in progressive disease (usually irreversible)

**Labs in Rheumatoid Arthritis (*Clin Chem Lab* 2001;39:189; *Ann Rheum Dis* 2003;62:870)**

| Test | Se | Sp | Comments |
|---|---|---|---|
| **Rheumatoid factor** | 66% | 91% | IgM, IgA, or IgG that binds IgG Fc region; 10–30% of pts are RF ⊖ at presentation; many will turn RF ⊕ over time; False ⊕: Seen in bacterial/viral infection, healthy pts >70 y, malignancy |
| **Anti-cyclic citrullinated peptide (CCP)** | 68% | 98% | Autoantibody to post-translational modification of arginine; ↑ correlation w/ functional status, erosions, & persistent (vs. self-limited) disease |

- **Prognosis:** ↑ Risk of early mortality (mostly 2/2 ↑ risk of CV disease); important to assess for & minimize cardiac RFs

- **Treatment:** 1º goal is remission with no e/o active disease, requiring early & aggressive comanagement w/ rheumatology (*BMJ* 2011;343:4027; *Arthritis Rheum* 2005;52:3381)
  Initial control & acute flares can be managed w/ NSAIDs & steroids (limit both); adverse effects of weak opioids (tramadol, codeine) may outweigh benefits (*JAMA* 2013;309:485); close monitoring for drug toxicity & efficacy w/ a goal of "tight control" (disease remission or low activity)

**Disease-modifying antirheumatic drugs:** Early Rx to prevent joint damage/disability; selection of agent(s) based on disease severity; combination tx in severe/refractory disease

**Nonbiologic:** MTX (1˚ tx for most RA pts; limit EtOH consumption, administer w/ folic acid), hydroxychloroquine (baseline optho exam), sulfasalazine, leflunomide; HQ & sulfasalazine used in pts w/ low disease activity & absence of poor prognostic factors

**Biologic:** TNF inhibitors (Etanercept, infliximab, adalimumab, golimumab, certolizumab pegol), IL1 receptor antagonist (anakinra), IL6 receptor antagonist (tocilizumab), T-cell costimulation blocker (abatacept), anti-CD20 B-cell (rituximab); screen for HBV, HCV, TB prior to initiation (see *"HBV" "HCV" "TB"*)

**Supportive care:** PT, OT, pt education, exercise

**Surgery:** Consider joint replacement in pts w/ uncontrolled pain or severe disability despite optimal medical Rx

- **Patient information:** *JAMA* 2011;305:1824

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## Infectious Arthritis

- **Bacterial:** (*Lancet* 2010;375:846)
  **Risk factors:** Previous joint pathology (RA, OA, gout, prosthetic joints), immunosuppressed, cutaneous infection, IVDU, prior intrarticular steroid injection
  **Management:** Early arthrocentesis w/ cell counts & Cx; obtain BCx; early abx; if detected/high suspicion → ED/orthopedics for serial arthrocentesis ± surgical wash out; also involve ID for prosthetic joint infections (*Infect Dis Clin N Am* 2012;26:29)
  **Nongonococcal septic arthritis:** *S. aureus* > > other gm ⊕ or GNR;

typically monoarthritis (large joint) but 20% involve >1 joint; systemic sx may be lacking; direct inoculation vs. spread from contiguous infection vs. bacteremia (e.g., endocarditis)

**Disseminated gonococcal infection:** Usually young, sexually active (acute oligo- or poly-, typically migratory, skin lesions); see *"Polyarticular Arthritis"*

- **Viral:** Nonerosive usually managed symptomatically (*Infec Dis Clin N Am* 2005;19:963)

  **Parvovirus B19:** Assoc w/ exposure to children; mono → polyarticular within 48 h; sx mimic RA but very acute; ± cytopenias; usually self-limited (1 wk after presentation); dx w/ IgM anti-$B1_9$ ± PCR

  **Rubella:** Assoc w/ LAD, maculopapular rash, & symmetric RA-like arthritis; self-limiting w/in 2 wks; dx w/ IgM anti-Rubella

  **Hepatitis: HCV** assoc w/ chronic arthritis in 2–4% ( ± cryoglobulinemia syndrome), many w/ false ⊕ RF, usually anti-CCP; acute **HBV** assoc w/ transient RA-like arthritis, rarely PAN

  **HIV:** ↑ risk of septic arthritis, arthralgias common, ↑ risk of spondyloarthropathies (esp reactive/psoriatic arthritis, may be severe but ↓ frequency in HAART era)

- **Lyme:** Migratory arthralgias → asymmetric "recurrent brief attacks" (wks/mos) of mono- or oligoarthritis (knees + other large joints); ↑ joint sx if untreated; early tx prevents arthritis; typically responds to 4 wks PO abx (e.g., doxycycline), may require IV, persistent/chronic arthritis is rare (unclear etiology); assoc w/ strongly IgG ⊕ serology & *B. burgdorferi* DNA by PCR of synovial fluid (see *"Tick-Borne Illness"*) (*Infec Dis Clin N Am* 2008;22:289)
- **Other:** Mycobacterial & fungal infection rare; suspect if RFs present

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## SERONEGATIVE SPONDYLOARTHROPATHIES (*AFP* 2004;69:2853)

- **Background:** Distinguished by axial-predominant arthritis (ankylosing spondylitis subtype) vs. peripheral-predominant arthritis (all other subtypes); variably assoc w/ dactylitis (inflammation of entire finger/toe) & enthesitis (inflammation where tendon inserts to bone), as well as extra-articular manifestations such as ocular disease (e.g.,

uveitis) & skin disease; diagnosis and prompt rheum referral key

- **Inflammatory back pain:** SI joints (**sacroiliitis**), apophyseal joints of spine; characterized by **IPAIN (I**nsidious onset, **P**ain at night, **A**ge of onset $<40$ y, **I**mproves w/ exercise/hot water, **N**o improvement w/ rest), AM stiffness, responsive to NSAIDs (*Rheumatology* 2010;37:1978)
- **Ankylosing spondylitis:** Most common; ♂ > ♀; characterized by prominent inflammatory back pain (esp in AM); extra-articular manifestations include iritis, tendonitis, AI; +HLA-B27 in 90% of pts; MRI detects SI joint inflammation earlier than radiograph; tx w/ NSAIDs & TNF inhibitors (*Lancet* 2011;377:2127)
- **Reactive arthritis:** Acute onset of sterile, asymmetric, mono- or oligoarthritis (usually lower limb) 1–2 wks after GI or GU infection (e.g., *Yersinia, Salmonella, Campylobacter, & Chlamydia*) which can be asx; ± urethritis, conjunctivitis; 50–80% w/ +HLA-B27; tx underlying infection if GI or GU sx; tx arthritis w/ NSAIDs & steroids for severe disease; avg duration is 3–5 mos but can become chronic (*Best Pract Res Clin Rheumatol* 2011;25:347)
- **Psoriatic arthritis:** Typically mono-/oligoarthritis early → polyarthritis later; dactylitis prominent; >50% have hx psoriasis (psoriasis vulgaris most common); 20% w/ +HLA-B27; leads to joint deformity/erosive disease if untreated; DMARDs variably useful; TNF inhibitors effective (*Ann Rheum Dis* 2012;71:319) (see *"Psoriasis"*)
- **Inflammatory bowel disease:** 3 different subtypes assoc w/ IBD: (a) axial arthritis resembling ankylosing spondylitis or isolated sacroiliitis; (b) peripheral arthritis type 1 affects large joints (oligo-) of LE & acutely assoc w/ IBD flare; (c) peripheral arthritis type 2 affects small joints (poly-) in a symmetrical manner & persists regardless of IBD activity (see *"IBD"*)

# RHEUMATOLOGIC TESTS

## Inflammatory Markers (*Mod Rheumatol* 2009;19:469)

- **C-reactive protein:** Produced by liver; part of innate immune system, regulates inflammation, activates complement; rapidly Δs, direct measure of inflammation
- **Erythrocyte sedimentation rate:** Indirect measure of inflammation, slowly Δs; ↑ ESR suggests acute-phase proteins (e.g., fibrinogen, globulin) in plasma causing RBC aggregation; ↑ by pregnancy, ↑ age, certain medications (e.g., OCPs), anemia

## Antinuclear Ab (*AFP* 2002;65:1073; *Arthritis Rheum* 2002;47:434; *Clin Chem Lab Med* 2001;39:189)

- **When to perform:** *Not a test to r/o rheumatologic disease;* use when clinical suspicion for CTD exists; may be present in healthy pts (♀ > ♂, ↑ age), infection, malignancy, hepatic or pulmonary disease, pregnancy; ANA ⊕ by definition in drug-assoc lupus, MCTD, & autoimmune hepatitis
- **Titer:** 1:40 (low ⊕, seen in 25–30% of healthy pts); 1:80 (low ⊕, seen in 1–15% of healthy pts); ≥1:160 (⊕, ⊕ in 5% of healthy pts), proceed w/ further w/u; ⊕ titer may precede sx by several years (*NEJM* 2003;349:1526; *Arthritis Res Ther* 2011;13:1) → monitor pts w/ low ⊕ but no further diagnostic study w/o sx
- **Staining pattern:** 40+ patterns; specific for ENAs & related conditions (e.g., homogenous staining → anti-dsDNA → SLE; nucleolar → Scl-70 → systemic sclerosis), but multiple Ab & conditions for each staining pattern

**Characteristics of ANA Testing by Disease**

| Disease | Se/Sp (%) | ± Likelihood |
|---|---|---|
| SLE* | 93/57 | 2.2/0.1 |
| Systemic sclerosis* | 85/54 | 1.9/0.3 |
| RA† | 41/56 | 0.9/1.1 |
| DM/PM† | 61/63 | 1.7/0.6 |
| Sjogren syndrome‡ | 48/52 | 0.99/1.01 |

*ANA a useful test in this disease
†ANA not a useful test in this disease
‡ANA may be a useful test to r/o underlying SLE if suspected

## Extractable Nuclear Antigens (ENA) (*Am J Clin Pathol* 2002;117:316; *Lupus* 2011;20:250)

- **When to perform:** ⊕ ANA indicates presence of antinuclear specific Ab or ENAs; should *not* be ordered before obtaining an ANA w/ ⊕ titer unless clear sx present

### Diseases with Associated Extractable Nuclear Antigens (*Clin Chem Lab* 2001;39:189)

| Disease | Antibodies | Notes |
|---|---|---|
| **SLE** | Anti-dsDNA (H), Anti-Sm (S), Anti-Ro (S), Anti-La (S), Anti-RNP (S), Anti-histone (H) | Anti-Ro assoc w/ congenital CHB; Anti-histone a/w drug-induced LE |
| **DM/PM** | Anti-Jo-1 (C,S) | |
| **Systemic sclerosis/ CREST** | Anti-Scl-70 (N), Anti-CENP-B (Ce) | Anti-Scl-70 assoc w/ SSc > CREST; Anti-CENP-B a/w CREST > SSc |
| **Sjogren's** | Anti-Ro (S), Anti-La (S) | **Staining Patterns**<br>(H) = Homogenous or peripheral<br>(C) = Cytoplasmic<br>(N) = Nucleolar<br>(S) = Speckled<br>(Ce) = Centromere |
| **MCTD** | Anti-RNP (S) | |
| **PBC** | Anti-Mitochondria (C) | |
| **Autoimmune Hepatitis** | Anti-Smooth muscle (C) | |

CREST = **C**alcinosis, **R**aynaud's, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias syndrome

## Anti-neutrophil Cytoplasmic Antigen (ANCA) (*Clin Chem Lab* 2001;39:189)

- **p-ANCA:** Perinuclear pattern; target is usually myeloperoxidase & not specific for single disease entity; assoc w/ systemic vasculitis, GN, SLE, RA, exposures
- **c-ANCA:** Classical/cytoplasmic pattern; targets PR-3 = major autoAg in granulomatosis w/ polyangiitis (GpA, previously Wegener Granulomatosis); 10–30% of pts w/ GpA are cANCA ⊖; ↑ titer assoc w/ relapse; may be present in pauci-immune GN

## Cryoglobulins (*Lancet* 2012;379:348)

- **Background:** Immunoglobulin generated by clonal B-cell; precipitate in cold, dissolve on rewarming
  **Type 1:** Monoclonal Ig (IgG or IgM) assoc w/ myeloproliferative disease (e.g., MM); can lead to vascular occlusion & hyperviscosity
  **Type 2:** Mixed cryoglobulin (polyclonal IgG & monoclonal IgM) assoc w/ HBV & HCV; can lead to immune-complex–mediated vasculitis

**Type 3:** Mixed cryoglobulin (polyclonal IgM & IgG) assoc w/ autoimmune disease (e.g., SSC), infection (HBV, HCV, HIV), & malignancy (hematologic > > solid)

- **Interpretation:** ↑ levels may be pathogenic as in mixed cryoglobulinemia (vasculitis), but low levels likely nonpathogenic in other disease (e.g., SLE); 10% of cryoglobulinemia idiopathic; if ⊖ test but ↑ clinical suspicion, test should be repeated; high false-⊖ rate
- **Cryocrit:** Concentration of cryoglobulin; level assoc w/ severity of disease; serial testing advised

# SYSTEMIC LUPUS ERYTHEMATOSUS

## Background *(Arthritis Rheum* 2007;56:2092; *NEJM* 2011;365:2110)

- **Definition:** Chronic inflammatory disease 2/2 Ab formation & immune complex deposition, w/ notoriously varied presentation that can affect nearly every organ
- **Epidemiology:** 20–150/100,000; 7:1 ♀ : ♂ ratio; 65% of pts w/ onset btw 16 & 55 y
- **Pathophysiology:** Suspected to involve genetic (complement deficiency), hormonal (estrogen), immunologic (autoantibodies), & environmental factors
- **Clinical course:** Variable; periods of acute flares, remission, & chronic relapse; many pts organ system involvement characteristic of their particular illness; skin, joints, kidneys, central nervous system, & blood elements; for cutaneous lupus, see *"Rheumatologic Skin Disease"*
  **Precipitating factors:** Sun exposure (derm), infections, stress, surgery, pregnancy

### Classification Criteria and Clinical Manifestations (*Arthritis Rheum* 1982;25:1271)

| | ACR Criteria | Clinical Features |
|---|---|---|
| Systemic | *If ≥4 of 11 criteria below are met (either serially or simultaneously), Se & Sp for SLE is 96%* | Systemic sx include fatigue, fever, malaise, wt loss/gain, weakness |
| Derm >80% | **1. Malar rash**<br>**2. Discoid rash** (erythematous plaques w/ keratosis & plugging)<br>**3. Photosensitivity**<br>**4. Oral/nasopharyngeal ulcers** | Raynaud's, alopecia<br>Malar "butterfly" rash: facial erythema sparing nasolabial folds & exacerbated by UV light (photosensitivity)<br>Ulcerations usually painless<br>Nail dystrophy not uncommon |
| Msk >90% | **5. Arthritis** (nonerosive, ≥2 peripheral joints) | Myalgias, arthritis (migratory & symmetric involving hands), Raynaud's |
| CV & Pulm | **6. Pleuritis** or **pericarditis** | Pericarditis, myocarditis, CAD, valvular dz, vasculitis, pleurisy, pleural effusions, pneumonitis, ILD, pHTN, hemorrhage |
| Renal 16–38% | **7. Proteinuria** (>500 mg/d or ≥3+ dipstick) *or* casts (RBC, Hgb, granular, tubular, mixed) | Lupus nephritis (hematuria, proteinuria, or ↑ Cr) (~50% w/ clinically evident renal dz, but most have involvement on bx) |
| Neuro 10–80% | **8. Seizures** *or* **psychosis** | Cognitive dysfunction, stroke syndromes, neuropathy, HA, delirium<br>Psych (depression, anxiety, mania) |
| Heme 36% | **9. Hemolytic anemia** (w/ ↑ retic) *or* **leukopenia** (+4000/mm$^3$) *or* **lymphopenia** (<1500/mm$^3$) *or* ↓ **PLT** (<100K) | Anemia of chronic dz may also be present<br>LAN, splenomegaly<br>Venous or arterial thromboembolism |
| Sero-logies | **10. +Anti-DNA** *or* **+Anti-Sm** *or* **antiphospholipid antibodies**<br>**11. +ANA** | **Antiphospholipid syndrome (APLS):** Thrombocytopenia, venous & arterial thrombosis, recurrent miscarriages |
| GI 25–40% | | Dysphagia, abdominal pain, nausea, mesenteric vasculitis, pancreatitis, gastritis, ulcers (often 2/2 NSAIDs) |
| Misc | | Infectious complications<br>Ophthalmologic (keratoconjunctivitis sicca) |

## Evaluation and Prognosis (*AFP* 2003;68:2179)

- **Diagnosis:** Based on meeting ≥4 of the ACR criteria above, simultaneously or over time
- **History:** Presence of sx described above; precipitating events for lupus flare
- **Exam:** Full exam, incl CV (pericardial rub, murmurs), **skin**, joints, liver/spleen
- **Workup:** CBC (cytopenias), Chem-12, CK, ESR, CRP, UA (proteinuria); complement testing (C3, C4 frequently low in active disease); (see *"Rheumatologic tests"*)

**Autoantibody Testings in SLE (*Arthritis Rheum* 2002;47:546; 2004;51:1030)**

| Test | Notes |
|---|---|
| **ANA** | *1st-line test;* ⊕ at high titer (1:160) in virtually all pts w/ SLE; if ⊕, should proceed w/ additional autoantibody testing |
| **Anti-dsDNA** | Correlated with overall SLE disease activity, & in particular, renal involvement; Se 57%, Sp 97.4% for SLE |
| **Anti-Smith (Sm)** | Low Se (24%) but high Sp (98%) for SLE |
| **Antiphospholipid** | Includes LA, ACL, & anti-β2 |

- **Imaging:** Not required, but may confirm clinical sx; radiographs (joints, CXR for effusions), renal U/S, echo, CT C/A/P, MRI (neuro deficits), angiography (vasculitis)
- **Other:** Biopsies may be warranted for confirmation of specific organ involvement (i.e., skin, kidney); ECG for pericarditis; crucial to review meds for drug-induced lupus (see below)
- **Prognosis:** Course can vary tremendously btw pts, ranging from relatively quiescent disease to rapidly progressive organ damage; 5 y survival >90%; Active disease the most common cause of death, along w/ complications from immunosuppression (infection)
  **Poor prognostic factors:** Renal disease, HTN, ♂, extremes of age at presentation, African ancestry, antiphospholipid antibodies/syndrome, socioeconomic status, ↑ disease activity

## Treatment (*Arthritis Rheum* 1999;42:1785)

- **General approach:** Avoid sun, smoking, & pregnancy (during active disease); Rheum referral if disease suspected & for continuing co-mgmt; hydroxychloroquine & immunosuppressive Rx require monitoring for toxicities; pt education on signs of flare
- **Medications:**
  **NSAIDs:** Useful for musculoskeletal sx, fevers, HAs, & mild serositis
  **Hydroxychloroquine:** Useful for skin & musculoskeletal sx, & mild overall disease
  **Glucocorticoids:** Reserved for significant organ involvement (renal & CNS disease); Topical steroids for skin lesions (see *"Rheumatologic Skin Disease"*)
  **Immunosuppression:** Reserved for glucocorticoid Rx failure &

significant organ involvement; includes MTX, cyclophosphamide, azathioprine, mycophenolate, belimumab (*NEJM* 2013;368:1528), & possibly rituximab

- **Monitoring:** Follow clinical manifestations; serologic studies can also be useful (anti-dsDNA titers, complement levels, ESR, CRP)
- **Patient information:** *JAMA* 2011;306:668

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### DRUG-INDUCED LUPUS

- **Background:** Mechanism unclear; related to drug-induced autoantibodies (particularly antihistone, & ANA, but *not* dsDNA); 1:1 ♂:♀ ratio
- **Associated medications: Procainamide, hydralazine, penicillamine,** INH, minocycline, quinidine, anti-TNF drugs, IFN, methyldopa, chlorpromazine, diltiazem; many other drug classes implicated, including anticonvulsants, antimicrobials, & βB
- **History:** Fever, rash, myalgias, arthritis, serositis
- **Treatment:** Withdrawal of offending medication; sx should resolve within several mos; symptomatic treatment w/ NSAIDs & steroids may be considered

# SHOULDER PAIN

## Background (*BMJ* 2005;331:1124)

- **Epidemiology:** Prevalence 21–34% in primary care; 3rd most common MSK complaint; in young pts often related to injuries (e.g., GH joint instability or overuse); in older pts more commonly rotator cuff tendinitis, tears, adhesive capsulitis, & OA
- **Anatomy:** Glenohumeral (GH), acromioclavicular (AC), and sternoclavicular (SC) joints; Rotator cuff (RC) "SITS" muscles: **S**upraspinatus (abduction & external rotation; most commonly injured), **I**nfraspinatus (external rotation & abduction), **T**eres minor (external rotation & abduction), & **S**ubscapularis (internal rotation)

## Evaluation (*AFP* 2000;61:3079; 3291; 2008;77:453; *JAMA* 2000;284:1559; 2004;292:1989; 2013;310:837)

## Differential Diagnosis of Shoulder Pain

| Disorder | Presenting Features |
|---|---|
| **Cervical disease** | Pain radiating *below* elbow, ↓ C-spine ROM |
| **Labral tear** | Fall on outstretched arm or repetitive overhead loading activities; p/w deep shoulder pain catching sensation, instability |
| **RC impingement & tendinopathies** | Anterolateral pain worse with abduction and/or reaching, typically in context of repetitive activity at or above level of shoulder (swimming, wt lifting, tennis, throwing) |
| **Biceps tendinitis** | Gradual onset anterior shoulder pain typically w/ heavy lifting |
| **RC tear** (*NEJM* 2008;358:2138) | Pain & weakness w/ lifting shoulder (i.e., combing hair); suspect full thickness tear if pain w/ abduction 60–120° (painful arc sign), weakness w/ external rotation & ⊕ drop-arm test (below) |
| **Adhesive capsulitis** (*AFP* 2011;83:417) | Progressive, ↓ active & passive ROM, w/ pain, often at night in pts w/ DM, thyroid disease, trauma & restricted ROM (i.e., stroke); plain films & MRI typically nl; clinical dx |
| **Osteoarthritis** (*AFP* 2008;78:605) | >50 y, pain w/ activity, stiffness, ↓ ROM, crepitus w/ arm elevation; may affect AC (pain w/ elevation of arm >90°) or GH joint (pain w/ external/internal rotation when arm is in neutral position); Radiographs necessary to distinguish from adhesive capsulitis |
| **GH joint instability** | Shoulder pain in throwing athletes |
| **Other** (*AFP* 2004;70:1947) | Fracture; referred pain from C-spine herniation, nerve entrapment, MI, septic arthritis, UE DVT, PE, avascular necrosis, PMR |

- **Exam:** Examine C-spine, both shoulders & arms; palpate AC, SC, & GH joints, biceps tendon, subacromial bursa, trapezius muscles; distinguish pain w/ **active** motion (muscular or tendon) from **passive** motion (concerning for **joint** involvement); distinguish rotator cuff tear from impingement or bursitis by assessing weakness w/ external rotation & abduction; assess sensation, reflexes, & motor strength for nerve impingement

## Shoulder Exam Maneuvers

| Test | Maneuver (*AFP* 2000;61:3079) | Positive in |
|---|---|---|
| **Apley scratch test** | Touch superior & inferior aspects of opposite scapula | Rotator cuff injury or OA |
| **Drop-arm test** | Cannot smoothly adduct arm/shoulder to waist | Rotator cuff tear |
| **Neer test** | Fully pronate arm then place arm in full flexion | Subacromial impingement |
| **Hawkin test** | Elevate arm forward to 90° while forcibly internally rotating the shoulder | |
| **External rotation** | Flex both elbows to 90° while the examiner provides resistance against external rotation | Teres minor & infraspinatus tear or impingement |
| **Empty can/ full can test** | 90° elevation in the scapula plane & full internal rotation (empty can) or 45° external rotation (full can); examiner applies downward pressure at wrist | Supraspinatus tear or impingement |
| **Yergason sign** | Elbow flexion to 70°; pt forces supination against resistance | Biceps tendinitis |

- **Workup:** Image if hx trauma concerning for fracture/dislocation, or exam concerning for joint involvement/RC tear, gross deformity, localized swelling/tenderness over AC or SC joint, joint instability; consider imaging in pts w/persistent shoulder pain despite w/ 2–3 mos of conservative Rx; **start w/ radiograph** (*AFP* 2000;61:3291; *J Am Coll Radiol* 2011;8:602)
  **Radiograph:** True AP (glenohumeral joint) & axillary lateral & Y view (AC joint)
  **MRI w/o contrast:** 95% Se & Sp in RC tears; can identify abnormality in asx pts; indicated w/ persistent pain, unrevealing plain films, nonspecific H&P
  **Arthrography:** Invasive; good at identifying complete RC tears, labral tears, or capsulitis
  **Ultrasound:** Good for complete RC tears, bursitis, but operator-dependent
  **CT:** May be useful for subtle dislocation, prosthetic joints

## Treatment (*AFP* 2003;67:1271; 2008;77:493)

- **General approach:** For most shoulder pain in older adults without e/o joint instability, marked muscle weakness or atrophy, or infection, initial trial of NSAIDS ± PT (if limited ROM or strength) for 2–4 wks; if no improvement, consider nerve block or referral; if impingement, tendinitis or bursitis, earlier injection may be useful
- **Shoulder impingement:** Ice, rest, PT, glucocorticoid injection in

refractory cases

- **Adhesive capsulitis:** PT, APAP; glucocorticoid injection, prednisone, or surgery referral for manipulation under anesthesia or release in refractory/severe cases
- **Osteoarthritis:** Generally NSAIDs, PT, rest
- **Rotator cuff tears:** Surgical repair of acute, complete tears; rest, ice, NSAIDs, PT, glucocorticoid injection for partial thickness & chronic full thickness tears w/ surgical referral in refractory cases
- **Dislocation or fracture:** Relocation & immobilization but w/ early ROM to prevent adhesive capsulitis, PT indicated
- **When to refer:** Urgent eval needed in fracture, dislocation, separation, rotator cuff tear, joint instability/infection; ortho referral if gross deformity or joint instability as joint separation may require surgery; injury in high-functioning athlete; suspect full labral tear or full thickness RC tear; if sx not improving w/ 3 mos of conservative mgmt & PT
- **Patient information:** *AFP* 2008;78:612; 2011;83:423

# NOTES

# BELL'S PALSY

## Background (*NEJM* 2004;351:1323; *AFP* 2007;76:997)

- **Definition:** Bell's palsy is an idiopathic unilateral acquired facial nerve palsy; some suggestion that this may be 2/2 HSV-1 (⊕ HSV DNA in affected CNs)
- **Physiology:** CNVII innervates ipsilateral muscles of facial expression; also contains parasympathetic fibers → lacrimal, salivary glands, some taste to anterior 2/3 of tongue
- **Epidemiology:** 0.2–0.3% annual risk; rarely recurs; incidence peaks in 40s, ↑ risk assoc w/ DM, HTN, pregnancy, HIV (*CID* 2007:44:e27)
- **Natural history:** Most pts (70%) fully recover w/o tx & most improve w/in first 3 wks; *Poor prognosis:* Elderly, DM, HTN, pregnancy, complete paralysis, pain other than in ear, severe pain, ↓ taste; *Good prognosis*: Partial paralysis, early (1st wk) recovery of motor function, recovery of taste *before* motor function

## Evaluation (*NEJM* 2004;351:1324)

- **General approach:** Obtain complete hx & perform full HEENT & neuro exam on all pts; **clinical diagnosis** based on classic findings; pts w/ atypical features require further testing; those w/ red flags require emergent eval

### Classic Presentation

| | |
|---|---|
| **History** | Sudden onset; rapid evolution to max facial weakness w/in 48 h; ipsilateral hyperacusis (2/2 paralysis of stapedius muscle), ear pain or fullness, ± retroauricular pain preceding weakness, ± ↓ lacrimation, salivation, & taste (anterior 2/3 of tongue); fullness of face (but no sensory loss) |
| **Exam** | Partial or complete ipsilateral paralysis of CNVII, including forehead, is only expected finding; assess eyebrow elevation, **eye closure**, nasolabial fold, cheek puff, lip purse, taste & platysma muscle may include ↓ lacrimation, salivation, or taste depending on segment affected |

- **Features suggestive of alternative diagnosis** (*BMJ* 2004;329:553)
  *Hx:* **Gradual onset** (suggests compression, e.g., neoplasm), **headache**, loss of sensation or add'l neuro sx (CNS lesion), trauma

(mechanical injury or CNS lesion), hearing loss, vertigo (CPA lesion, Ramsay Hunt), **recurrent**

*Exam:* **Bilateral disease**, palpable mass (peripheral compression, e.g., parotid tumor), otoscopic abnormalities (cholesteatoma, vesicles of Ramsay Hunt), oral lesions (VZV vesicles, tonsillar asymmetry suggestive of tumors), rash (Lyme), **other CN/neuro abnormalities**

- **Differential diagnosis:**

  *CNS lesions* (stroke, neoplasm, demyelination, CPA mass):

  *Pons/CNVII nucleus:* ⊕ **Brainstem signs** like contralateral body hemiparesis, sensory loss, ataxia, nystagmus, abnl eye movements

  *Cerebral/supranuclear:* **Forehead spared**, salivation & taste intact despite ↓ lacrimation; arm/leg weakness

  *Peripheral lesions:* Ramsay Hunt syndrome (VZV reactivation in CNVII; can occur as pain w/o vesicles, i.e., *zoster sine herpete*), Lyme, Guillain–Barré (often b/l), parotid tumor, ear lesion (otitis media, cholesteatoma), sarcoid, Sjögren's
- **Labs:** Not indicated if classic hx/PE, consider Lyme testing if ↑ clinical suspicion or high-risk pt in endemic area (see "*Tick-Borne Illness*"), consider HIV testing
- **Imaging:** If gradual onset, suspicious HA but no suggestion of acute central processes which requires ED referral → neuroimaging, LP if suspect neuro Lyme disease
- **Other: Nerve conduction studies (NCS)** may be useful for prognosis, but not routine

## Treatment (*Neurology* 2012;79:2209; *NEJM* 2007;357:1598)

- **Corticosteroids:** 40–60 mg prednisone QD × 7 d should be started ASAP, ideally within 48 h of sx onset (prompt tx → 40% ↑ RR of complete recovery of motor function at 6 mos c/w placebo; NNT 6–8) (*Cochrane Database System Rev* 2010;CD001942)
- **Other:** Antivirals (for presumed HSV) not shown to be effective in most RCTs (*NEJM* 2007; 357:1598) but question of modest benefit & may be offered; valacyclovir & famciclovir preferred 2/2 ↑ adherence; PT not shown to be beneficial or harmful (*BMJ* 2009;339:b3354; *Cochrane Database System Rev* 2012;CD006283)

- **Early complications:** Incomplete eye closure can → corneal abrasion; artificial tears q1h; eye ointment; eye patch at night, consider ophtho referral
- **Late complications:** Synkinesis (voluntary movement of one muscle → involuntary movement of another, e.g., winking → mouth twitching) & facial spasms can be treated w/ botulinum toxin
- **When to refer:** If suspect CNS lesion → **ED;** Ramsay Hunt → **ENT,** late complications or atypical presentation → N**eurology**

# CONCUSSION

## Background (*AFP* 2012;85:123; *Neurology* 2013;80:2250)

- **Definition:** Clinical syndrome in which direct blow or impulsive forces transmitted to head → immediate transient impairment of neuro function (including AMS or LOC) that resolves spontaneously; reflects complex pathophysiological process
- Considered a mild TBI characterized by *functional,* not structural problems; symptoms typically resolve w/in 3–7 d ( *J Neurotrauma* 2009;26:2365); during this time pts may be at ↑ risk of brain injury w/ even mild head trauma ("Second Impact Syndrome") (*Clin Sports Med* 1998;17:37)
- **Epidemiology:** 1.6–3.8 million sports concussions annually (*J Head Trauma Rehabil* 2006;21:375); elderly also at ↑ risk (see "*Fall Prevention"*)
- **Postconcussive symptoms:** HA, dizziness, & difficulty concentrating can last days–weeks, rarely months; no e/o single concussion → permanent neuro impairment; research ongoing to determine effects of multiple head injuries on cognitive function (*JNNP* 2010;81:1116)

## Evaluation (*NEJM* 2007;356:166; *AFP* 2012;85:123; *Neurology* 2013;80:2250)

- **History:** Obtain detailed history of mechanism of injury; ask about anticoagulation use; most common sx are **headache** (87%), **dizziness** (65%), & **confusion** (57%); can also present w/ postural instability, memory loss, blurred vision, drowsiness, impaired concentration, nausea, photo-/phonophobia, nervousness, irritability;

LOC in only 10%; may be assoc w/ convulsions immediately after injury (*J Neurotrauma* 2009;26:2365)

- For sx review, consider checklist, e.g., Post-Concussion Symptom Scale or Graded Symptom Checklist (www.mayoclinic.org/medicalprofs/enlargeimage5992.html, www.cdc.gov/concussion/pdf/TBI_schools_checklist_508-a.pdf)
- **Physical:** Neuro exam, focusing on attention, memory, balance; C-spine eval; consider assessment tools such as the Standardized Assessment of Concussion (www.knowconcussion.org/wp-content/uploads/2011/06/SAC.pdf)
- **Red Flags:** Any focal neuro deficits, coagulopathy, e/o basilar skull fracture (hemotympanum, raccoon eyes, Battle sign) → ED eval
- **Imaging:** *Not needed to diagnose concussion;* indication is to r/o more serious TBI; American College of Emergency Physicians/CDC guidelines recommend head CT for pts presenting to ED w/in 24 h of injury if:
  (1) **LOC or post-traumatic amnesia** & 1 of the following: Focal neuro deficit, HA, vomiting, age >60, drug or EtOH intox, short-term memory def, e/o trauma above clavicle, post-traumatic seizure, GCS <15, coagulopathy
  (2) **No LOC or post-traumatic amnesia** & 1 of the following: Vomiting, severe HA, age >65, physical signs of basilar skull fracture, GCS <15, coagulopathy or dangerous mech of injury (ejection from car, fall >3' or >5 stairs, pedestrian struck by car) (*Ann Emerg Med* 2008;52:714)

## Treatment ( *J Clin Neuroscience* 2009;16:755)

- **Reassurance and education:** Indicated for all pts → ↓ incidence + duration of postconcussive sx; counsel pts to f/u by phone or visit until sx resolved (*AFP* 2012;85:123)
- **Rest:** Short period of rest recommended, then resume activities as tolerated; athletes gradually ↑ cognitive/physical activity as tolerated in step-wise fashion, & if sx return, fall back to lower level of activity; should *not* return to play while symptomatic
- **Symptom management:** Dizziness/nausea → meclizine & antiemetics; HA → mild prn analgesics, if prolonged → consider standard

migraine tx (see "*Headache"*); if seizures immediately after injury → no need for AEDs unless seizures persist/recur

- **When to refer:** If sx persist greater than 1–2 wks, including HA not responsive to 1st-line agents or persistent cognitive complaints → **Neurology**

# DIPLOPIA

## Background (*Emerg Med Clin North Am* 1997;15:649)

- **Definition:** Appearance of duplicated visual image where there should be one
- **Pathophysiology:** normal binocular vision requires intact, coordinated function between globe, extraocular muscles, CNs, & cortical functioning; lesions anywhere along this pathway can lead to sensation of double vision
- **Cranial nerves involved in eye movement:**
  *CNIII* (oculomotor): Innervates medial, sup & inf rectus, inf oblique, lev palpebrae superioris, pupil constrictors (parasympathetic); *CNIV* (trochlear): Innervates superior oblique; *CNVI* (abducens): Innervates lateral rectus
- **Etiology:** CN palsies common cause; these can be idiopathic, ischemic, traumatic, compressive ( ↑ ICP, aneurysm); can also be due to pathology of the extraocular muscles themselves (trauma, myasthenia gravis); wide range of etiologies & severity means appropriate eval & triage crucial

## Evaluation (*Principles of Neurology*; 2009:261)

- **History:** Ask about onset, trauma, PMHx including DM, HTN, thyroid disease; obtain key features of diplopia hx to determine localization:
  (1) **Monocular** (persists w/ 1 eye closed) **or binocular** (disappears w/ 1 eye closed)?
  (2) **Horizontal** (images side-to-side) **or vertical** (above-&-below)?
  (3) **Alleviating/aggravating factors:** Tilting head, medial vs. lateral gaze, focus on near vs. distant objects, worse w/ fatigue or at end of day (**MG**)
  (4) **Assoc sx:** Ask about HA, N/V, weakness, numbness, dyscoordination, pain w/ eye movement (myopathy)

**Localization of Common Diplopia Complaints**

| Clinical Feature | Localization |
|---|---|
| Monocular (persists w/ 1 eye closed) | Ocular defect → refer to ophtho |
| Binocular (disappears w/ 1 eye closed) | Neuro defect → refer to neuro |
| Horizontal (side-to-side) images | CNIII or VI lesion |
| Vertical (above-&-below) images | CNIV lesion, skew deviation |
| Improves w/ head tilt | CNIV (if tilt toward *unaffected* side) or CNVI (if tilt towards *affected* side) |
| Sx worse w/ near focus | CNIII |
| Sx worse w/ distant focus | CNVI |
| HA, N/V, weakness, numbness, dyscoordination | Intracranial pathology |

- Ask about onset, any hx trauma, PMHx including DM, HTN, thyroid or neuro disease
- **Exam:** Full eye & CN exam: Assess for proptosis (Graves disease), ptosis (CNIII), lid lag (hyperthyroidism); fundoscopy exam for papilledema, pupil asymmetries (dilated pupil w/ CNIII lesion) & response to light (see "*Vision complaints*")
- **Alignment testing:**
  *Corneal reflection:* Shine light in pt's eyes while pt looking straight ahead; assess position of light's reflection in pt's corneas—asymmetry suggests misalignment
  *Cover–uncover test:* Assess for corrective movements as pt refixates (misalignment) (www.youtube.com/watch?v=yyIA-dl49Lg)
  *EOM testing:* Track examiner's finger in an H shape; check for diplopia in each quadrant
- If concern for myasthenia, perform repetitive strength testing (expect decremental response) & check sustained upgaze; check neck flexion and extension
- **Red flags:** **Headache,** N/V, anisocoria, impaired pupillary light response, ptosis, multiple CN palsies, other neuro deficits, eye pain

## Etiologies (*Principles of Neurology* 2009:261)

- **Cranial Nerve III palsy:** Horizontal or "diagonal" diplopia
  *Findings:* Impaired eye "down & out" when pt looks straight ahead, diplopia worst when pt looks superiorly & toward unaffected side; ± dilated pupil, ptosis
  *Etiology:* Most frequently **compression** by aneurysm or tumor (painful, usually w/ dilated pupil/impaired light response, but can have nl pupil if only a partial palsy) (*J Neurosurg* 2006;105:228);

can also be due to **ischemia/infarction** (typically seen in **DM**) which is typically pupil-sparing & painless, although can present with pain over eyebrow

- **Cranial Nerve VI palsy:** Horizontal diplopia; most common CN palsy (*JNNP* 2004;75:iv24)
  *Findings:* Most severe w/ lateral gaze toward affected side
  *Etiology:* Idiopathic, ischemic microvascular disease (typically in poorly controlled **DM**), traumatic, ↑ ICP (6th nerve is most susceptible 2/2 long intracranial course)
- **Intranuclear ophthalmoplegia:** Horizontal diplopia, caused by lesions affecting MLF, which connects CNIII & VI brainstem nuclei
  *Findings:* Impaired medial gaze w/ nystagmus of contralateral eye; unlike CNIII palsy convergence remains intact
  *Etiology:* Most frequently demyelinating dx (**MS**); in older pts, suspect brainstem infarct
- **Cranial nerve IV palsy:** Vertical diplopia, relatively rare as isolated finding
  *Findings:* Most severe when pt looks down & toward unaffected side; worsened by head tilt toward affected side (Bielchowsky sign)
  *Etiology:* Traumatic (majority of cases—can occur even w/ very mild trauma), postsurgical, idiopathic, ischemic (*Neurology* 1993;43:2439; *Neurology* 2009;72:e93)
- **Skew deviation:** Vertical diplopia that does not fit the pattern of a CNIV palsy; diplopia often equal in all directions of gaze; 2/2 lesions above CN nucleus (brainstem, vestibular system, cerebellum) (*Continuum* 2009;15:150)
- **Other:** Cavernous sinus syndrome (⊕ proptosis, eye pain), superior orbital fissure syndrome (⊕ eye pain, ptosis), orbital apex syndrome (visual loss + palsy), **MG** (diplopia common initial presentation, sx usually ↑ w/ fatigue & assoc w/ ptosis), **Guillain-Barré syndrome** (Miller Fisher variant: Diplopia, ataxia, areflexia), hyperthyroid (2/2 inflammation of EOM), Wernicke encephalopathy (⊕ nystagmus, gait disturbance)

## Management

- Isolated **monocular** diplopia → **Ophthalmology w/in 24–48 h**

- Isolated **binocular** diplopia → **Neurology/Neuro-ophthalmology w/in 24–28 h**
- **Binocular diplopias with red flags** (above) → **ED for Neurology eval/imaging**

# DIZZINESS AND VERTIGO

## Background (*Continuum* 2012;18:1060; *Principles of Neurology* 2009:288)

- **Definition:** Vertigo is the inappropriate sensation of self or environment moving
- The term *dizziness* can be used to describe
  (1) true vertigo
  (2) near-syncope (2/2 cerebral hypoperfusion)
  (3) disequilibrium (sense of imbalance, can accompany vertigo or be distinct)
  (4) "lightheadedness" often assoc w/ anxiety disorders
- **Physiology:** Angular acceleration detected by fluid movement in the 3 semicircular canals (1 in each axis); linear acceleration detected by movement of otoliths in adjacent utricle/saccule; these impulses → vestibular nuclei in pons/upper medulla which are interconnected w/ the cerebellum, cerebral cortex, & CNs involved in eye movements (III, IV, VI) via the MLF pathway
- **Etiology:** Can be due to peripheral (inner ear, most common) or central (brainstem, cerebellum) lesions
- **Epidemiology:** Vertigo lifetime prevalence 20–30%, accounts for 1.7% of US ambulatory visits (*Otolaryngol Clin N Am* 2012;45:925)
- Most processes benign but some central lesions require emergent tx, so important to assess for any sx suggestive of brainstem & cerebellar pathology

## Evaluation (*AFP* 2005;71:1115)

- **General approach:** First, establish pt is experiencing vertigo & not other cause of dizziness; next, determine by hx/PE if central or peripheral vertigo
- **History:**

*Establish vertigo as cause of sx:* Ask pt to describe dizziness; if they can't elaborate further, ask "did you feel like the room was spinning, or did you feel like you were going to pass out?" (if c/w presyncope, see "*Syncope*")
*Onset:* Sudden onset suggests central cause or Ménière
*Duration:* Brief episodes (<1 min) suggest BPPV
*Aggravating factors:* Precipitated by changing head position (BPPV), motion (peripheral process)
*Assoc sx:* Central process: **Diplopia, other neuro sx, gait instability, N/V**; Peripheral process: HA, prominent N/V, assoc tinnitus; Systemic (not vestibular) process: CP, palpitations
*Other:* Hx trauma (carotid dissection), stroke risk factors, **medication list**

- **Exam:** VS (assess for orthostasis if ? of presyncope), otoscopic exam
  CN*s;* complete exam, looking for nystagmus, diplopia, Horner
  *Cerebellar exam:* Assess for dysmetria, ataxia, wide-based gait (CNS), Romberg
  *Hearing:* Assess for sensorineural hearing loss w/ Weber & Rinne tests (see "*Hearing Loss*")
- **Provocative maneuvers:** Caution in pts w/ severe neck or vascular disease
  **Dix–Hallpike:** Tip pt backward w/ head overhanging edge of table & tilted to side (45°); attempt on both sides; ⊕ test = nystagmus & vertigo, often after 2–5 s delay, w/ *affected* ear down → BPPV; however ⊖ test doesn't definitively r/o BPPV
  **Head-impulse test:** Ask pt to focus on fixed object straight ahead, examiner turns pt's head abruptly to each side (~30°): ⊕ test = when head turned toward affected side, eyes make a corrective saccade to redirect gaze to desired target → peripheral lesion
  **Nystagmus:** Assess for nystagmus in all directions; peripheral lesions classically have horizontal nystagmus worst when looking toward affected side (eccentric gaze)
  **Head Impulse-Nystagmus-Test of Skew (HINTS):** 3-step exam; if all 3 findings suggest central cause → Se/Sp 100%/96% for stroke (*Stroke* 2009;40:3504)

**Features of Central versus Peripheral Vertigo**

| | Peripheral | Central |
|---|---|---|
| **Head-impulse test** | ⊕ Saccades | Absent |
| **Nystagmus**<br>*Direction w/ head in fixed position* | Often horizontal, but can be mixed horizontal/rotational or vertical/rotational | Pure horizontal, pure vertical, or pure torsional |
| *Direction variability* | **Unidirectional—never Δs direction** | **Δ direction w/ gaze** |
| *Effect of visual fixation* | Inhibits | No effect |
| *Reversal of head position* | Can Δ direction of nystagmus | No effect |
| **Skew** | Absent | Present |
| **Other** | Pronounced nausea<br>Deafness/tinnitus | Postural instability/falls<br>Other neuro signs |

- **Diagnostics:** If suspect central etiology, ED eval for further w/u; no imaging for BPPV
- **Red flags:** Neuro deficits, severe HA/nausea, ⊕ HINTS test, central nystagmus or any concern for mass/structural lesion

## Differential Diagnosis (*NEJM* 1998;339:680; *Otolaryngol Clin N Am* 2012;45:925)

- **Peripheral causes:** Constitute >2/3 of cases
- **Benign paroxysmal positional vertigo:** Common, ♀ > ♂, ↑ w/ age, prevalence ~2%
  *Etiology:* Dislodged otoliths in semicircular canals (90% posterior canal, tx w/ Epley, below)
  *S/sx:* Recurrent, transient episodes last **<1 min**, can be triggered by specific head position Δs (lying on 1 side, turning over), ⊕ Dix–Hallpike) (*Semin Neuro* 2009;29:500)
  *Tx:* Repositioning maneuvers (Epley, Semont, Brandt–Daroff), see AAN video at: youtube.com/watch?v=hq-IQWSrAtM; caution: 36% of posted videos inaccurate (*Neurology* 2012;79:376)
  *Epley:* Start w/ Dix–Hallpike to affected side & maintain for 1–2 mins, turn head 90° to unaffected side, hold add'l 1–2 mins, roll body to unaffected side & turn head add'l 90° to face downward, hold 1–2 mins more, then slowly return to upright position (*Pract Neurol* 2008;8:211; *Semin Neuro* 2009;29:500)
- **Ménière disease:** Age 20–40, 10–50% b/l, prevalence <0.1%
  *Etiology:* 2/2 expansion of endolymphatic sacs in labrinyth; idiopathic or 2/2 trauma, infection
  *S/sx:* Recurrent vertigo + fluctuating deafness/tinnitus; sense of ear pressure; abrupt onset, attacks last **minutes–hours**

*Tx:* Supportive (PT), meclizine, scopolamine, promethazine, mild sedative, salt restriction; for severe/refractory disease → chemical labyrinthectomy vs. surgery (*Continuum* 2012;18;1087)

- **Acute Vestibular Neuronopathy** or "acute vestibular neuritis" (*Neurologic Clinics* 2012;30:61)
  *Etiology:* Presumed viral; can occur post-URI
  *S/sx:* Episodes can last days–weeks, typically worst in 1st day; subacute onset, episodes occur spontaneously but exacerbated w/ head movements, ⊕ head-impulse test
  *Tx:* Supportive (PT), no e/o improved sxs w/ corticosteroids, full recovery can take weeks (*Cochrane Database Syst Rev* 2011;5:CD008607; *Otol Neurotol* 2010; 31:183)
- **Central Causes:**
  **Posterior circulation TIA/stroke:** Assess for risk factors (age >60, HTN, HLD, DM, smoking, CHF, AF) & assoc sxs; neck pain/trauma → suspect **vertebral dissection:** 20% of stroke cases in young pts, incidence 1/100,000 → ED
  **Posterior fossa mass:** HA, gradual onset, other neuro sx (above) → ED
  **Meds/Toxins:** Barbiturates, benzos, EtOH, AEDs (incl gabapentin), hypnotics (*Am Fam Med* 2010;8:196) if no e/o brainstem lesion may consider close observation w/ removal of offending agent
  **Vestibular migraine:** ♀ > ♂, past hx migraine, nl exam, or may have central nystagmus → if suspect, refer to neurology

## When to Refer

- If red flags (above), pt high risk for stroke & cannot r/o central process → refer to ED for urgent CT or MRI
- Consider neuro referral if dx unclear or for difficult to control/persistent sx, including BPPV unresponsive to Epley; may also consider vestibular PT for BPPV & Meniere

# WEAKNESS

## Background

- **Neuromuscular weakness** is defined by lack of muscle strength; however, the term "weakness" is often used nonspecifically & can be used to describe fatigue, pain, joint dysfunction/injury, psychosomatic or "functional" weakness
- **Asthenia:** Weakness which is not loss of peak muscle power but rather fatigue, ↓ endurance, ↓ initiative, generalized state 2/2 an underlying systemic disease (e.g., chronic or acute illness, depression, anemia)
- Appropriate eval of muscle strength is important to determine if weakness present & help determine etiology; "weakness" may be presenting complaint for wide range of diseases (e.g., epidural abscess, UTI, OA); so precise hx/PE important

## Evaluation (*Continuum* 2011;17:1040; *AFP* 2005:71:1327)

- **General approach:** Obtain hx to narrow Ddx; determine if true motor weakness exists on exam, & if so, localize the lesion
- **History:**
  *Onset:* Acute (vascular), subacute (meds, rheumatologic, infectious), or chronic (metabolic)
  *Precipitants:* Stress (functional), trauma, fever/infection
  *Distribution* (localizes deficit): Focal or global? Symmetric? Proximal, distal?
  *PMHx:* CKD, HIV, cancer, recent critical illness, FHx
  *Meds/toxins:* Statins, fibrates, corticosteroids, colchicine, chloroquine, EtOH, cocaine
  *Assoc sx:* Incontinence/retention of stool or urine (spinal cord process), diplopia (myasthenia), slurred speech, sensory sxs, HAs (complex migraines, stroke/ICH)
- **Exam:** Investigate any other systemic sx as directed by hx; examine for muscle bulk & tone, assess symmetry; eval muscle strength, clonus, DTRs, sensory exam (✓ for level if concern for cord lesion)
- **Muscle strength assessment:** Verbally encourage pt to maintain resistance for fixed period of time ("push against my hand for 3 seconds, as hard as you can…1,2,3")

**Grading of Muscle Strength**

| | |
|---|---|
| 0 | No muscle contraction |
| 1 | Flicker/trace of muscle contration |
| 2 | Limb/joint movement but ⊖ antigravity strength |
| 3 | Able to maintain strength against gravity but unable to resist |
| 4 | Able to resist temporarily, but cannot sustain/power ↓ |
| 5 | Normal power against resistance |

- **If strength impaired, localize the lesion:** Upper vs. lower motor neuron
  *UMN* (cortex, corticospinal tracts to spinal cord): Often affects UE extensors/LE flexors → posture of UE flexion/LE extension (e.g. elbows bent/knees straight), ↑ tone, ↑ reflexes, present Babinski sign
  *LMN* (anterior horn cells, peripheral nerves, NMJ, muscle): Distribution varies based on lesion; ↓ or nl tone, ↓ DTRs, ± fasciculations/atrophy; to determine nerve root vs. peripheral nerve (see "*Peripheral Neuropathy*")
  Sensory sx can be present or absent in either LMN or UMN (nonspecific)
- Reliability of strength assessment (*JNNP* 2002;73:241): May be unable to accurately assess true strength in setting of joint pain, muscle pain, joint disease, asthenia, embellishment of sx, or poor effort; findings below suggestive but not specific
  *Give-way weakness:* Pt initially demonstrates full strength, but then gives out (asthenia)
  *Co-contraction:* When testing "weak" agonist muscle, contraction of antagonist muscle can be felt, e.g., feel *triceps* contract when ask pt to flex forearm (embellishment of sx)
  *Hoover's sign:* In supine pt, compare *voluntary* hip extension strength – "push down against my hand with your right heel" – with *involuntary* hip extension strength triggered by contralateral hip flexion – "lift your left leg off the table" – (embellishment, hip disease)
- If strength appears intact → complete full hx/PE looking for cause of asthenia
- **Red flags:** Acute onset, rapid progression, SOB (esp w/ sitting up) or resp involvement, bulbar sx (difficulty speaking, chewing, swallowing; urinary retention) → ED referral

- **Labs:** Consider Na, K, Phos, Mg, Ca, CK, TSH, $B1_2$, LDH, LFTs, neuropathy w/u (see *"Peripheral Neuropathy"*)
- **Imaging:** If concern for intracranial process; CT = faster → 1st study if concern for acute stroke/ICH; otherwise MRI preferred
- **Other:** EMG/NCS to localize peripheral nerve d/o, muscle bx to determine cause of myopathy

## Differential Diagnosis (*Semin Neurol* 2011;31:115)

**Selected Differential Diagnosis of Muscle Weakness**

| Diagnosis | Clinical Features |
|---|---|
| Stroke, ICH | Sudden onset UMN pattern weakness |
| Spinal cord lesion | Sensory level, crossed sensory sxs (e.g., absent ipsilateral light touch, absent pain & temp contralateral), incontinence, BLE (± UE) weakness |
| Motor neuron disease (ALS) | Concomitant UMN + LMN weakness |
| Myasthenia Gravis | Weakness fatiguable, worse as disease progresses, can be assoc w/ diplopia |
| Myositis (PMR, DM) | Proximal symmetric weakness, ± muscle pain, can be assoc w/ heliotropic rash in DM |
| Mononeuropathy (see *"Peripheral Neuropathy"*) | Sudden onset focal weakness (e.g., foot drop) w/ sensory loss |

## Treatment

- As per underlying d/o; if true weakness present & dx unclear or neuro cause established → neurology referral
- If red flags present (above) or other concern for acute intracranial process → ED

# HEADACHE

## Background (*J Clin Epidemiol* 1991;44:1147; NAMCS 2009, cdc.gov/nchs/ahcd)

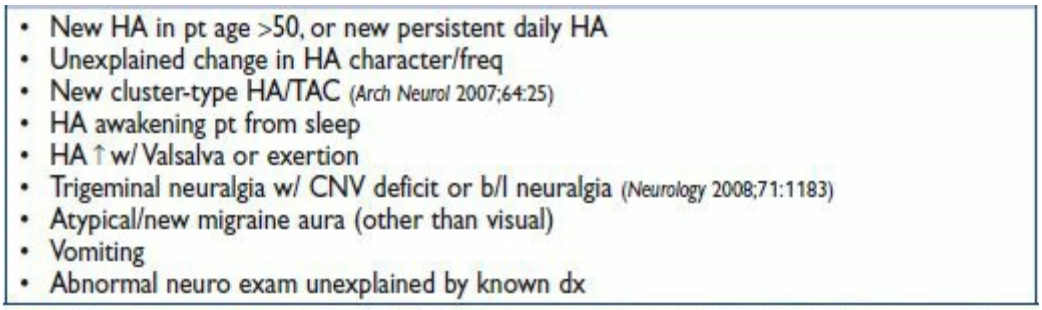
- 17% of US adults have had a severe headache in the past 3 mos; ♀ > ♂ by 2:1, more common in younger adults, people living in poverty (*CDC NCHS* 2012;10:256)
- Lifetime prevalence of HA as high as 90–100%, w/ 78% tension, 16% migraine

- Common complaint in primary care; accounts for >1% of all outpt visits in US
- **Classification: Primary** HA syndromes not due to another cause: E.g., tension, migraine, cluster; **Secondary** HA syndromes are due to systemic illness or structural neuro abnormalities; **1°** HA syndromes often chronic conditions, established in early adulthood; new HA "pattern" should raise suspicion for 2° cause

## Evaluation

- **General approach:** Attempt to determine HA etiology through hx; careful neuro exam can help r/o emergent/malignant causes
- **History**: First, determine if HA is new or old: "Have you ever had a headache like this before?" "How long have you been having these headaches?" → helps guide Ddx
  *Temporal qualities:* Speed of onset, duration, time to max intensity, freq
  *Location:* Unilateral (if so, always on same side?), retro-orbital
  *Triggers/alleviating factors:* Trauma, position change (worse w/ supine → ↑ ICP), sleep disruptions, stress, posture, neck pain
  *Assoc sx:* Phono- or photophobia, aura, N/V, vertigo, eye pain or visual changes, other neuro sx, fevers, myalgias
  *Medications:* Including OTC analgesics (rebound), opioids, nitrates, caffeine, tobacco, EtOH, prior HA therapies
  *Other*: PMHx (immunosuppression), FHx of HA
- **Exam:** VS (fever, HTN): Neuro exam w/ emphasis on CNs incl fundoscopic exam, visual fields, EOM; assess for meningismus
- **Imaging:** If suspicion for intracranial process & outpt w/u, MRI w/ gad preferred; if concern for emergent intracranial process → ED referral & likely CT (faster)

**Indications for Imaging**



(*BMJ* 2010;341:c4113; *JAMA* 2006;296:1274; AAN US Headache Consortium 2000 guidelines, aan.com)

- **Red flags:** *New focal neuro deficit*, incl ↓ visual acuity, diplopia, *"thunderclap" HA:* Explosive onset, "worst HA of life" (SAH), *Evidence of ↑ ICP:* Papilledema, HA ↑ when supine, ⊕ N/V, CNVI palsy (mass, venous sinus thrombosis), *meningismus* (SAH or meningitis), *altered mental status* (meningitis/encephalitis), *immunosuppressed w/ fever* (CNS infection)

## Differential Diagnosis

- **Tension Headaches:** Onset typically over hours, does not require change in daily activity
  *Definition:* ≥2 of following features: Bilateral, tightening quality, no change w/ movement, mild–mod severity & no N/V (anorexia possible), ≤1 of photophobia or phonophobia
  *Epidemiology:* Can also be seen in migraine pts
  *Triggers:* Sleep deprivation, dehydration, hunger; assoc w/ myofascial sensitivity of head
  *Counseling:* Identify stressors, comorbid contributors (e.g., depression)
  *Acute Tx:* NSAIDs, APAP, ASA, analgesics (but risk of med overuse HA); tx cervicalgia if present
  *Ppx:* TCAs (nortriptyline), biofeedback (*Continuum* 2012;18:823)
- **Trigeminal autonomic cephalgias** (*Continuum* 2012;18:883; *JNNP* 2002;72:ii19): Characterized by autonomic sxs (rhinorrhea, lacrimation, red/tearing eye, miosis/ptosis), typically unilateral, subtypes differentiated by time course
  **Cluster:** Unilateral orbital/temporal pain, restless, worse w/ EtOH & nitro, 15 mins–3 h attacks, typically clustered in bouts of ~7 d unless chronic variant; *Tx:* Oxygen, nasal/SC sumatriptan, nasal lidocaine; CCB (verapamil) for ppx
  **Hemicrania continua:** ♀ > ♂, stabbing pain, continuous ≥3 mos; *Tx:*

Indomethacin

**Paroxysmal hemicrania:** ♀ > ♂, 2–45 min attacks; *Tx:* Indomethacin

**Short-lasting Unilateral Neuralgiform headache with Conjunctival injection & Tearing (SUNCT):** Incidence ♂ > ♀; *Definition:* Stabbing orbital pain, 15 s–5 mins, triggers precipitated by cutaneous stimulation; *Tx:* Few proven txs; consider lamotrigine

- **Trigeminal neuralgia:** Onset >40 y, sharp unilateral electric shock sensation lasting s, precipitated by touching face or chewing (see "*Jaw & Facial Pain*")
- **Secondary headache:** Can present similar to migraine or as a change in freq/quality/intensity of pt's typical HA syndrome

  **GCA**: Age >50, ♀ > ♂; fever/constitutional sx, jaw claudication, vision loss (50%) assoc w/ PMR; requires prompt tx if suspected (see "*Vision Complaints*")

  **Pseudotumor cerebri** (Idiopathic Intracranial HTN): ♀ > ♂, age 20–40s, assoc w/ obesity, **meds** (Vit A derivates, tetracycline, OCPs); *S/sx:* Worse w/ supine position, blurred vision/grey spots, pulsatile tinnitus, e/o ↑ ICP (see Red Flags, above); → ED if new case suspected; *Dx:* MRI w/ gad & MRV (to r/o mass/VST), bland LP w/ opening pressure >25 cm; *Tx:* Wt loss, acetazolamide, CSF diversion (large-volume LPs, shunt) → refer to Neurology/Neuro-ophthalmology

  **Other:** ↑ ICP (CNS mass/edema, hydrocephalus), ↓ ICP (CSF leak, overshunting), GCA, vascular causes (stroke, aneurysm/AVM, venous sinus thrombosis), post-trauma (concussion, ICH), meningeal irritation (meningitis, SAH), posterior reversible encephalopathy syndrome or PRES, TMJ syndrome, glaucoma
- **Medication overuse** (rebound headache): A subtype of secondary headaches which occurs in pts w/ a primary headache syndrome

  *Definition: O*ccurs in pts who use ergots, opiates, triptans, or combined analgesics >10 days/month or plain analgesics >15 days/month

  *S/sx:* HA worse after starting meds & improves after cessation of meds

  *Tx:* Multiple approaches reasonable; consider short course corticosteroids, taper w/ ppx med on day 1, ppx med alone, most important is withdrawal of offending med; mod-severe cases may

require neurology input (*Continuum Neurol* 2012;18:807)

## Chronic Headache Management

- **Headache diary:** To identify triggers, pattern, freq, assoc sx, & response to tx
- **Medication: Ppx** if >1 debilitating HA/mo + PRN abortive med
- **Counseling:** Avoid triggers when possible, caution: re: use of abortive tx >2–3×/wk → med overuse HA
- **Neurology referral:** Complex migraine w/ known neuro deficits; HA w/ autonomic features (e.g., TACs) or chronic HA (>15 HA/mo)
- **Patient information:** National HA foundation at www.headaches.org, under "My Headache"

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# MIGRAINE

## Background (*Lancet* 2004;363:381; *JAMA* 2006;296:1274; *Med Clin N Am* 2009;93:245)

- **Epidemiology:** ~15% of women, 6% of men; prevalence peaks ~30–39 y; most pts have 1–4 migraines/mo; vast majority (>90%) have onset prior to age 40; ⊕ FHx present in 80% of pts; HAs often interfere w/ work & QoL
- **Pathophysiology:** Still uncertain; thought that peptides released from nerves innervating meningeal blood vessels → activation of perivascular trigeminal nerves → dilatation of meningeal arteries, perivascular inflammation; trigeminal nerves terminate in brainstem → thalamus → higher cortical centers (hyperalgesia, allodynia) (*NEJM* 2010;363:63)

## Classification

- **Migraine without aura:** 70–80% of cases; recurrent HA lasting 4–72 h with N/V **or** photo-/phonophobia & ≥2 of the following: Unilateral, throbbing, mod–severe intensity, aggravated by routine activity; may progress to include allodynia
- **Chronic migraine:** Migraine present for ≥15 days per month
- **Migraine with aura:** 18% of cases; lasts <1 h, often at beginning of migraine; visual aura most common; scotomas w/ colored edges,

"zigzag lines"); **carries ≠ risk of stroke**—2× ↑ RR for pts <45 y, 9× ↑ RR if smoker, 7× ↑ RR w/ OCPs: *Estrogen-containing OCPs contraindicated*

- **Complex migraine:** P/w neuro deficits (weakness, numbness, aphasia); must r/o stroke prior to dx; multiple subtypes organized by sx (basilar, vestibular, retinal)

## Evaluation

- **History:** Features which ↑ suspicion of migraine dx include hx motion sickness, ice cream HA or "brain freeze," jet-lag, hangover HA, esp after red wine
- **Triggers:** 85% of pts can identify triggers (may require help of HA diary); most of these pts have multiple triggers (mean ~3), individual HA may be multifactorial

**Migraine Triggers (*Med Clin N Am* 2009;93:245)**

| Classification | Examples |
|---|---|
| Environmental | Change in weather (50%), heat, ↑ humidity, ↑ altitude |
| Emotional | Stress (80%), letdown after stress, vacation |
| Schedule disruptions | Lack of sleep, oversleeping, fatigue, missed meal |
| Sensory | Bright lights, glare, strong perfumes, cigarette smoke |
| Alcohol | (50%) can be general or limited to 1 type (red wine most common) |
| Food | (45%) chocolate, cheese, citrus, fried foods, cured meats/fish |
| Hormonal | Menstrual (50% of women, only trigger in 14% of women) |
| Other | Minor head trauma, NTG, exertion, dehydration |

## Abortive Treatment (*NEJM* 2010;363:63)

- **Counseling:** *Environment:* Advise quiet, dark room if episode occurs, avoid motion, stay hydrated; *Meds:* Take abortive Rx ASAP for max efficacy; avoid using >2×/wk as can → overuse HA; plan to develop "toolbox" of different medications for different presentations (mild/early vs. severe vs. refractory) w/ pt
- **Headache diary:** To determine triggers & response to tx (sample at americanheadachesociety.org); can be reviewed at f/u visit
- **Triptans:** 5HT agonists
  *Mechanism:* Thought to inhibit release of vasoactive peptides & ↓ signaling to thalamus

*Efficacy:* 6 mg SC sumatriptan most effective w/in class; for oral triptans, no clear benefit between agents, although in meta-analysis, 100 mg sumatriptan ≥ frovatriptan > naratriptan (*Cephalalgia* 2002;22:633); no clear evidence that triptans are more effective than other abortive tx & generally more $$$; if 1 triptan ineffective in 2 attacks, switch to another triptan; may consider combination tx w/ NSAID

*Administration:* ↑↑ Efficacy if given at HA onset, typically ineffective if pt has progressed to allodynia; onset 20–60 mins

*Formulation:* PO most common, but nasal sprays, SC, PR, & disintegrating tabs also available

*Sample Rx:* Sumatriptan 50–100 mg at 1st onset of HA; may repeat × 1 after 2 h (max 200 mg/24 h) or rizatriptan 5–10 mg; may repeat × 1 after 2 h (max 30 mg/24 h)

*Side effects:* Paresthesias, flushing, *mild, brief* neck or chest pressure/tightness (not thought to be 2/2 coronary ischemia); can → overuse HA

*Drug interactions:* Do not use w/in 24 h of ergot derivatives; ↑ risk of serotonin syndrome w/ SSRI or SNRI use

*Contraindications:* Complex migraine, known CAD/stroke; severe hepatic or renal disease, uncontrolled HTN, hx coronary vasospasm, avoid w/ elderly pts or ↑ CAD risk (✓ baseline ECG, consider further eval) (*Headache* 2000;40:599; *Headache* 2004;44 Suppl1:S31)

**Selected Abortive Medications**

| Medication | Considerations | Adverse Effects |
|---|---|---|
| **NSAIDs** | Often 1st-line for mild–mod HA, OTC | PUD, AKI, ↑ risk of med overuse HA |
| **ASA/APAP/Caffeine** | 1st-line for mild–mod HA, OTC | Individual s/e; ↑ risk of overuse HA |
| **Compazine** | Antiemetic properties | Antidopaminergic (i.e., restlessness, akathisia, dystonia), ↑ QTc |
| **Metoclopramide** | Antiemetic properties | Antidopaminergic (see above) |
| **Magnesium** | Adjunct for photophobia | Constipation |

- Opioids not recommended; ↑ risk of rebound & abuse potential; (*Headache* 2012;S1:3)

## Prevention

- **Indications:** Should be considered for pts w/ >1–2 episodes or 3 d of sx/mos
- **Oral contraceptive pills:** Consider continuous monophasic low-dose OCPs in pts w/ menstrual trigger; however, **contraindicated** in pts w/ aura & can worsen sx or cause pt to develop aura → d/c Rx (*BMJ* 2009;339:b3914)
- **Herbal/alternative therapies:** Some data for butterbur (s/e: drowsiness, allergic reaction, caution if liver disease) & for coenzyme Q10; riboflavin w/ mixed results & fever; few appear unlikely to be better than placebo (*Headache* 2009;49:966)
- **Other:** For refractory or chronic migraine, local nerve block w/ botulinum toxin can be performed by neurologist (*Cephalalgia* 2010;30(7):804–814)

**Migraine: Preventive Medications**

| Medication | Comorbid Indications | Adverse Effects |
|---|---|---|
| Propranolol | HTN, varices/GIB ppx | Depression, fatigue, ↓ BP/HR, ED |
| Topiramate | Obesity, seizure d/o | Paresthesias, nausea, wt loss, memory/ cognitive Δ, renal stones, teratogenic |
| Valproic Acid (VPA) | Seizure d/o, Mood d/o | Wt gain, ↑ LFTs, ↓ PLTs, tremor, ↑ NH3, med interactions, teratogenic |
| TCAs | Depression (↓ dose for migraine) | Arrhythmia, dry mouth, constipation, sedation, ↓ s/e in nortriptyline vs. amitriptyline |
| Verapamil | HTN, AF | ↓ BP/HR, dizziness, facial flushing |
| Gabapentin | Peripheral neuropathy | Dizziness, sedation, wt gain, edema, ↓ mood |

(Adapted from *Neurology* 2012;78:1337)

# PERIPHERAL NEUROPATHY

## Background (*Continuum* 2012;18:13; *Neurology* 1993;43:817)

- **Definition:** Diseases affecting cell body or processes of the lower motor neuron
- **Epidemiology:** Neuropathy affects ~2–8% of US adults & 21% of DM pts presenting to PCP office
- **Pathophysiology:** Peripheral nervous system contains somatic

(sensory & motor) & autonomic nerves; peripheral neuropathy may affect single or multiple components

- **Classification:** *Mononeuropathy:* Damage to individual nerve (e.g., median nerve in carpal tunnel syndrome); *mononeuropathy multiplex:* Individual nerves affected in series (vasculitis); *polyneuropathy:* Multiple nerves, typically symmetric (EtOH-related neuropathy)
- **Etiology:** Damage to nerves may be inflammatory, demyelinating, axonal, vasculitic, traumatic, toxic, or infectious—careful hx & exam determining pattern of lesions can help to narrow differential

## Evaluation (*Continuum* 2012;18:139)

- When presented w/ pt who reports sx which may be attributed to neuropathy, attempt to characterize what types of nerves are affected & the distribution; also consider *radiculopathy:* disease at the level of a spinal cord nerve root (see table below)
- **History:** First, characterize pattern of neuropathy (sx, onset, distribution); second, look for etiological clues (PMHx, soc hx, meds, diet, occ hx)
- **Characterize neuropathic pattern:**
  **Sensory sx:** Paresthesias, allodynia (typically nonpainful stimuli → painful), hyperalgesia ( ↑ sensitivity to painful stimuli), difficulty distinguishing hot vs. cold, ↓ proprioception (often more noticeable in dark or when no visual clues)
  *Predominantly sensory etiologies:* DM, $B1_2$ deficiency, HIV, amyloid, leprosy, Sjögren's, sarcoid, uremia, paraneoplastic
  **Motor sx:** Weakness (see *"Weakness"*), fasciculations, weakness, atrophy. *Predominantly motor etiologies:* GBS, CIDP, porphyria, lead, botulism
  **Autonomic sx:** Orthostasis, gastroparesis, constipation, bladder or ED, hypoglycemic unawareness in DM
  **Onset:** Acute (GBS, vasculitis, infection) or subacute, chronic (toxin, Vit deficiency, neoplastic, metabolic, CIDP)
  **Distribution:** Peripheral or proximal? Symmetric or asymmetric?
- **Etiological clues:**
  **Assoc sx:** Fever, constitutional sx, thyroid sx, rash, HA, N/V, dry eyes/mouth, recent illness

**PMHx:** DM, HIV, amyloid, CKD/ESRD, cancer, sarcoid, autoimmune disease, celiac, gastric bypass (malabsorption), HCV (seen in cryoglobulinemia), thyroid disease, amyloid; consider leprosy, Chagas in appropriate populations (*Continuum* 2012;18:126)
**Social hx:** EtOH use, diet (vegan [$B1_2$ def]), carnivorous fish (ciguatera toxin), solvent use/abuse ("huffing")
**Meds/toxins:** Generally a dose- or time-dependent process (see below)
**Other:** Occupational hx (lead, solvent, grout exposure), **FHx**

**Medications/Toxins/Vitamin (*Continuum* 2012;18:139)**

| | |
|---|---|
| **Anti-infective** | INH, MNZ, nitrofurantoin, chloroquine, FQs, ethambutol |
| **Immunosuppressants** | Etanercept, infliximab, leflunomide, tacrolimus |
| **Other** | Colchicine, disulfiram, thalidomide, dapsone, phenytoin |
| **Toxins** | Arsenic, gold, lead |
| **HAART** | Didanosine, stavudine, zalcitabine |
| **Cardiovascular** | Amiodarone, hydralazine, ?statins |
| **Oncologic** | Cisplatin, docetaxel, paclitaxel, suramin, vincristine (vinblastine) |
| **Vitamins** | Vit $B_6$ (deficiency or excess), Vit $B_{12}$ deficiency, Vit E deficiency (malabsorption syndromes) |

- **Exam:** VS (orthostatics), e/o systemic disease (cachexia, atrophy, orthostatics, hyperpigmentation, skin/nail/hair changes, organomegaly, ulcers, nerve hypertrophy)
- Full neuro exam, looking for e/o central process (CN involvement, ataxia, hyperreflexia); **motor exam** (see "*Weakness*") & **sensory exam**: Pinprick (dysesthesia or hypoesthesia), proprioception (large fiber sensory involvement), Tinel—lightly percuss over the nerve → radiating pins/needles (dysesthesia) which mimic complaint = entrapment; **gait** for foot drop
- **Diagnostics:** CBC, Cr, HbA1c/fasting glucose, $B1_2$ (see "*Folate and Vitamin $B_{12}$ Deficiency*"), TSH, SPEP + immunofixation; consider HIV, RPR, ANA, ESR, HBV, HCV, anti-TTG/gliadin, heavy metal screen, Lyme, rheumatologic testing depending on clinical picture
- **Electromyelography/Nerve conduction studies:** Usually w/ neurology guidance, not needed for all pts; used to assess disease severity, assist in localization, or distinguish demyelination from

axonal neuropathy

- **Other:** Skin bx/autonomic testing if suspect small fiber neuropathy; MRI if ? of radiculopathy or plexopathy; LP if ? of GBS/CIDP, expect cytoalbuminologic dissociation
- **Red flags:** Rapidly progressive, ascending, areflexia, following flu-like/diarrheal illness or immunization (GBS), back pain, progressive, bowel/bladder Δs, saddle anesthesia, ↓ rectal tone (cord compression), painful, multiple noncontiguous nerve involvement (vasculitis)

## Differential Diagnosis

- **Distal symmetric polyneuropathy:** Most common type of peripheral neuropathy; due to axonal damage; *Etiologies:* DM, HIV, EtOH, medication-induced, idiopathic, ESRD, GBS; *Features:* "Stocking-glove distribution" due to axonal length-dependent; hand sx begin once leg sx have "reached" knees; slowly progressive, painless or painful; *Eval:* Labs as above, consider NCS
- **Length-independent polyneuropathy:** Suggests demyelinating disease; *Features:* Early proximal sx or ↓ reflexes; multiple nerves affected, can be symmetric or asymmetric; *Etiologies:* CIDP, Lyme, HIV, sarcoid, amyloid, paraneoplastic, genetic d/o
- **Autonomic neuropathy:** Diabetes, amyloid, GBS, Sjögren, Fabry disease; *Eval:* Consider autonomic function testing, gastric emptying study
- **Small fiber sensory neuropathy:** Length-dependent distribution of neuropathic pain despite otherwise normal neuro exam; due to DM, autoimmune, paraneoplastic, celiac; Skin biopsy may aid in diagnosis
- **Mononeuritis multiplex:** Multiple nerves affected, often in stepwise, asymmetric fashion; *Etiology:* Vasculitis, Sjögren, sarcoid, DM, Lyme, hereditary
- **Mononeuropathy:** Focal lesion of a single nerve; compression/entrapment most common; can also be due to trauma, Lyme, or DM; presents w/ numbness & paresthesias; consider radiculopathy as well (see table below); *Eval:* EMG/NCS to localize/quantify injury; consider w/u for DM, thyroid, arthropathies; *Tx:* Reduce external compression as able; if severe, refractory,

involves motor function, consider surgical referral

### Radiculopathy & Focal Nerve Injuries

| Lesion | Exam Deficits | Notes |
|---|---|---|
| C6 root | *Motor:* Elbow flex, supination, wrist ext<br>*Sensory:* Shoulder, lateral arm, forearm, hand, tips of digits 1–3<br>*DTR:* biceps ± brachioradialis | ⊕ *Spurling sign:* Sx reproduced by hyperextending or rotating neck, relieved by putting hand on head |
| C7 root | *Motor:* Elbow ext, pronation, wrist/finger flex<br>*Sensory:* Posterior arm, forearm, digits 2–3<br>*DTR:* Triceps | ⊕ Spurling sign<br>Most common cervical radiculopathy |
| Radial (wrist) | *Motor:* No weakness<br>*Sensory:* Dorsolateral hand, snuffbox<br>*DTR:* None | Heavy watch/handcuffs on superficial radial nerve |
| Radial (axilla) | *Motor:* Wrist drop (wrist dorsiflex, finger ext, thumb abduct, triceps, brachioradialis, supinator)<br>*Sensory:* As above + posterior forearm<br>*DTR:* Biceps, brachioradialis | Heavy watch/handcuffs on superficial radial nerve<br>"Saturday Night Palsy" (compression from sleeping on arm, crutches, humeral fx [spares triceps]) |
| Ulnar | *Motor:* Often subtle, can have impaired digit adduction<br>*Sensory:* Palmar aspect of digits 4 + 5, palm + medial forearm<br>*DTR:* None | Often compression at elbow "cubital tunnel syndrome"; sx ↑ w/ elbow flex, *Froment sign:* Thumb flexion when trying to adduct thumb, ulnar claw hand |
| L4 root | *Motor:* Knee ext, ankle dorsiflex, hip adduct<br>*Sensory:* Medial foot & calf (medial malleolus)<br>*DTR:* Patella | ⊕ Straight leg raise, Femoral stretch test (radicular pain *below* knee on combined hip ext/knee flex) |
| L5 root | *Motor:* Hip abduct, ankle dorsiflex, 1st toe ext, **foot inversion + eversion**<br>*Sensory:* 1st dorsal web space of foot, dorsal foot<br>*DTR:* ± Achilles | ⊕ Straight leg raise, Trendelenburg gait, foot slap (inability to maintain dorsiflex, causing forefoot to "slap" on ground) |
| S1 root | *Motor:* Ankle plantarflex, knee flex<br>*Sensory:* Lateral heel, posterolateral calf<br>*DTR:* Achilles | ⊕ Straight leg raise, heel slap gait (inability to slowly lower heel to ground, causing the heel to "slap") |
| Femoral | *Motor:* Hip flex, knee ext; *spares hip adduct*<br>*Sensory:* Anterior thigh, medial calf<br>*DTR:* Patella | Consider RP bleed, recent lithotomy position, DM lumbosacral plexopathy |
| Peroneal | *Motor:* Foot eversion, dorsiflex; *spares foot invertors*<br>*Sensory:* Superficial: Dorsum of foot<br>Deep: 1st dorsal web space<br>*DTR:* None | Most often due to compression at fibular head, (rapid wt loss w/ crossing legs, casts, stockings) |
| Lateral Fem Cutan. | *Motor:* None<br>*Sensory:* Lateral thigh<br>*DTR:* None | "Meralgia paresthetica," due to compression at inguinal ligament (belts, wt gain, tight jeans) |

(*NEJM* 2005;353:392; *AFP* 2008;78:835; *Med Clin N Am* 2009;93:285)

## Diabetic Neuropathy (*Continuum* 2012;18:60)

- Half of diabetic pts will develop neuropathic complications; distal symmetric polyneuropathy most common; counsel pts re: ulcer

avoidance (7× ↑ risk if neuropathy)
- *Autonomic neuropathy:* ↑ Risk hypoglycemic unawareness & cardiac arrhythmia
- *Treatment-related neuropathy* ("insulin neuritis"): Acute, painful/sensory, occurs when poorly controlled → tight control, typically in DM1; assoc w/ autonomic sxs or severe wt loss; resolves over several mos; can recur
- *Lumbosacral radiculoplexus neuropathy* ("diabetic amyotrophy"): Abrupt onset of severe unilateral thigh pain followed by atrophy & weakness; usually distal > proximal; assoc w/ wt loss; improves over mos, may have significant residual deficit; DM2 > DM1; consider EMG/NCS, which show radiculopathy/plexopathy
- *Focal neuropathies:* Assoc w/ CN palsies (see "*Diplopia*"), thoracic radiculopathies

## Treatment (*Continuum* 2012;18:161)

- **When to refer:** Neurology referral for any mod–severe disease unless typical slow distal symmetric polyneuropathy; if red flags present (above) pts should be referred to ED
- General approach: Avoid neurotoxic agents; treat underlying cause as possible
- **Pain:** Multiple agents available (below); opioids: Limited role, (see "*Chronic Pain*")

**Neuropathic Pain Treatment**

| Medication Class | Example Rx (starting + max dose) | Notes |
|---|---|---|
| **TCAs** | Amitriptyline 10–25 mg QHS (max 150 mg QD) | *Evidence:* Level A for DM, postherpetic neuralgias<br>*S/e:* Dry mouth, constipation, orthostasis, urinary retention; caution if CAD, glaucoma, sz, LUTS |
| **SNRI** | Duloxetine 30 mg QD (max 60 mg BID) | *Evidence:* Level A for DM<br>*S/e:* Nausea, ↑ BP; caution if liver dz, HTN |
| **Ca channel α-2-δ ligands** | Gabapentin 300 mg QD; max 1200 mg TID<br>Pregabalin 25–75 mg QD; max 300 mg BID | *Evidence:* Level A for DM, postherpetic neuralgia, cancer pain (gabapentin);<br>*S/e:* Sedation, dizziness, edema, wt gain<br>Renally cleared, caution if ↓ GFR |
| **Lidocaine Patch** | 1–3 patches; Apply 12 h on, 12 h off | *Evidence:* Level A for postherpetic neuralgia<br>*S/e:* Local itch, rash; systemic abs possible (do *not* apply heating pad over patch) |
| **Capsaicin patch/crm** | Crm TID–QID to affected area (results after 2 wks)<br>*Alt:* Topical anesthetic, then 1–4 patches × 60 mins q3mos | *Evidence:* Level A for HIV, postherpetic neuralgia<br>S/e: Pain, erythema (↓ w/ ongoing use) |
| **Tramadol** | 50 mg QD; max 400 mg QD (ER) | *Evidence:* Level A: DM, phantom pain<br>S/e: N/V, constipation, dizziness, sedation; avoid if substance use d/o, suicide risk |

# PARKINSON'S DISEASE

## Background

- **Definition:** Parkinsonism is a movement disorder syndrome characterized by "TRAP": Tremor, Rigidity, A-/bradykinesia, & Postural instability
- **Parkinson's disease:** Progressive neurodegenerative d/o; most common cause of parkinsonism; 2nd most common neurodegenerative disease
- **Epidemiology:** Affects ~1% of US adults >60 y (*Neurology* 1995;45:2143); incidence ↑ w/ age; affects ♂ > ♀ (*NEJM* 2005;353:1021); significant cause of morbidity & disability in the elderly
- **Etiology:** Idiopathic, thought to be 2/2 ↓ DA in substantia nigra (*Lancet* 2009;373:2055)
- **Natural history:** Progressive d/o; average pt → disability (not independent w/ ADLs) ~7 y after dx, but significant variability;

often heralded by increasingly severe gait disability (*Mov Disord* 2008;23:790); presence of hallucinations strong predictor of SNF placement (*J Am Geriatr Soc* 2000;48:938); *poor prognosis:* Rigidity/hypokinesia (rather than tremor) as presenting sxs predict more rapid disease progression (*Mov Disord* 1996;11:236)

## Evaluation (*JAMA* 2003;289:347; *NEJM* 2005;353:1021)

- **Parkinson's disease is a clinical diagnosis,** if suspected, eval w/ careful hx & neuro exam (including gait assessment); if diagnosis known, continue to monitor for complications below
- **History:** Determine onset of sx; PMHx; HIV, stroke risk factors (vascular parkinsonism); medication list (drug-induced parkinsonism: Metoclopramide, compazine, antipsychotics, CCBs, possibly SSRIs)

**Typical Presentation**

| | |
|---|---|
| **Tremor** | Initial presentation in ~70% of pts; typically occurs at rest; asymmetric, slow (4–6/s), "pill-rolling" of 1 hand |
| **Rigidity** | ↑ tone, cogwheeling, worse when pt performing repetitive movements w/contralateral limb |
| **Bradykinesia, Akinesia** | Initial c/o can be "weak" or "clumsy" limb; major cause of disability in PD: Observe during interview & assess w/ toe or finger tapping (pt will have ↓ amplitude & irregular cadence) |
| **Postural instability or gait disorder** | Pt can c/o impaired balance, ↑ falls; ↓ arm swing on exam; shuffling gait, stooped posture at later stages |
| **Other sx** | Depression, sleep disturbances (daytime hypersomnolence, restless leg syndrome), hypophonia, micrographia, muscle aches, orthostasis, dysphagia, cognitive changes (↓ executive function), ↓ olfaction |

- **Diagnostics:** Not routinely required, can consider MRI if atypical presentation
- **Levodopa challenge:** Improvement w/ carbidopa/levodopa → 70.9% sens, 81.4% spec for predicting eventual dx of PD (*Mov Disord* 2002;17:795)
- **Features which suggest an alternative diagnosis at onset: ≠ Falls Ø tremor,** symmetric onset, rapid progression, poor response to dopaminergic therapy

## Differential Diagnosis

- **Other parkinsonian syndromes** (*Neurol Clin* 2001;19:607)
  *Progressive Supranuclear Palsy:* Early falls, rigidity (neck > extremities), vertical gaze palsies, eyelid apraxia (difficulty opening eyes), tremor less prominent c/w PD
  *Multiple System Atrophy:* Prominent autonomic sxs (orthostatic HoTN, ↓ sweating, urinary retention, dry mouth) & cerebellar signs
  *Dementia with Lewy Bodies:* Dementia w/ AMS, visual hallucinations (*Neurology* 2005;65:1863)
  *Corticobasal Degeneration:* Prominent unilat sxs, alien hand syndrome in 60% (feeling of no control over 1 hand's mvts)
- **Secondary causes of parkinsonism** (*Lancet* 2009;373:2055)
  *Medications:* Relatively common; list of common agents noted above
  *Toxins:* CO, cyanide, manganese, MPTP (street opioid contaminant)
  *Vascular:* 2/2 small vessel strokes
  *Other:* Infection (encephalitis, HIV), metabolic (Wilson, hypoparathyroid), head trauma

## Treatment (*Neurology* 2006;66:983)

- **Referrals:** All pts w/ suspected parkinsonism should be referred to Neurology or a movement d/o specialist; consider PT, OT, & home safety assessment
- **Pharmacologic Rx:** Does not alter disease course; intended to ↓ sx & ↑ function; these are all typically prescribed by neurologist
  **Dopaminergic agents:** Typically prescribed by neurologist/provider experienced in PD
  Dopamine (levodopa/carbidopa) or DA agonists (ropinirole, pramipexole) typically 1st-line; tolerance & disease progression → ↑ doses over time
  *S/e:* GI sxs (N/V, abdom pain), dizziness, orthostatic HoTN, hallucinations, impulsive behavior, vivid dreams, insomnia, dystonia, dyskinesias
  **Other agents:** Catechol-*O*-methyltransferase inhibitors (entacapone), MAOI (selegiline, rasagiline), anticholinergics (frequent s/e), amantadine
- **On–off phenomenon:** (aka motor fluctuations): "On" effect immediately after taking med → excessive movements, dyskinesias; "off" effect ~4 h later, as dopaminergic effect wears off → freezing,

prominent rigidity
*Rx:* Adjunctive tx w/ rasagiline, entacapone, pramipexole, & ropinirole all shown to ↓ "off" time, at expense of ↑ "on" sxs (*Neurology* 2006;66:983)

- **Deep brain stimulation:** Surgical implantation of electrodes in subthalamic nucleus or globus pallidus; *Indications:* Pts w/ intractable motor fluctuations who are levodopa responsive & neuropsychiatrically intact w/o dementia; can → ↓↓ motor sxs
- **Management of comorbidities** (*Mov Disord* 2005;20:958; *Biol Psych* 2002;17:1031)
  *Depression:* 40–50% of PD pts; consider TCAs, paroxetine, venlafaxine, no SSRI if using MAOI (*Cochrane Database Syst Rev* 2003;3:CD003465)
  *Sleep disturbance:* May consider modafinil for daytime hypersomnolence
  *Psychotic sx:* Can be 2/2 PD or dopaminergic tx; consider antipsychotics only after r/o toxic/metabolic cause & ? trial of ↓ dopaminergic med dose; avoid typical antipsychotics (DA antagonists → ↑ motor sx); quetiapine or clozapine preferred
  *Dementia:* Consider anticholinesterases (rivastigmine, donepezil) (*NEJM* 2004;351:259)
  *Falls:* ↑ Risk if BZD use, prior falls, advanced disease, ⊕ Romberg (*J. Neurol* 2001;248:950) → early home safety eval (see "*Falls*")
  *GI tract dysmotility:* ↑ Risk constipation & aspiration 2/2 brainstem + enteric nerve dysfunction; consider stool softeners, low threshold for dysphagia eval → aspiration precautions
  *Orthostasis:* Common in late stage PD, can be worsened w/ levodopa; 1st, remove other offenders (βBs), encourage fluid/salt intake; may consider fludrocortisone ± midodrine
- **Patient information:** www.parkinsons.org.uk/default.aspx?page=10495

# RESTLESS LEGS SYNDROME

## Background (*AASM ICSD-2* 2005; *Neurol Clin* 2012;30:1137)

- **Definition:** Movement disorder, often idiopathic but frequently assoc

w/ systemic disease, characterized by (*Sleep Med* 2003;4:10): (1) Urge to move limbs assoc w/ paresthesias (2) Sx occur at rest (3) Sx worse at night (4) Physical activity provides partial relief

- **Etiology:** As yet undefined; thought to be DA-related, possibly due to ↑ of dopaminergic transmission → postsynaptic desensitization (*BMJ* 2012;344:e3056); genetic predisposition has also been implicated (⊕ FHx in 15–58% of pts)
- **Periodic leg movements in sleep:** Jerking movements of legs during sleep, occur in 80–90% of pts w/ RLS & supports this dx
- **Epidemiology:** Some degree of RLS affects 5–15% of adults, ~2% of adults affected enough to require tx; prevalence ↑ w/ age (up to 20% in pts >80 y); more common in Caucasian ethnicity, ♀ > ♂ (2:1) (*Arch Intern Med* 2005;165:1286)
- **Risk factors:** Has been assoc w/ Fe deficiency, ESRD/uremia, DM, MS, PD, autoimmune disease, OSA, venous insufficiency, & pregnancy

## Evaluation

- **History:** Pt typically presents complaining of features above; can also c/o insomnia, bedmate may endorse periodic limb movements of sleep; ⊕ FHx
- Single question with Se/Sp 100/96% for dx of RLS: "When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?" (*Eur J Neurol* 2007;14:1016)
- **Medications:** Meds/agents that can induce/exacerbate RLS: Antidopaminergic (neuroleptics), diphenhydramine, TCAs, SSRIs, mirtazapine, EtOH, caffeine, lithium, βBs
- **Exam:** In isolated RLS, should be normal
- **Diagnostics:** ✓ Iron studies (incl ferritin) & CBC; w/u for 2° causes as indicated; may consider polysomnography if dx unclear

## Treatment (*Sleep* 2012;35:1039; *JAMA Intern Med* 2013;173:496; *Mayo Clin Proceed* 2004;79:916)

- **General approach:** Treat secondary causes when possible (OSA, Fe deficiency); nonpharmacologic tx offered to all pts; further tx indicated for pts w/ frequent or >mod discomfort

- **Iron supplements:** Oral supplements may ↓ sx in pts w/ Fe deficiency (ferritin <50 ng/mL)
- **Nonpharmacologic treatment;** evidence incomplete but suggestion that LE compression devices, cognitive behavioral tx, & exercise may ↓ RLS sxs; avoid exacerbating meds/toxins as able; trial of brief walking, hot baths, or leg massage before bedtime (*BMJ* 2012;344:e3056)
- **Dopamine agonists:** Pramipexole, ropinirole are **1st-line,** effective, well-tolerated
  *Side effects:* Nausea, dizziness, somnolence, nasopharyngitis; ↓ impulse control, vivid dreams
  *Administration:* Either agent should be taken ~2 h prior to sx onset
  *Example Rx:* Pramipexole 0.125 mg QHS; may ↑ by 0.125 q2–3d until relief obtained (max 2 mg)
  Ropinirole 0.25 mg QHS; may ↑ by 0.25 q2–3d as needed (max 4 mg)
- **Gabapentin:** Alternative to dopamine agonists; less evidence for efficacy, but consider if coexisting neuropathic pain or in pts w/ mild sx, s/e include somnolence; adjust dose in CKD
- **Other:** Typically initiated by neurologist for refractory cases; levodopa effective but risk of augmentation (earlier/quicker/more severe sx, ↓ duration of med effect) → used in pts w/ intermittent sx; clonidine, BZD, & opiates also used
- **End-stage renal disease:** IV iron dextran during dialysis → sig. but transient ↓ sx (*Am J Kidney Dis* 2004;43:663)
- Superficial venous insufficiency: RLS sxs may improve w/ laser ablation or sclerotherapy (see "*Peripheral Vascular Disease*") (*Phlebology* 2008;23:112; *Dermatol Surg* 1995;21:328)
- **When to refer:** Refractory disease or dx unclear → neurology
- **Patient information:**
  www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm

# SEIZURE

## Background (*Neurology* 2011;77:1005; *Epilepsia* 1975;16:1)

- **Definitions: Seizure:** Symptoms which arise from episode of abnormal

electrical activity in brain; can be generalized (onset in both hemispheres) or focal (part of 1 hemisphere); focal seizures may or may not → impairment of consciousness/awareness; **Epilepsy:** ≥2 unprovoked seizures; **Status epilepticus:** Seizure lasting >30 mins or >1 seizure over 30 mins w/o interval return to baseline

- **Epidemiology: Epilepsy** affects ~2 million in US; ~6% of population will experience a seizure in their lifetime
- **Risk factors:** ⊕ FHx, perinatal injury, febrile seizures, head trauma, CNS infection, stroke, brain tumor
- **Provoked seizure:** Due to discrete, temporary trigger rather than underlying seizure d/o (metabolic, drugs, EtOH/SUD, head injury, CNS infection, stroke, eclampsia; seizure after sleep deprivation considered unprovoked)

## Evaluation (*AFP* 2007;75:1342; *Postgrad Med J* 2009;85:667)

- **General approach:** Determine characteristics of event, whether provoked or unprovoked, assess for any neuro abnormalities/ongoing deficits
- **History:** Event details from pt/witness: Time of day, aura (epigastric sensation, bad smell), focal onset, duration, eyes open, incontinence, tongue biting, postictal confusion; ask about provoking sx (above) meds & diseases that can ↓ seizure threshold: Systemic illness, sepsis, hepatic/renal dx, UTI (*BMJ* 2012;345:e4576)
- **Exam:** Full neuro exam (frequently nl); examine tongue & extremities for ictal injuries; skin exam for e/o neurocutaneous d/o (tuberous sclerosis, neurofibromatosis, Sturge–Weber)
- **Initial studies:** CBC, lytes, glucose, tox, pregnancy test; (note that GTCs may transiently ↑ lactate, CK, WBC); ✓ECG to exclude arrhythmia
- **EEG:** Predicts sz recurrence, characterizes epilepsy syndrome; Se ~50%, ↑ if w/in 24 h
- **Imaging:** All pts w/ new seizure → MRI w/ contrast preferred, seizure protocol

## Differential Diagnosis

- **Etiologies of seizure:** Idiopathic/unknown, structural, metabolic,

genetic, perinatal, infection (encephalitis, meningitis, cysticercosis), neoplasm, stroke, ICH, trauma, EtOH/substance withdrawal, metabolic

- **Seizure mimics:** Syncope (up to 90% pts w/ syncope can p/w myoclonic jerks), physiological sleep myoclonus, sleep d/o, complex migraines, movements d/o, limb shaking TIA, transient global amnesia, & nonepileptic seizures (aka pseudoseizures; frequently coexist w/ epilepsy, in up to 10–30%)
- **Features suggesting seizure:** Tongue biting, head turning, cyanosis, postictal confusion, incontinence, eyes open during event

## Management (*Continuum* 2010;16.3:105)

- If provoked single seizure → treat underlying cause
- **Avoid meds that ↓ seizure threshold:** *Anti-infectives:* FQs, high-dose β-lactams, INH, chloroquine, mefloquine; *Analgesics:* Tramadol, opiates, meperidine; *Psych:* Bupropion, clozapine
- **Antiepileptic drugs:** Initiated & managed by neurology; *Indications:* for all pts w/ >1 seizure or structural abnormalities, abnl EEG, or abnl neuro exam, stroke hx; *Considered* in pts w/ ↑ risk of sz complication or per pt preference; starting AEDs after 1st seizure → ↓ sx recurrence over next 2 y, but no effect on long-term recurrence/remission rate; *Goal:* Monotherapy; AED chosen based on sz type, pt age, comorbidities, med interactions & s/e profile; *S/e:* Sedation common; all AEDs may ↑ suicidal thoughts → monitor pts for SI
- **Counseling** (*Postgrad Med J* 2009;85:667)
  **Driving:** Laws vary by state, most require sz-free period × 3–18 mos; some states require providers to report directly to DMV, list at epilepsyfoundation.org/resources/healthcareprofessionals.cfm
  **Safety:** Counsel not to swim alone, avoid bathtubs; caution near fire, working at heights, operating dangerous machinery, extreme sports
  **Triggers:** Importance of minimizing EtOH/drugs, sleep deprivation, med noncompliance

## Antiepileptic Medications (*Continuum* 2010;16.3:121)

| Medication | Monitoring | Side Effects |
|---|---|---|
| Carbamazepine | ✓CBC, LFT, lytes; CYP450 inducer (↓ warfarin, ↓ OCPs); avoid w/ MAOI, avoid in Asians 2/2 ↑ SJS | ↓ Na, ataxia, cytopenias, aplastic anemia, agranulocytosis, rash, SJS |
| Phenytoin | CYP450 inducer (as above); ✓yearly DEXAs; avoid in pts w/ bradycardia/heart block | Ataxia, nystagmus, hirsutism, gingival hyperplasia, ↑ LFTs, ↓ BMD, blood dyscrasias, SJS |
| Valproate | ✓CBC, LFT, lipase; good for pts w/ migraine, bipolar, depression; avoid in hepatic dx, young women | Teratogen; tremor, ↓ hair, ↑ wt, N/V, ↓ PLT, ↑ LFTs, ↑ $NH_3$, ↓ BMD, pancreatitis, blood dyscrasias |
| Oxcarbazepine | ✓Na; CYP450 interact (↓ OCPs); contraind in generalized sz | ↓ Na, apathy, confusion, acne |
| Lamotrigine | Slow titration required → d/c at 1st sign of rash; good for pts w/ bipolar, chronic pain, elderly | Rash, SJS, diplopia, ataxia, blood dyscrasias |
| Levetiracetam | Caution w/ depression, bipolar | Irritability, aggression, emotional lability, anxiety, depression, SI |
| Topiramate | Avoid in pts w/ kidney stones; CYP450 interact (↓ OCPs); good for pts w/ migraine, obesity | Cognitive dysfunction, fatigue, ↓ wt, tingling, kidney stones |
| Zonisamide | Avoid in pts w/ kidney stones | Cognitive dysfunction, kidney stones, ↓ wt, ataxia, blood dyscrasias, SJS |
| Lacosamide | Contraindicated in pts w/ AV block | ↑ PR interval; AF |

## When to Refer

- **Neurology:** New unprovoked szs, pts on >1 AED, or no response to meds
- **Emergency department:** If suspicion of CNS infection, fever or immunocompromised → send to ED for LP; if new neuro deficits/not back to baseline → send to ED for urgent imaging (r/o ICH, stroke, tumor)

# STROKE, TIA, & POSTSTROKE CARE

## Background (*Circulation* 2012;125:e2)

- **Definitions: Ischemic stroke:** Loss of brain function due to inadequate cerebral blood supply (85% of all strokes, 15% hemorrhagic); **TIA:** "Transient episode of neurologic dysfunction caused by focal brain,

spinal cord, or retinal ischemia, w/o acute infarction," resolving in <24 h, w/ no lesions seen on MRI (*Stroke* 2009;40:2276)

- **Epidemiology:** 3% of US adults have hx prior stroke; incidence ↑ w/ age (mean 71–75 y for 1st stroke), but 34% of strokes occur in pts <65 y; 2% of US adults report hx diagnosed TIA, although true prevalence likely ↑↑ as often underreported; racial/ethnic disparities exist (incidence African-American, Native American > Caucasian > Hispanic)
- Stroke major cause of mortality & disability; half of elderly who survive stroke will have mod–severe disability; TIA considered "warning sign" for stroke; → 10–17% risk of stroke w/in 90 d, with $^1/_2$ of events occurring w/in 2 d, if survive this period, 43% 10-y risk of MI, stroke, or vascular death
- **Risk factors:** HTN, AF, tobacco use, dyslipidemia, physical inactivity, DM, CKD/ESRD
- **Etiology:** Atheroemboli from aortic arch, cervical vessels (most common), cardioembolic thrombus (AF, CHF), small-vessel thrombosis ("lacunar" stroke); can also be 2/2 cervical vessel dissection, hypercoagulable state, hyperviscosity, paradoxical embolus through R → L shunt, endocarditis, infection (syphilis, CNS zoster), vasculitis

## Evaluation (*Stroke* 2009;40:2276)

- **Pts reporting symptoms concerning for prior TIA:**
  **Was it a true TIA?** Consider seizure, migraine, syncope, conversion d/o, mononeuropathy (e.g., Bell's palsy or peroneal neuropathy)—see respective chapters
  **What is their post-TIA risk of stroke?** *ABCD2 score* (Age, BP, Clinical features of TIA, Duration of sxs, DM) validated to predict short-term risk (*Lancet* 2007;369:283); score calculator available at www.mdcalc.com/abcd2-score-for-tia/
- **All patients with currently suspected TIA or stroke → ED; document "last seen well" time** (to help ED team determine if pt tPA candidate)
- **Patients with remote symptoms concerning for possible TIA:** (E.g., episode of vision loss 2 wks ago) → consider urgent outpt w/u, preferably in conjunction w/ neurologist; clinical judgment required,

may use *ABCD2* scoring to help assess risk: **Hospitalize** if present w/in 72 h of event &: *ABCD2* score ≥3, uncertain if outpt w/u can be completed w/in 2 d, or other e/o focal ischemia (*Stroke* 2009;40:2276)

- **Studies for eval of possible TIA: MRI w/ diffusion-weighted imaging;** CT acceptable & **cervical vessel imaging** (MRA, CTA, or U/S) (to r/o stroke or critical vascular stenosis), ECG + rhythm strip, Holter, TTE, CBC, electrolytes, glucose, CBC, lipid profile; consider further w/u depending on clinical suspicion (cardiac event monitoring, endocarditis w/u, hypercoagulability w/u) (*Stroke* 2004;35:1647)

## Ischemic Stroke Treatment

- **Modifiable risk factors:** BP control (in chronic setting), glycemic control, smoking cessation, moderation of EtOH, ↑ physical activity, wt loss (*Stroke* 2011;42:227)
- **Antiplatelet therapy: All TIA/stroke pts should be on antiplatelet tx** unless already anticoagulated or contraindication; all regimens in table below acceptable; for recurrent TIA/stroke, no data to support changing regimen; ASA + warfarin ↑ bleeding risk w/o ↓ stroke risk (may be indicated in pts w/ CAD; see "*CAD*") (*Stroke* 2011;42:227)

**Antiplatelet Agents for TIA/Stroke**

| Agent | Advantages | Disadvantages |
|---|---|---|
| ASA 81 mg (or 325 mg if other indications, i.e., s/p MI) | Inexpensive, generally 1st line | GI s/e |
| ASA/dipyridamole 1 capsule | Slight (1%) risk reduction vs. ASA in 1 trial (*Lancet* 2006;367:1665) | Tolerance limited by HA, BID dosing |
| Clopidogrel 75 mg | No sig. difference vs. ASA/dipyridamole (*NEJM* 2008;359:1238) | Higher cost |

- **Lipid-lowering agents:** SPARCL trial showed modest (↓ 2.2%) absolute risk reduction in recurrent ischemic stroke for high-dose atorvastatin vs. placebo (*NEJM* 2006;355:549); begin statin if atherosclerosis & LDL >100; goal LDL <70 (*Stroke* 2011;42:227)
- **Complications:** Assess for **depression:** Poststroke depression affects

~26% of pts; risk factors include prior social isolation, hx mood d/o, ↓ of independence after stroke; can be assoc w/ poor outcome (*Stroke* 1998:29:2311); **fall risk** (see "*Fall Prevention*"); **aspiration risk** (all pts w/ recent stroke should have had at least initial SLP eval, may need ongoing tx)

- **Referrals:** All pts w/ hx TIA or stroke should be seen by neurology; pts w/ recent stroke should be eval by multidisciplinary team including PT, OT, & SLP

## Special Populations

- **Stroke due to atrial fibrillation:** All pts should be anticoagulated unless contraindicated (*Stroke* 2011;42:227); due to risk of hemorrhagic transformation, most neurologists wait 1–2 wks poststroke to start anticoag, though no consensus; "bridging" w/ heparin not necessary (*Arch Neurol* 2008;65:1169) unless other indication (see "*Atrial Fibrillation & Flutter*")
- **Stroke and cardiomyopathy**: **For pts w/ EF <35%**, warfarin superior to ASA 325 in ↓ ischemic stroke risk but no benefit in composite outcome of death, ischemic stroke or ICH (WARCEF *NEJM* 2012;366:1859); ∴ in CHF pts w/ stroke hx, either warfarin or antiplatelets acceptable for 2° stroke prevention (*Stroke* 2011;42:227)
- **Stroke due to cervical artery dissection:** Highest stroke risk in 1st few days

  *Extracranial* → Tx w/ antiplatelet or anticoag × 3–6 mos (*Stroke* 2011;42:227); no data for superiority of anticoag vs. antiplatelet tx (tx practice varies)

  *Intracranial* → Due to SAH risk, anticoag generally avoided (*NEJM* 2001;344:898)
- **Carotid stenosis (see "*Carotid Disease*")**
- **Intracranial stenosis:** No data to support stenting or other intervention over med mgmt; in pts w/ >70% intracranial stenosis, 30 d stroke risk ↑ w/ intracranial stenting vs. intensive med mgmt (SAMPRIS, *NEJM* 2011;265:993)
- **Patent foramen ovale:** Common (15–25% of population), closure not consistently shown to decrease recurrent stroke risk; 3 large trials showed no sig benefit of PFO closure vs. med tx alone for 2°

prevention of cryptogenic stroke in 1° intention-to-tx analyses; in prespecified per-protocol & as-treated analyses of RESPECT trial, there was a benefit of ↓ recurrent stroke/death (CLOSURE, I *NEJM* 2012;366:991; PC TRIAL, *NEJM* 2013;368:1083; RESPECT, *NEJM* 2013;368:1092)

Reasonable to start pts on ASA or other antiplatelets (*Stroke* 2011;42:227); If PFO discovered during stroke w/u, obtain LE U/S to r/o DVT → paradoxical embolus

- **Cerebral amyloid angiopathy:** Age-related fragility of small arteries, which can rupture → lobar hemorrhage; Dx by microhemorrhages c/w CAA on susceptibility-weighted MRI; if present, avoid anticoag 2/2 ↑ risk ICH

# TREMOR

## Background (*JAMA* 2003;289:347)

- **Definition:** Rhythmic, oscillatory, involuntary movement with a constant frequency
- **Classification:**

**Resting tremor:** Evident when affected body part not voluntarily activated & remains *supported against gravity* (most commonly seen in parkinsonism)

**Action tremors:**

*Postural:* Occurs when head/limbs are held in a fixed posture against gravity

*Kinetic:* ↑ By voluntary movement; intention tremors ↑ during goal-directed movement

## Common Tremor Syndromes

**Tremor Characteristics**

| Type | Rest | Postural | Kinetic |
|---|---|---|---|
| Physiologic | | ++ | + |
| Essential Tremor | ± | ++ | + |
| Parkinsonian | ++ | + | ± |
| Dystonic | ± | ++ | ++ |
| Neuropathic | | ++ | + |
| Cerebellar | | ± | ++ |
| Psychogenic | + | + | + |

±, Occasionally present; +, may be present; ++, typical (Adapted from *Postgrad Med J* 2011;87:623)

- **Enhanced physiologic tremor** (*AFP* 2003;68:1545): All persons have some degree of postural tremor; enhancement of this is most common cause of action tremors
  *S/sx:* Low amplitude, high frequency (~10–12 Hz); best visualized by holding arms outstretched **w/** fingers spread apart
  *Etiologies:* ↑ *Sympathetic activity* (anxiety, fear), *endocrinopathy* (hyperthyroidism, hypoglycemia, hypercortisolism, pheo), drugs (caffeine, lithium, TCAs, SSRIs, corticosteroids, valproate, theophylline, amphetamines), withdrawal (EtOH, BZD)
  *Tx:* Underlying condition; also responds to propranolol (can be used in stressful social situations & for performance anxiety)
- **Essential tremor:** Very common (up to 5% prevalence), progresses w/ age & can → substantial disability (*Postgrad Med J* 2011;87:623)
  *S/sx:* Bilateral, usually symmetric, ~4–8 Hz postural action tremor; most frequently starts in hands/arms (~95% of pts), can also affect head ("yes-yes" or "no-no" sign = "titubation"), jaw, voice, rarely legs (*Neurology* 2005;64:2008); can improve w/ EtOH consumption
  *Etiology:* Genetic component, FHx in ~50% cases (autosomal dominant pattern)
  *Tx*: 1st-line agents are propranolol & primidone → avg tremor ↓ by 50%
  *Propranolol:* Dose range 60–320 mg/d (avg ~185 mg/d); s/e: Light-headedness, fatigue, impotence, bradycardia (*Neurology* 2005;64:2008)
  *Primidone:* Dose range 50–1000 mg/d (avg ~480 mg/d); s/e: Sedation, nausea, dizziness/unsteadiness, confusion
  *Other tx:* BZD, gabapentin, or topiramate are 2nd line, refractory & severe cases may benefit from neurosurgical intervention (DBS or

ablation)

- **Cerebellar tremor:** Intention tremor, large amplitude, ↑ as limb moves closer to a target (e.g., finger-to-nose, heel-to-shin); assess for other cerebellar signs (dizziness, nystagmus, dysmetria, ataxia) → imaging (urgently if new finding)
- **Other:**

  **Dystonic tremor:** Assoc w/ dystonia (sustained abnormal posture), can improve by touching affected region

  **Orthostatic tremor:** Limited to legs & trunk, occurs exclusively while standing

  **Psychogenic tremor:** Contains rest, postural, & action components; inconsistent features, distractibility w/ verbal & motor tasks, "loading" (pressing down on tremulous extremity ↑ tremor), & "entrapment" (tapping rhythm w/ unaffected limb → tremor frequency matching the tapped rhythm)

# NOTES

# ALLERGIC RHINITIS

## Background (*Lancet* 2011;378:2112)

- **Definition:** Inflammation of the nasal membranes in response to known or unknown allergen(s); also known as "hay fever" → rhinorrhea, sneezing, nasal congestion/pruritus
- **Pathophysiology:** 1st exposure → production of allergen-specific IgE → IgE binds receptors on mast cells & basophils; subsequent exposures → allergen crosslinks IgE on cell surface → cellular activation (i.e., mast cell degranulation)
- **Epidemiology:** Prevalence is ↑; highest in teens; currently affects >7% of US adults; ♀ = ♂; accounts for >13 million US health care visits annually (*Vital Health Stat* 2011;13:169 www.cdc.gov/nchs)
- **Risk factors:** Include genetics (multiple loci), high SES, ↑ exposure to pollutants, animal dander, dust mites
- **Complications:** Nasal inflammation sx can affect QoL & productivity; additionally, ↑ incidence/severity of URIs (2/2 mucosal inflammation) & bacterial sinusitis (2/2 sinus obstruction) (*Otolaryngol Head Neck Surg* 2007;137:S1)
- **Comorbidities:** 40% of pts w/ AR also have asthma; tx of AR → improved asthma sx & ↓ hospitalizations (*J Allergy Clin Immunol* 2002;109:57); ocular sx occur in 50–70% of pts w/ AR (see *"Red Eye"*); also strongly assoc w/ AD ("atopic march")

## Evaluation (*Clin Exp Allergy* 2000;30:1314;1417

- **General approach:** Establish sx severity & potential triggers, consider Ddx & assess for comorbidities (OSA, asthma, atopy)
- **History:** Assess sxs, including functional (impaired sleep & work)
  *Meds:* Important to r/o rhinitis medicamentosa as cause of sx (see below); include OTC decongestants & nasal sprays, OCPs, ASA, NSAIDs, anti-HTN
  *PMHx/Soc hx:* Hx atopy (asthma, AD), OSA, environmental or food allergies, occupational hx, risk factors (above), current pregnancy, cocaine use

**Allergic Rhinitis Triggers**

| | |
|---|---|
| **Seasonal** | Outdoor **molds**, tree **pollen** (spring), grasses (summer), weeds (fall) |
| **Perennial** | Animal hair (cat, dog, etc.), **dust mites**, **cockroaches** (urban areas) |
| **Occupational** | Agricultural workers, animal lab workers, food services |

- **Exam:** HEENT + skin (atopic dermatitis) & lung (asthma) exam
  *Eyes:* Bilateral conjunctival hyperemia ± clear d/c (allergic conjunctivitis), **infraorbital "shiners"** (↑ venous stasis 2/2 nasal congestion)
  *Ears:* Serous otitis media (Eustachian tube dysfunction)
  *Nose:* Saddle-nose deformity (granulomatosis w/polyangiitis, aka Wegener's) or septal deviation (trauma) or perforation (cocaine), **pallor of mucosa**, **pallor/edema of turbinates; "allergic salute"** (rubbing nasal tip upward w/ palm → supratip crease); polyps (chronic sinusitis, ASA Se)
- **Differential diagnosis:** Up to 30% of rhinitis nonallergic
  *Infectious:* Acute viral rhinosinusitis, chronic rhinosinusitis (consider immunodeficiency)
  *Medication-induced:* S/e of ASA/NSAID, ACEI, PDE5, or α-blockers; rhinitis medicamentosa ("rebound" 2/2 chronic use of topical nasal decongestants, e.g., oxymetazoline, also seen w/ cocaine)
  *Autoimmune:* Churg–Strauss, granulomatosis with polyangiitis (Wegener's), sarcoid
  *Idiopathic:* Vasomotor rhinitis (nonallergic, noninfectious)
  *Structural:* Nasal polyps, deviated septum, adenoid hypertrophy
  *Other*: Pregnancy, assoc w/ menstrual cycle (2/2 ↑ circulating estrogen/progesterone)
- **WHO classification** (*JACI* 2001;108:S147)
  *Frequency:* Intermittent (< 4 d/wk or < 4 wks) vs. persistent (> 4 d/wk or > 4 wks)
  *Severity:* Moderate–severe (≥ 1 of the following: Sleep disturbance, impaired school/work performance, impaired daily activities, troublesome sx) vs. mild (no significant sx)

## Management ( *JACI* 2008;122:S1; *Lancet* 2011;378:2112)

- **Allergen avoidance**: Identify/avoid triggers when possible
  *Dust mite:* Humidity control, dust mite covers for bedding, HEPA vacuuming of carpeting

*Pollen:* Avoid outdoors during AM (when pollen counts highest), use air conditioners when possible, don't hang clothes out to dry

*For further allergen avoidance suggestions, see "Asthma"*

- **Nasal irrigation:** Beneficial for chronic rhinorrhea; may be used alone or as adjuvant; Neti pot superior to saline mist (advise pts to use sterile saline); may also be done w/ low-pressure irrigation squeeze bottle (*AFP* 2010;81:1440)
- **Pharmacotherapy:** Multiple tx options; **intranasal corticosteroids most effective** for mod–severe disease; oral antihistamines ± nasal decongestants reasonable for intermittent or milder disease; avoid topical nasal decongestants b/c of risk of rebound congestion & rhinitis medicamentosa
- **Intranasal therapy technique:** Direct spray superiorly/laterally ("toward ipsilateral ear")

**Pharmacotherapy**

| Class | Example Rx & Notes |
|---|---|
| **Intranasal corticosteroids (1st line for mod–severe disease)** | Fluticasone (50 µg/spray): 2 sprays/nostril QD or 1 spray/nostril BID<br>Can ↓ to 1 spray/nostril QD for maintenance; onset ~12 h, should be used consistently for ↑ efficacy<br>Also effective in mixed rhinitis (e.g., irritant)<br>*S/e:* nasal irritation, epistaxis, bitter taste; systemic s/e rare<br>No difference in efficacy w/in class (*J Laryngol Otol* 2003;117:843) |
| **Oral antihistamines** | Fexofenadine (OTC): 60 mg BID **or** 180 mg once daily<br>Cetirizine 5–10 mg QD<br>**2nd-generation preferred** (↓ sedation, ↓ anticholinergic effects, although may be ↓ effective rhinorrhea tx)<br>Faster onset, less effective than ICS for severe disease or nasal congestion; can be used prn but more effective if used regularly<br>Fexofenadine/loratadine/desloratadine less sedating, cetirizine more sedating |
| **Nasal antihistamines** | **Azelastine: 1–2 sprays/nostril BID**<br>Equal or superior efficacy to oral Rx for nasal sx; less effective than intranasal corticosteroids<br>*S/e:* bitter taste, somnolence |
| **Oral decongestants** | Pseudoephedrine: IR: 60 mg q4–6h; Extended release: 120 mg q12h or 240 mg QD (max 240 mg/24 h)<br>Good for short term ↓ nasal congestion<br>*S/e:* HTN, insomnia, palpitations, urinary retention |
| **Intranasal anticholinergics** | Ipratropium (0.03%): 2 sprays/nostril BID–TID<br>Good for ↓ rhinorrhea; not effective at ↓ congestion |

- **Other:**
  **Leukotriene receptor antagonists:** Montelukast 10 mg PO QD; also effective in asthma (consider use in pts w/ both diseases); similar efficacy in AR to oral antihistamines
  **Intranasal anticholinergics (ipratropium):** ↓ Rhinorrhea, not effective at ↓ congestion
  **Mast cell stabilizer (intranasal cromolyn):** Can be used as ppx (take just before exposure → 4–8 h protection) or maintenance (best if started prior to exposure); less effective than intranasal corticosteroids

## When to Refer

- Allergy/immunology: For severe/refractory/recurrent sx; for allergen-specific IgE skin/serum testing; if dx uncertain *immunotherapy (desensitization):* Allergen exposure to alter immune response (often requires 3–5 y of tx)
- Otolaryngology: If suspect structural etiology (e.g., deviated septum)

# EYE TRAUMA

## General Approach

- Single insult can → multiple injuries (e.g., fist to orbit → orbital fracture, hyphema, retinal pathology)
- Detailed hx re: mechanism & general ophthalmic screening exam critical
- **Urgent referral** necessary if any ambiguity re: mechanism of trauma or full extent of ocular injuries; all pts w/ ↓ vision should be referred promptly
- Do not prescribe topical anesthetics (e.g., proparacaine); overuse → severe corneal damage; Rx topical corticosteroids & eye patch only in conjunction w/ specialist
- **Prevention:** Remind pts of importance of eye protection (e.g., safety goggles/glasses w/ yard & household chores; appropriate occupational eyewear)

## Orbit, Adnexa, and Globe

- **Orbital fracture:** Follows blunt trauma (e.g., MVC, fist, fall); *Sx:* Pain w/ eye movement, diplopia; *Findings:* Periorbital ecchymosis, point tenderness ± palpable orbital rim deformities, painful or ↓ EOMs; *Tx:* Ice pack, noncontrast CT orbits
- **Lid lacerations:** Superficial-appearing injuries may mask more significant injury to lacrimal, canalicular, & SC structures as well as to globe
  *Tx:* Tetanus update prn, cool gauze to injury, referral for repair
- **Retrobulbar hemorrhage:** *Sx:* Acutely ↓ vision & pain after trauma or ophthalmic surgery, difficulty opening eye; *Findings:* Periorbital edema & ecchymosis, "tight orbit" (tense to palpation), proptosis, ↓ VA, RAPD, ± limited motility, conjunctival hemorrhage, & chemosis, *Tx:* **Urgent referral to ophthalmologist or ED capable of performing lateral canthotomy & cantholysis**, imaging not necessary for dx
- **Ruptured globe:** Can follow penetrating **or** blunt injury; have ↑ suspicion in elderly w/ fall resulting in facial trauma (esp. w/ hx prior eye surgery); may also have intraocular FB; *Sx:* Pain, ↓ vision, sensation of fluid draining from eye; *Findings:* ↓ VA (ranges from mild ↓ to NLP), subconjunctival hemorrhage (↑ suspicion if circumferential & bullous), irregular pupil, shallow anterior chamber w/ penlight, low IOP c/w contralateral eye, leaking intraocular fluid visualized w/ fluorescein & Wood lamp; *Tx:* **Emergent referral for any suspected rupture to facilitate repair w/in 24 h** as this ↓ risk of endophthalmitis; (*Br J Ophthal* 2010;94:111), instruct pt to remain NPO, update tetanus prn, place protective shield (**not** a gauze patch) over the eye

## Cornea and Conjunctiva

- **Conjunctival laceration:** Mechanism of injury critical to determine possibility of globe penetration or intraocular FB (e.g., ↑ risk if 2/2 power tools vs. plant branch) *Sx:* Mild pain, FB sensation; *Findings:* Conjunctival injection, focal fluorescein staining (areas of defect), ± subconjunctival hemorrhage, ± free flap of conjunctiva; *Tx:* 0.5% erythromycin ointment QID & referral w/in 1–2 d if small (<1 cm)

w/o evidence of surrounding trauma (e.g., hemorrhage); **all else → same-day referral**

- **Corneal or conjunctival foreign body:** Corneal more common, often occupational assoc (e.g., mechanic w/ metallic corneal FB); *Sx:* Pain, FB sensation, photophobia, tearing, ± ↓ vision; *Findings:* ± ↓ VA, FB visible on cornea, conjunctiva, or w/ upper lid eversion; *Tx:* Conjunctival: *If provider comfortable*, may remove conjunctival FB w/ cotton swab & tx w/ 0.5% erythromycin oint QID × 5 d; Corneal: **Refer w/in 24 h**
- **Corneal abrasion:** Often hx mild identifiable trauma; *Sx:* Pain, FB sensation, photophobia, tearing, ± ↓ vision depending on proximity to visual axis; *Findings:* ± ↓ VA, pain relieved w/ topical proparacaine, area of fluorescein staining w/ Wood lamp, possible FB found w/ eversion of upper lid; *Tx:* No contact lens wearing until healed; patching not routinely done; **no topical anesthetics;** APAP & cool compresses prn*; Peripheral abrasion:* 0.5% erythromycin oint QID × 5 d for small (e.g., 1–2 mm diameter); if larger or contaminated object (e.g., fingernail, organic material) add FQ (e.g., 0.3% ofloxacin 1gtt QID × 5 d); **refer if not improved w/in 48 h;** *Central (involving visual axis):* **Refer w/in 24 h**
- **Chemical exposure:** Alkali exposure (e.g., plaster, cement, lye) far more damaging than acid, **rapid neutralization of pH critical;** *S/sx*: Pain, ↓ vision, diffuse conjunctival hyperemia & chemosis; *Mgmt:* **Immediate testing of pH** prior to any other eval, fine scale litmus paper placed under lower lid; nl 6.8–7.2) followed by proparacaine administration & irrigation w/ Ringer or saline for 30 mins; recheck & continue cycle until pH neutralized; sweep under upper & lower lids to remove particulate debris w/ eversion & inspection if possible; *Tx:* Refer w/in 24 h in all cases; w/ erythromycin oint QID in interim; **immediate referral if unable to neutralize pH or ⊕ limbal ischemia** (vessels at boundary btw cornea & conjunctiva replaced by marbled whitening) or **corneal haze**
- **UV/thermal keratitis:** Follows unprotected exposure to welder's arc, tanning bed, electric sparks; *Sx:* Bilateral FB sensation, photophobia, tearing; *Findings:* Pain relieved w/ topical proparacaine, punctate or confluent fluoroscein staining visible w/ Wood lamp, mild

conjunctival hyperemia, ± mild lid edema but no lid burns; *Rx:* Artificial tears prn, erythromycin oint QID × 5 d; **refer if severe or no improvement w/in 24 h**

- **Superglue exposure:** Warm compress to separate lids/lashes; tx as corneal abrasion
- **Subconjunctival hemorrhage:** See *"Red Eye"*

### Anterior Chamber

- **Traumatic iritis:** Typically develops w/in 3 d of trauma; *Sx:* Pain, photophobia, tearing, ± ↓ vision; *Findings:* WBCs in anterior chamber (seen w/ slit lamp), consensual photophobia, conjunctival injection, ± ↓ VA; *Tx:* **Refer to ophthalmology w/in 24 h**, no steroids
- **Hyphema:** Typically follows blunt orbital trauma (e.g., soccer ball or fist) but should also maintain suspicion for penetrating injury; *Sx:* Dull pain, ± ↓ vision; *Findings:* ± ↓ VA, clot or layered blood in the anterior chamber visible w/ penlight; *Tx:* **Same-day referral to ophthalmology:** Bed rest, protective shield over eye, avoid NSAIDs & anticoagulants

### Retina and Optic Nerve

- **Vitreoretinal pathology:** Typically follows blunt trauma; may include vitreous hemorrhage, retinal tear or detachment; *Sx:* ↓ Vision, flashing lights, floaters, sensation of veil coming down over vision; *Findings:* ± ↓ VA, ± altered fundus visualization (impaired if significant vitreous hemorrhage or nl if peripheral retinal pathology); *Tx:* **Same-day referral to ophthalmology**

## HEARING LOSS

### Definition (*Otolaryngol Head Neck Surg* 2012;146:S1, *NEJM* 2008;359:833)

- **Conductive hearing loss (CHL):** Hearing loss 2/2 abnormalities in the structures which "conduct" sound waves to the cochlea: auricle, external auditory canal, tympanic membranes, middle ear airspace or ossicles
- **Sensorineural hearing loss (SNHL):** Hearing loss 2/2 abnormality of

the structures that transmit neural impulses to the auditory cortex: cochlea, auditory nerve
- **Mixed hearing loss:** Hearing loss w/ conductive & sensorineural components
- **Severity:** Mild 20–40 dB loss, Mod 40–70 dB, Severe 70–90 dB, Profound >90 dB

## Background

- Hearing loss is underdiagnosed & undertreated, despite affecting >25% of those over 65; assoc w/ social isolation, functional decline, poor QoL, depressive sx & cognitive deficits; ↑ *Risk:* ↑ Age; ♂ > ♀, Caucasian, HTN, DM, CKD, immunosuppressed
- **Screening:** Required in Medicare annual wellness visit; endorsed by USPSTF in pts >65: "Would you say you have any difficulty hearing?"; ask family members when feasible

## Evaluation (*JAMA* 2012;307:1185; *AFP* 2012;85:1150)

- **History: Auditory sx:** Duration, sidedness & symmetry, pain, otorrhea, head/ear trauma, **acoustic trauma** (duration & sound intensity); *Assoc sx:* Tinnitus, vertigo; *Medical:* Occupational noise exposure; **ototoxic meds** (salicylates, NSAIDS, APAP, aminogylcosides, cisplatin, diuretics, quinine), hx infection (Lyme, syphilis, meningitis), hx ear infections, tympanostomy tubes, FHx hearing loss
- **Exam:** Inspect auricle, mastoid, canal, TM, pneumatic otoscopy for drum mobility
- **Whisper test** → stand each side at 2 ft from ear (⊕ test indicated by failure to repeat at least 3 of 6 letter/number combinations)
- **Tuning fork tests** (*NEJM* 2008;359:833)
  *Weber:* Hold 512 Hz tuning fork in middle of forehead, ask pt where it is best heard (L, R, symmetric) → sound lateralizes to the "blocked ear" in CHL or to the "better ear" in SNHL
  *Rinne:* Compares bone & air conduction on each side by placing fork firmly over mastoid (bone conduction) then by holding in front of auricle (air conduction) → Rinne ⊕ when air >bone (nl), Rinne ⊖ when bone >air (c/w **CHL** ≥25 dB)

## When to Refer

- Sudden hearing loss → emergent ENT referral; gradual SNHL → ENT, audiologist; gradual CHL—depends on etiology; see CHL, below

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# Conductive Hearing Loss

## General Approach (*Otolaryngol Head Neck Surg* 2008;139:S1)

- **Diagnosis:** Usually **apparent on exam** of auricle, canal, & tympanic membrane; most common causes in adults are cerumen impaction > otosclerosis & otitis media
- **Cerumen impaction:** Often 2/2 cotton swab use → medial packing of cerumen over time; Tx: Irrigation w/ warm water → limited curettage under direct visualization; if ineffective, then cerumenolytic ($H_2O_2$) × 5 d, then repeat; if ineffective → ENT referral for otomicroscopy & removal; pts w/ TM perforation, prior ear surgery, otitis externa, vertigo or abnormal canal should be managed directly by ENT (*AFP* 2007;75:1523)

### Common Causes and Treatment of Conductive Hearing Loss

| Etiology | Diagnosis | Treatment |
|---|---|---|
| **Cerumen impaction** | Visualized on otoscopy | See above |
| **Otitis externa or eczema** | Pain, itchiness, edema | See *"Otitis"* |
| **Exostosis** (external canal osteoma) | Otoscopy ± temporal bone CT | Observe if nonobstructing + asx, o/w ENT referral |
| **Acute otitis media, OM w/ effusion** | Pneumatic otoscopy, tuning fork exam, tympanometry | See *"Otitis"* |
| **TM perforation** | Otoscopy, tympanometry | **$H_2O$ precautions,** ENT referral for repair if persistent |
| **Cholesteatoma** (cyst in middle ear) | Otoscopy, audiometry, CT scan of temporal bone | ENT referral for, possible tympanoplasty/ mastoidectomy |
| **Ossicular fixation** (e.g., otosclerosis) | Audiometry, otoacoustic emissions, possible CT of temporal bones | ENT referral for middle ear exploration, ossiculoplasty (stapedectomy) |

*(Nadol JB. Surgery of the Ear and Temporal Bone 2004)*

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# Sensorineural Hearing Loss

## General Approach

- Most common cause of hearing loss in older adults; presbycusis leading cause of SNHL in elderly; pts often c/o difficulty "filtering out" background noise

## Causes (*Otolaryngol Clin N Am* 2012;45:941)

- **Presbycusis:** Age-related hearing loss (90% of SNHL in elderly)—a gradual, symmetric loss of hearing, starting in high frequencies & progressing to mid frequencies (necessary for speech recognition)
- **Noise-induced hearing loss:** Symmetric SNHL from occupational exposure, industrial equipment, firearms—**preventable** w/ regular use of hearing protection
- **Ménière disease:** Fluctuating, progressive asymmetric hearing loss, aural fullness, tinnitus & peripheral vertigo attacks lasting 2–3 days —treat w/ dietary Na restriction, ENT referral for possible diuretic Rx (*Otolaryngol Clin N Am* 2010;43:1011)
- **Sudden sensorineural hearing loss:** A sudden asymmetric loss of hearing/deafness in one ear, new onset tinnitus → an otologic emergency—pt needs rapid eval & high-dose steroid tx (*Otolaryngol Head Neck Surg* 2012;146:S1)
- **Trauma:** External trauma to temporal bone may involve the cochlea resulting in profound, permanent SNHL; barotrauma from scuba diving or sudden pressure changes may result in hearing loss, tinnitus or vertigo
- **Neoplastic disease:** Tumors at the CPA can p/w progressive or sudden onset hearing loss, vestibular schwannoma most common, but metastatic disease to CPA can also result in hearing loss → refer to ENT for eval/MRI
- **Other:** *Ototoxicity:* NSAIDS, cisplatin, aminoglycosides, loop diuretics; *Infection:* Bacterial meningitis, recurrent AOM, toxoplasmosis, syphilis; *Congenital:* Anatomic or genetic d/o, in utero infections (CMV, VZV, syphilis) or exposure (EtOH, isotretinoin, cisplatin ↑ bili), anatomic abnormalities

## Management ( *JAMA* 2012;307:1185)

- **Listening strategies:** Lip reading, directly facing the pt, speaking

slowly

- **Amplification:** Improve outcomes of speech perception, understanding & hearing related QoL, but are **expensive**, infrequently covered by insurance
  *Pt education:* Key for managing expectations; hearing aids help but cannot erase deficit, take multiple adjustments to be set properly & can take a few mos to be helpful
- **Cochlear implantation** (*NEJM* 2010;363:1438): Considered in setting of profound SNHL in postlingually deafened adults → significant gain in speech recognition

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## TINNITUS

### Background (*NEJM* 2002;347:904)

- **Definition:** The false perception of sound in the absence of an acoustic stimulus
- Poorly understood condition, frequently assoc w/ hearing loss, ♂ > ♀, ↑ w/ ↑ age

### Evaluation

- Sound may be a buzzing, rushing, whooshing, or clicking, usually worse in quiet room
- If pulsatile tinnitus correlates to the cardiac cycle → **imaging** (CTA or MRI) of the neck/skull base to r/o vascular abnormality; auscultate over the ear/mastoid to differentiate subjective (no noise, usually benign) from objective tinnitus (heard by clinician, can suggest ICA/vertebral artery aneurysm)

### Treatment

- **Tinnitus retraining therapy:** When performed by a specialist may help improve QoL in tinnitus (*Cochrane Database Syst Rev* 2010;CD007330); sound masking, anxiolytics, antidepressants frequently used but have not demonstrated efficacy in RCTs (*Cochrane Database Syst Rev* 2012;CD006371)
- Pulsatile or unilateral tinnitus should → ENT eval

# HOARSENESS

## Background (*Otolaryngol Head Neck Surg* 2009;141:S1; *JAMA* 2009;302:1954)

- **Definition:** Hoarseness (dysphonia) is a change in voice quality, pitch, amplitude, or vocal effort that impairs communication or reduces voice-related QoL
- **Epidemiology:** ♀:♂, 3:2; lifetime prevalence 30%, point prevalence ~7%; ↑ in at-risk populations (usually occupational, e.g., telemarketers, aerobic instructors, teachers, singers) (*Laryngoscope* 2005;115:1988)
- **Physiology:** Phonation requires harmonic function of the cartilaginous **skeleton, mucosa** (incl vocal folds), **muscles** (intrinsic & extrinsic), & **nerves** (vagus, recurrent, & superior laryngeal); pathology can occur at any level

## Evaluation

- **History:** *Characteristics:* Chronicity, onset, fatigability, "running out of air", voice "cracking"
  *Assoc sx:* URI, dysphagia, odynophagia, globus, throat clearing, allergies, aspiration, cough, acid reflux, constitutional, hemoptysis, dyspnea, otalgia
  *PMHx:* intubation, trauma, neck/chest surgery, XRT, DM, parkinsonism, MG, MS, ALS, allergies, CA, hypothyroidism, GERD
  *Meds:* ACEI, antihistamines, antipsychotics, inh corticosteroids, anticoagulants
  *Soc hx:* Tob, EtOH, occupation, exposures, vocal abuse
- **Exam:** HEENT (assess for oronasopharyngeal lesions, laryngoscopy, cervical LAD, thyromegaly), pulm (consolidation or focal wheezing), neuro (tremor, weakness, bulbar signs)
- **Vocal quality:** Coarse: irregular vocal cord (e.g., laryngitis/mass), breathy; incomplete glottic closure (e.g., vocal fold paresis); wet/gurgling; pooling of secretions (e.g., supraglottic infection); tremulous (parkinsonism)
- **Diagnosis:** Most acute cases can be diagnosed clinically; **laryngoscopy** necessary if ↑ risk of serious condition, if sx are persistent or concern

for airway obstruction

## Management

- **Refer for full ENT exam and laryngoscopy** if dysphonia persists >2 wks in absence of acute URI, esp. if ⊕ tob or heavy EtOH use (↑ risk laryngeal CA) or other concern for CA; Imaging **not** indicated prior to laryngoscopy

**Selected Conditions and Management**

| Condition | Presentation/Characteristics | Management |
|---|---|---|
| Acute laryngitis | In setting of URI, voice misuse, protracted coughing | Supportive/rest; **no role for abx or steroids** |
| Chronic laryngitis (CL) | Irritants: Inhaled fumes/smoke, gastric acid, vocal strain, postnasal drip | Withdraw/treat irritants, monitor for resolution |
| Fungal laryngitis* | Inhaled corticosteroids, prolonged abx use, ± dysphagia as well | Antifungal swish & swallow × 14 d |
| Laryngopharyngeal reflux (subset of CL) | Throat clearing, persistent cough, dyspepsia, & globus present in >95% *(Curr Opin; Otolaryngol Head Neck Surg* 2006;14:143) | Acid suppression/PPI (no evidence to initiate w/o other GERD sxs) |
| Benign vocal fold lesions* | Polyps, nodules, polypoid corditis | 2/2 chronic irritation; withdraw irritants |
| Neurologic causes* | Unilateral cord paralysis: Nerve injury, compression, neuropathy | Laryngoscopic tx/VF injections or surgery |
| | Bilateral paresis: Consider MG, ALS (25% p/w dysphonia) | Refer for swallow eval |
| | Parkinsonism: Hypophonia, tremor, breathiness, monotone<br>Essential tremor (25% laryngeal tremor) | Tx of underlying d/o |
| Functional causes* | Often occupational; paradoxical vocal cord motion (dysphonia w/ stridor), conversion d/o | Voice therapy *(Otolaryngol Head Neck Surg* 2008;138:557) |

*Diagnoses requiring laryngoscopy. *(Rubin et al. Diagnosis and Treatment of Voice Disorders, 2006)*

# JAW & DENTAL PAIN

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## DENTOFACIAL PAIN

## Background

- Jaw/dental pain may be 2/2 pathology in various structures, including nerves (CNV), joints (Temporomandibular joint), bones (maxilla/mandible), teeth, salivary glands, soft tissue (gums, oral mucosa)

## Evaluation (*NEJM* 2008;359:2693)

- **History:** Onset & duration of symptoms most important; assess for facial erythema/swelling (dental or salivary infection), cold/hot sensitivity (pulpitis), pain/swelling w/ meals (sialadenitis), dysphagia/dyspnea (deep neck space infection), trismus (TMJ d/o or muscular inflammation); shooting facial pain or numbness (neuralgia); hx XRT or bisphosphonate exposure (osteonecrosis), severe dental infection (osteomyelitis), tobacco & EtOH abuse (oral cavity malignancy)
- **Physical exam:** Full head & neck exam; *Dental exam:* Inspect teeth & palpate → tenderness (caries/periapical infection); *TMJ exam:* Nl jaw opening is 35–55 mm; tenderness over joint (capsulitis), limited range of opening (ankylosis), tenderness of muscles of mastication (myofascial pain); *Oral cavity exam:* Oral tongue, floor of mouth firmness (sialadenitis, Ludwig angina), nonhealing ulcers of tongue or oral mucosa (malignancy); CN exam → dysesthesias (CNV branches suggests neuralgia)
- **Diagnostic studies:** Dental pathology → panoramic radiograph of jaw; TMJ dysfunction → MRI of joint to assess articular disk & soft tissues; Salivary gland infection, deep neck space infection → CT w/ contrast of neck; oral cavity or oropharyngeal ulcer/mass → referral to specialist **prior** to imaging; salivary gland mass, cranial neuropathy → MRI w/ contrast to assess for tumor/lesion

## Management (*Oral Maxillofac Surg Clin North Am* 2009;21:293)

- **TMJ d/o:** Most common amongst people ages 20–50 y, ♂:♀ >3:1
  *Etiology:* Myofascial pain (most common), intra-articular disc d/o, OA, & RA
  *Sx:* Unilateral pain localized to jaw, TMJ, muscles of mastication but can radiate to ears, posterior neck; sx ↑ in AM esp in pts who clench/grind teeth at night; pts also c/o limited or asymmetric

opening/closing of jaw, & TMJ sounds (e.g., clicking)
*Tx:* NSAIDs, jaw rest (soft diet, prevention of wide opening), hot compresses, physical Rx, muscle relaxants, trigger point injections; consider TCAs (*NEJM* 2008;359:2693)

- **Salivary gland dysfunction:** Submandibular > parotid; ↑ incidence in ⊕ tob, diuretic use, HCV, Sjögren/sicca syndrome
  *Etiology:* Sialolith (can → sialadenitis); also (rare): Sarcoid, Sjögren, HIV, CA *Sx:* Unilateral tenderness/pain under mandible (submandibular) or preauricular/maxillary buccal mucosa (parotid); sialolith may be palpable/visible *Tx:* Initially conservative; **massage**, warm compress, sialogogues (e.g., lemon drop candy), hydration, NSAIDs, abx if e/o 2° infection (purulence from duct, erythema, fever) (*Otolaryngol Head Neck Surg* 2011;145:935)
- **Odontogenic disorders** (cdc.gov): Advanced periodontal disease affects 4–12% of US adults; poor oral health disproportionately affects non-Caucasian ethnicities, poor; ↑ risk in smokers, sicca/Sjögren, eating d/o, methamphetamine abuse, chemotherapy, pregnancy, antipsychotic meds
  *Etiology:* Gingivitis (inflammation of the gums), periodontitis (inflamm → loose teeth), pulpitis/pulp necrosis (dental caries), dental abscess
  *Sx:* Tooth/jaw pain, heat/cold sensitivitiy
  *Tx:* Analgesics; abx if e/o acute infection (purulence, erythema, F/C)
- **Trigeminal neuralgia:** Onset typically >50 y, ♀ > ♂; ↑ risk w/ HTN or ⊕ FHx; *Etiology:* Vascular compression or idiopathic
  *Sx:* Typically unilateral, (R > L), sharp/stabbing pain lasting <2 min; *Rx:* 1st r/o malignancy or MS w/ imaging (MRI)
  *Tx:* Carbamazepine > baclofen, lamotrigine; surgical tx if refractory: Decompression, rhizotomy (*Neurology* 2008;71:1183)

## When to Refer

- TMJ d/o: Severe, consideration of injections/interventions → OMFS
- **Sialolithiasis or sialadenitis:** If unresolved w/ conservative tx → specialist; if marked swelling (acute infection w/ abscess), CNVII involvement (w/ parotitis) → ED
- **Neuralgia/parasthesia:** If severe, not responsive to initial tx → Neuro

or neurosurgery

- **Oral cavity/oropharyngeal ulcer/mass:** Referral to specialist (OMFS or ENT) for endoscopy/biopsy
- **Caries or tooth pain:** Dentist; severe dental infection: E.g., facial swelling, trismus; (suggestive of deep neck space infection, can develop acute airway compromise) → ED for ENT/OMFS eval (*Emerg Med Clin North Am* 2000;18:481)

# OTITIS

## OTITIS EXTERNA

### Background (*Otolaryngol Head Neck Surg* 2006;134:S4)

- **Definition:** Inflammation of the external ear canal, often w/ infection, that may be acute (AOE <6 wks), subacute (6–12 wks), or chronic (>3 mos)
- **Microbiology:** Primarily bacterial (98% in North America) in origin (*P. aeruginosa, S. aureus*), fungal "otomycosis" (aspergillus, candida); viral (VZV, HSV)
- Lifetime incidence 10%; Often inciting traumatic or swimming event; ↑ incidence in summer
- **Risk factors:** Eczema of auditory canal, swimmers, humid environment, poor production or removal of ear wax, narrow auditory canals, hearing-aid use, mechanical trauma (including scratching/instrumentation of ear canal w/ cotton swab)

### Evaluation (*Otolaryngol Head Neck Surg* 2006;134:S4; *AFP* 2012;86:1055)

- **History:** Otalgia (70%), itching (60%), fullness (20%), ± hearing loss, ± jaw pain, ± vertigo; assess for risk factors (above)
- **Exam:** Tenderness of tragus/pinna, ear canal edema or erythema, ± otorrhea, ± regional LAD, ± TM erythema or cellulitis of the pinna
- **Red flags:** (Suggest necrotizing infection) pain/HA out of proportion to exam, fever, granulation tissue at cartilaginous bony junction
- **Ddx:** Otitis media w/ perforation (see below); atopic or contact dermatitis, psoriasis, seborrheic dermatitis, acne, SLE (rare); assess

for other skin conditions

## Treatment (*Cochrane Database Syst Rev* 2010:CD004740)

- **General approach:** If able to visualize intact TM, gentle ear cleaning w/ warmed 3% hydrogen peroxide, followed by otic gtt; avoid topical anesthetics (can mask sx of progression), PO analgesia prn
- **Topical otic agents:** Steroids, antiseptic, antibacterial, antifungal, & combination available; no difference shown between agents for empiric Rx; generic 2% acetic acid typically effective; apply TID–QID × 7–14 d; tilt head away from affected ear, instill 3–4 drops, light tragal massage w/ 10 mins of head tilt
- **Counseling:** Keep ear dry for 7 d, including no swimming; If water cannot be avoided, recommend cotton in ear coated on outside w/ petroleum jelly to keep dry; may take 1–2 wks to resolve; f/u (call vs. visit) if not improving w/in 3 d → ENT referral
- **Necrotizing (malignant) otitis externa:** Osteitis of temporal bone, can be life-threatening; almost always Pseudomonas; ↑ risk in immunosuppressed pts; *hx/PE:* See "Red Flags" above; *Mgmt:* ✓ CBC, ESR, Glu, Cr, culture canal, & CT of temporal bone, urgent referral → ED for IV, topical abx ± surgical debridement (*Lancet Infect Dis* 2004;4:34)
- **When to refer: For complicated OE** (beyond ear canal, DM, HIV, immunocompromised, prior ear surgery), if **not improving w/in 3 days,** or **malignant otitis externa**

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# Otitis Media

## Background (*JAMA* 2010;304:2161; *NEJM* 2002;347:1169)

- **Definitions:** *Acute otitis media (AOM):* is clinical dx, defined by acute onset of sx, e/o effusion & inflammation of middle ear;
  *Otitis media with effusion (OME):* Fluid without e/o infection, 2/2 URI ± Eustachian tube dysfunction
- **Microbiology:** Most commonly bacterial (*S. pneumoniae* > *H. influenzae, M. catarrhalis*)
- **Pathophysiology:** Viral infection of nasopharynx → Eustachian tube dysfunction → ↓ clearance of viruses & bacteria that reach middle ear

→ bacterial replication

- **Epidemiology/risk factors:** Incidence greatly ↓ w/ age, ↑ risk if: hx previous acute OM, recent viral URI or sinus infection, hx Eustachian tube dysfunction, AR, anatomical ear abnormalities (i.e., Down syndrome), immunosuppression, presence of OM w/ effusion

## Evaluation (*JAMA* 2010;304:2161)

- **History:** Duration, pain, fever, recent URI sx, presence of risk factors (above)
- **Exam:** For acute OM, pneumatic otoscopy must show e/o **fluid** in middle ear (bulging TM, ↓ or absent mobility, abnl TM opacity, air–fluid level) **& inflammation** of TM (erythematous patches or streaks, ↑ vascularity)
- **Red flags:** Pain/swelling over mastoid, bloody otorrhea, facial weakness, vertigo, nystagmus, HA, neck pain, photophobia

## Treatment (*JAMA* 2010:304:2161; *NEJM* 2002;347:1169; *Cochrane Database Syst Rev* 2013:CD000219)

- **General approach:** No large RCTs/guidelines in adults; abx can → significant clinical improvement by d 3 in children; APAP, NSAIDs prn for analgesia (*NEJM* 2011;364:116)
- **Antibiotics:** Amoxicillin 500 mg PO TID × 7–10 d (1st-line) or other *S. pneumo*-active Rx
- In pts in whom dx uncertain, afebrile, mild–mod disease, may consider "wait & see Rx": Give pt Rx, only to be filled if no improvement after 48–72 h (*JAMA* 2006;296:1235)
- **OME:** Neither abx nor decongestants shown to be helpful; >70% resolve in 4 wks; if persistent >3 mos → ENT referral (*Cochrane Database Syst Rev* 2012;9:CD009163)

## When to Refer

- Recurrent OM (>2 episodes/6 mos), OME lasting >3 mos or w/ TM perforation; unilateral persistent OME or otalgia (ENT exam to r/o nasopharyngeal tumor), AOM complications (TM perforation, mastoiditis, labyrinthitis, facial palsy, meningitis)

## Patient Information

- **Otitis externa:**
  www.nlm.nih.gov/medlineplus/ency/article/000622.htm,
  www.aafp.org/afp/2001/0301/p941.html

# RED EYE

## Background (*Fam Med* 1991;23:544)

- **Epidemiology:** 2% of all primary care visits include eye complaints (eye irritation > FB/trauma > eyelid complaints); many of these pts' chief complaint is "red eye"
- **Etiologies:** In US pts presenting to PCP, final dx conjunctivitis (52%) > superficial trauma/corneal abrasion (10%) > eyelid complaints (8%)

## Evaluation

- **History:** Onset, duration, sick contacts, seasonal allergies, trauma, eye drop use, contact lens use (e.g., sleeping in lens, failure to change regularly), prior eye surgery
- **Symptoms:** Uni- or bilateral, vision change, pain, irritation, FB sensation, discharge (severity & quality), pruritus, photophobia
- **Exam:** VA in each eye, level of discomfort & photophobia, presence of lid edema and/or discharge, diffuse or focal conjunctival hyperemia, pupillary reaction, EOM, corneal clarity, anterior chamber abnormalities (*hypopyon:* layering leukocytic exudate; *hyphema:* clotted or layering heme); preauricular LAN (see *"Vision Complaints" for full ophthalmologic exam*)

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## DIAGNOSIS AND MANAGEMENT

## General Guidelines for Management and Referral

- Initial management by PCP often appropriate; routine referral → ophtho if sx >3–4 wks
- **Red flags for vision-threatening etiologies:** Severe pain & photophobia, significantly ↓ vision relative to baseline or worse than 20/200, recent eye surgery or trauma, abnl pupil exam, corneal opacities, acute sx onset in a contact lens-wearer (*Cleve Clinic J Med* 2008;75:137)
- **Urgent referral for red flags & vision-threatening etiologies** (below) & consider for severe sx, diagnostic uncertainty, & recurrent

disease

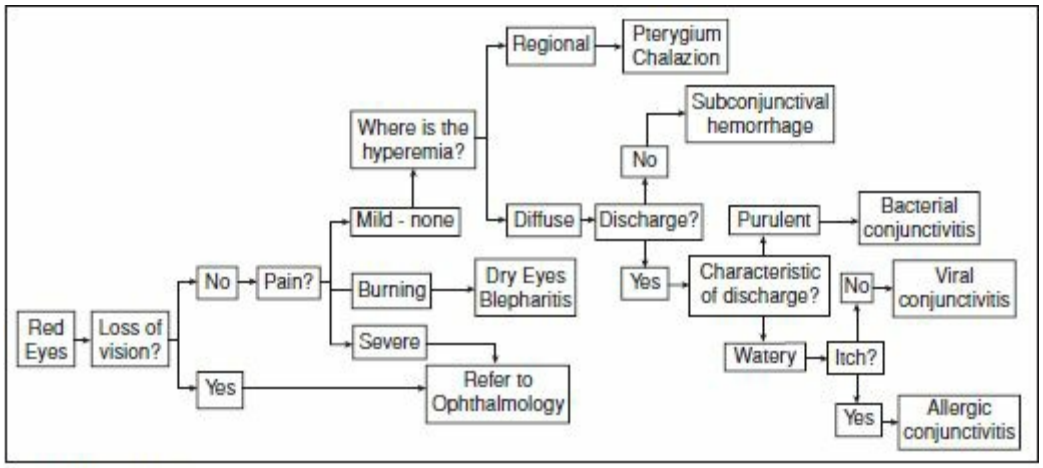
- Avoid topical NSAIDs & steroids w/o ophthalmology guidance due to potential s/e
- Avoid topical aminoglycosides due to corneal toxicity

**Common Causes of Red Eye**

| | |
|---|---|
| **Conjunctivitis** | *Findings:* Uni- or bilateral, diffuse hyperemia, d/c<br>*Rx:* See subsection below |
| **Subconjunctival hemorrhage** | *Etiologies:* Valsalva, eye rubbing, HTN, bleeding dyscrasia, anticoagulant use, idiopathic<br>*Findings:* Painless, usually unilateral, no vision change; nl pupils, cornea; well-demarcated plane of heme obscuring sclera<br>*Rx:* Artificial tears prn discomfort, check BP, check PLT & coags if recurrent, **urgent referral if follows significant trauma** |
| **Hordeolum ("stye")** | *Findings:* Lid erythema, typically focal palpable and/or visible tender nodule; ± conjunctival hyperemia, drainage, cellulitis<br>*Etiology:* Acute lid inflammation due to occluded Meibomian gland; if chronic → chalazion<br>*Rx:* Warm compresses QID, erythromycin oint BID, oral abx if cellulitis present (see Skin and Soft Tissue Infections) |
| **Blepharitis** | Chronic b/l lid margin inflammation → Chronic burning, itching, mild AM lid crusting, minimal d/c, sx worse in AM, dandruff-like flakes on lashes, mild diffuse hyperemia<br>*Rx:* Warm compresses BID, artificial tears prn, erythromycin oint BID if sev |
| **Dry eye syndrome** | *S/sx:* Bilateral burning, FB sensation, ↑ by wind/cold & prolonged eye use, ± reflex tearing; mild diffuse hyperemia, sx severity disproportionate to exam findings<br>*Etiologies:* ↓ Tear production or ↑ evaporation from altered composition; idiopathic, autoimmune, or 2/2 meds, abnl lids<br>*Rx:* Artificial tears QID, artificial tear gel QHS |

- **Other: Inflamed pterygium:** ± hx UV/sun exposure; irritation, FB sensation; *Findings:* Wing of hyperemic thickened tissue from conjunctiva (often nasal) → cornea; *Rx: UV protection*, artificial tears prn, referral if persistent

  **Episcleritis:** Idiopathic, self-limited unilateral, painless focal erythema, no pain, d/c, or vision change; *Findings:* Mild hyperemia of superficial vessels that moves w/ cotton swab, blanches w/ topical phenylephrine 2.5%; *Rx:* Artificial tears, referral if persistent www.aao.org/theeyeshaveit/red-eye/index.cfm)




(*AFP* 2010;81:137)

Figure **10-1** Diagnostic algorithm for red eye

## Vision-threatening Etiologies

| | |
|---|---|
| **Keratitis (corneal inflammation)** | *S/sx:* Unilateral pain & photophobia, tearing, ± ↓ vision, diffuse hyperemia<br>*Bacterial:* **Corneal opacity often visible w/ penlight**, ± mucopurulent d/c, ± hypopyon, often hx contact lens use<br>*Herpetic:* **Vesicles in V1 dermatome on affected side** (VZV), ± lid vesicles or hx oral lesions (HSV), corneal dendrites w/ fluorescein & Wood lamp → same-d referral |
| **Iritis** | *S/sx:* Typically unilateral, severe photophobia, ↑ tearing, ↓ vision, hyperemia of limbal vessels (immediately adjacent to cornea), sluggish pupillary reaction → Refer w/in 24 h |
| **Acute angle closure glaucoma** | *S/sx:* Sev unilateral eye pain & HA, halos around lights, N/V, ↓ vision, fixed & mid-dilated pupil, ± cloudy cornea, noticeable difference in firmness of globes to palpation through lids → same-d referral |
| **Endophthalmitis** | *RF:* Hx eye surgery, immunosuppression, IVDU, trauma, systemic bacteremia<br>*S/sx:* Severe pain, ↓ vision, variable degrees of conjunctival injection, + hypopyon → same-d referral |
| **Orbital cellulitis** | *RF:* Hx sinusitis, orbital trauma, facial surgery<br>*S/sx:* ± Diplopia, pain w/ EOM, HA, ± nasal congestion, ± fever, lid edema & erythema, ↓ vision, proptosis, ↓ motility<br>*Rx:* Orbital CT w/ contrast, CBC, **same-d referral** |
| **Myositis/idiopathic orbital inflammatory pseudotumor** | *S/sx:* Acute/subacute onset, ± ↓ vision, ± diplopia, ↓ motility, pain w/ EOM, proptosis<br>*Rx:* Orbital CT w/ contrast, **referral w/in 24 h** |
| **Scleritis** | Immune-mediated vasculitis, 50% assoc w/ systemic autoimmune dz<br>*S/sx:* **"Boring" HA-like pain**, nonblanching/violaceous injection of deep scleral vessels, globe tender to palpation, pain w/ EOM, wakes pt from sleep, vision change rare<br>*Rx:* Oral NSAIDs, **referral w/in 24 h** |

- Chemical splash, penetrating trauma, corneal trauma (see *"Eye Injury"*)

## Evaluation

- **Background:** Viral > bacterial, although difficult to distinguish clinically; culture not needed for routine cases; consider if severe purulence, recurrent disease, or if no improvement either after 7–10 d or after course of topical abx
- **Viral:** *Microbiology:* Frequently adenovirus, highly contagious; *hx:* ± Sick contact, URI sx, watery d/c, gritty sensation, mild photophobia, itching, crusty eyelids, unilateral can → bilateral; *Exam:* Diffuse hyperemia, seromucoid d/c, preauricular LAD common
- **Bacterial:** Acute *microbiology:* Typically *S. pneumoniae*, *S. aureus*, or *H. influenzae*, contagious; *Exam:* Unilateral, thick/purulent d/c; intense hyperemia, LAD rare
  **Hyperacute:** Severe, sudden variant of above, typically *N. gonorrhoeae;* **referral w/in 24 h** as ↑ risk of corneal perforation; **chronic:** Duration wks–mos, usually *C. trachomatis*, suspect if no improvement w/ ocular abx
- **Allergic** (*J Allergy Clin Immunol* 2000;106:1019): Commonly occurs w/ AR; *Precipitants:* Ragweed, grass pollen common; *hx:* chronic or seasonal pattern, hx atopy, "watery" d/c, severe pruritus; *Exam:* b/l, mild hyperemia, serous/stringly d/c

## Treatment (http://one.aao.org/CE/PracticeGuidelines/PPP.aspx)

- **Counseling:** No contact lens wearing while sx present if infectious etiology; if infectious, good hand hygiene to ↓ risk of transmission (including unaffected eye if unilateral)
- **Viral or mild bacterial:** Mostly self-limiting; cool compresses & artificial tears prn; may consider 0.5% erythromycin oint QID × 7 d
- **Mod–severe bacterial:** Broad-spectrum topical abx offer slight improvement in time to remission (e.g., Ofloxacin 0.3% 1 gtt QID × 7 d or Polytrim 1 gtt QID × 7 d) (*Cochrane Database Syst Rev* 2012;9:CD001211)
- Additional indications for broad-spectrum topical abx: Consider if persistent sx >1 wk, immunocompromised status, health care worker, or tx prerequisite to return to work/school

- **Allergic:** Avoidance of allergens when possible, artificial tears prn; OTC topical antihistamines gtt & mast-cell stabilizers (e.g., ketotifen 1 gtt OU BID until sx resolve), artificial tears prn (*see "Allergic Rhinitis"* for systemic tx)

# SINUSITIS

## Background (*Otolaryngol Head Neck Surg* 2007;137:S1)

- Symptomatic inflammation of the nasal cavity & paranasal sinuses, characterized by purulent nasal discharge, accompanied by sx of nasal obstruction (congestion, ↓ airflow), and/or facial pain (anterior, periorbital, or can manifest as HA)
- >12% of US adults have received sinusitis dx in the past year; accounts for >11 million health care visits annually (*Vital Health Stat* 2012;10:256)
- **Most commonly viral (sinus disease occurs w/ majority of URI)** & self-limited; however, 2% of viral ARS is complicated by bacterial infection (*Clin Infect Dis* 1996;23:1209)
- Bacterial complications rare (1/10,000 cases); orbital (orbital cellulitis or abscess) & CNS (meningitis or epidural abscess) most common

### Rhinosinusitis Definitions and Cardinal Features (*Otolaryngol Head Neck Surg* 2007;137:S1–S31)

| Term | Definition |
|---|---|
| **Viral Rhinosinusitis (VRS)** | S/sx present <10 d, w/o worsening<br>Sinus involvement in ~87% of URI (*NEJM* 1994;330:25)<br>Major pathogens: Rhinovirus, parainfluenza, or influenza |
| **Acute Bacterial Rhinosinusitis (ABRS)** | ≤4 wks of sx; clinically distinguished from VRS by sx that are:<br>**Persistent:** >10 d w/o improvement<br>**Severe:** Temp >102°F, severe facial pain **or**<br>**Worsening:** "Double-sickening": 5–6 d of typical URI, initially improving → new onset of fever, HA, ↑ nasal d/c<br>*Major pathogens: S. pneumoniae* & H. flu (75%), *M. catarrhalis*<br>Most commonly complication of VRS<br>*RFs:* Include allergy, mechanical obstruction of the nose, swimming, odontogenic infection, intranasal cocaine, impaired mucociliary clearance (CF, cilial dysfunction, smoking) |
| **Recurrent Acute Rhinosinusitis** | ABRS occurring ≥4 times/yr **w/o** s/sx of rhinosinusitis btw episodes; each episode must meet ABRS diagnostic criteria |

- **Chronic rhinosinusitis:** ≥12 wks of inflammation documented by imaging and/or rhinoscopic exam (edema, polyps, purulent mucus) and ≥2 of the following:
  (1) Mucopurulent drainage (anterior, posterior, or both)
  (2) Nasal congestion
  (3) Facial pain/pressure/fullness
  (4) ↓ sense of smell (hyposmia)
- **Invasive fungal:** *Risk factors:* DM, immunosuppression; commonly mucor, rhizopus, aspergillus **can be fulminant** (acutely ill, facial pain, dark/necrotic turbinates = surgical emergency → ED) **or chronic** (sx more indolent but includes red flags (orbital/CNS complaints), fetid smell, facial pain; consider in **all** immunocompromised pts or those w/ chronic sinusitis → ENT/ID referral (*Otolaryngol Clin North Am* 2000;33:367; *NEJM* 1997;337:254)

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## Acute Rhinosinusitis

### Evaluation (*NEJM* 2004;351:902)

- **History:** Nasal congestion, purulent nasal discharge (yellow/green/thick), facial pain/pressure, hyposmia/anosmia, tooth discomfort (Se/Sp 66%/49%), cough, HA, fever, malaise, halitosis, ear pressure/fullness
- **Physical:** Purulence of nasal cavity/posterior pharynx (Se/Sp 35%/78%), nasal turbinate edema, ↑ pain w/ leaning forward (Se/Sp 75%/77%)
- **Acute differential diagnosis:** URI, noninfectious rhinitis (see *"Allergic Rhinitis"*), HA (migraine, tension, cluster), odontogenic pain (see *"Jaw and Dental Pain"*)
- **Red flags** (suggest complicated or severe disease): High fevers, (>102°F), severe HA, eyelid edema/erythema, proptosis, visual changes, diplopia, ophthalmoplegia, ΔMS, stiff neck → send to ED/ENT
- **Imaging:** Sinus CT w/ contrast indicated in complicated ARS, tx-resistant or CRS, or if concern for neoplasm or other noninfectious cause of facial pain

## Treatment (*J Fam Pract* 2002;51:1049)

- **Symptomatic:** Recommended in both VRS & bacterial rhinosinusitis & includes *Analgesics/antipyretic:* APAP, NSAIDs
  *Oral decongestants:* Pseudophedrine, phenylephrine
  *Saline rinses:* Neti pot, nasal irrigation; → ↓ need for pain medication & ↑ comfort
  *Topical decongestants:* Oxymetazoline, neosynephrine; limit to 3 d to avoid rebound
- **Antihistamines** (i.e., loratadine, fexofenadine, cetirizine) if underlying allergy present showed to reduce rhinorrhea & nasal obstruction (*Allergy* 1997;52:650), no studies of efficacy for acute rhinosinusitis
- **Intranasal steroids:** Moderate benefit in acute setting, meta-analysis found sx benefit w/ NNT = 15 (*Cochrane Database Syst Rev* 2009;CD005149)
- **Antibiotics:** Ineffective against viral sinusitis & potential harm; for bacterial disease, data mixed re: effectiveness (likely in part 2/2 inclusion of VRS in trials → ↓ est of tx effect); overuse major contributor to abx resistance; however, can ↓ risk of serious complications, particularly in immunocompromised or comorbidities
  *Mild illness* (e.g., T <101°F) *or dx uncertain:* Reasonable to prescribe watchful waiting; initiate abx if no improvement after 3 d (consider "Wait and see" Rx (see *"Otitis")*
  *Mod illness, or mild illness in immunocompromised/comorbid conditions:* Empiric tx (table)
  *Severe illness, esp in immunocompromised host:* Referral (below)

**Antibiotic Therapy for Acute Bacterial Rhinosinusitis (*Clin Infect Dis* 2012;54:e72)**

| Antibiotic | Comments |
|---|---|
| **Amoxicillin/Clavulanate** 875/125 mg BID × 5–7 d | **1st line** (rather than amoxicillin) based on ↑ *H. flu* resistance to amox; evidence primarily in children; ↑ cost & ↑ risk of diarrhea |
| **High-dose Amoxicillin/ Clavulanate** 2 gm BID × 7–10 d | 1st line for pts from regions (≥10%) of invasive PCN-resistant *S. pneumo*, those w/ severe infection (e.g., e/o systemic toxicity w/ T ≥102°F, threat of suppurative complications), age >65 y, recent hospitalization, abx use w/in the past mo, or immunocompromised |
| **Doxycycline** | 1st line in PCN allergy 100 mg Q12h d 1, then 50 mg Q12h, 5–7 d |
| **FQs:** Levofloxacin 500 mg QD × 5–7 d, Moxifloxacin 400 mg QD × 7–10 d | 2nd line (PCN allergy); no evidence for ↑ efficacy over β-lactam; ↑ s/e |
| **Other** (TMP–SMX, macrolide, 2nd/3rd gen cephalosporin) | Avoid empiric use given ↑ resistance to *S. pneumo* (&, for TMP–SMX, to *H. flu*) |

## When to Refer (*Clin Infect Dis* 2012;54: e72)

- **Emergency department:** If suspect complications → ED for urgent CT w/ contrast, initiation of abx, & ENT eval, ophthalmology, possible neurosurgery consultation
- **Infectious disease:** Immunocompromised, multiple limitations on tx options or hx unusual organisms
- **Otolaryngology or allergy/immunology:** Recurrent ARS, CRS, AR pts who may be candidates for immunotherapy (see *"Allergic Rhinitis"*)
- **Treatment failure:** If pt worsens or fails to improve w/ initial mgmt at 5 d after initial eval, reassess & exclude other causes of illness, detect complications → ENT referral (if dx uncertain/cultures desires), allergy (if allergy suspected), or ID (if resistance suspected, immunocompromised host)

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# CHRONIC RHINOSINUSITIS

- **History:** **≥12 wks** nasal obstruction, facial congestion–pressure–fullness, discolored nasal d/c, & hyposmia; persistent unilateral sx should ↑ concern for neoplasm
- **Risk factors:** Allergy, CF, immunocompromised state, immunodeficiency (CVID, IgA deficiency), ciliary dyskinesia, Samter triad
- **Differential diagnosis:** AR, nonallergic rhinitis, septal deviation, nonrhinogenic facial pain; neoplasm

- **Evaluation: All pts w/ sx of chronic sinusitis merit CT imaging & ENT referral** for nasal endoscopy, ± allergy/immunology eval if hx consistent
- **Treatment:** (Once confirmed) intranasal corticosteroids, nasal irrigations, allergen control & reduction (antihistamines, allergen immunotherapy, avoidance measures), consider surgical tx in refractory disease (*Otolaryngol Head and Neck Surg* 2007;137:S1)

# SNORING

## Background (*J Clin Sleep Med* 2012;8:597; *JAMA* 2004;291:2013)

- **Snoring: Sound produced by turbulent airflow through upper airways during sleep**
- 30–50% of the adult population snores, occasional snoring near-ubiquitous; most people who snore do **not** have OSA, but OSA is assoc w/ snoring (see *"OSA"*)
- Snoring can occur w/o e/o ↑ airway resistance, but is also assoc w/ OSA & multiple other medical d/o, which should be considered if pt p/w this complaint
- **Etiologies:** Often idiopathic, but can be 2/2 **structural abnormalities** of upper airways (deviated septum, nasal congestion, turbinate or tonsillar hypertrophy, elongated soft palate/uvula, macroglossia), **obesity**, & **endocrinopathies** (hypothyroid, acromegaly)
- **Risk factors:** ♂ gender, obesity, ↑ neck circumference, enlarged turbinates, small chin/retrognathia, **EtOH**, tobacco, respiratory depressant medications, ⊕ FHx

## Evaluation (*NEJM* 2002;347:498; *Otolaryngol Head Neck Surg* 2011;145:S1)

- **History: Assess for e/o poor sleep quality:** Daytime somnolence, impaired school/work performance, MVCs; **apnea/hypopnea;** ask bed partner about sleep behavior, witnessed apnea or "choking" episodes; **snoring severity:** How often, how much, how loudly (*Otolaryngol Head Neck Surg* 2008;139:615); **medications** (resp depressants, hypnotics); **social hx** (EtOH, tobacco)
- **Exam:** Alertness, habitus (**BMI** ≥30 → ↑↑ risk OSA), wide neck

circumference

*Nasal exam:* ± Septal deviation, turbinate hypertrophy, polyps, nasal valve collapse

*Oropharyngeal exam:* ± Low-laying palate, elongated uvula, obstructive tonsils, large base of tongue; *Maxillo/mandibular bony anatomy:* Micro/retrognathia, malar insufficiency

## Treatment

- **Further studies:** If ↑ suspicion for OSA (↑ BMI, severe snoring, hx apneic episodes) → polysomnography; can dx OSA, determine severity of snoring & distinguish btw central vs. obstructive apneas; will guide tx (see *"OSA"*); further w/u dictated by hx
- If no e/o sleep apnea, snoring tx may be indicated for pt & bed partner comfort
- **Lifestyle modifications:** Wt loss, ↓ /avoid EtOH or other respiratory depressants; free, effective, accompanied by other health benefits
- **Treatment** of nasal concerns contributing to upper airway resistance (see *"AR" & "Sinusitis"*); may consider trial of external nasal dilators (e.g., nasal adhesive strips)
- **ENT referral** for fiberoptic naso/hypopharyngeal exam if suspect structural abnormalities or if failed medical management; pt may be candidate for oral appliances or surgical approaches

# VISION COMPLAINTS

## Background *JAMA* 2004;291:1487)

- 40% of vision loss is preventable; PCPs in unique position to emphasize prevention, manage modifiable risk factors, & recognize need for referral
- **"Legal blindness":** Corrected VA 20/200 or worse in better eye ***or*** visual field <20 degrees in better eye
- **Screening** (See *AAO PPP Guidelines* 2010; aao.org/ppp)
  *If ⊕ glaucoma RF:* Age 40–54 y q1–3y, 55–64 q1–2y, & >65 y q6–12mos
  *If DM:* Dilated exam at dx (T2DM) or 5 y s/p dx (T1DM), then yearly

## Focused Ophthalmic History

- **Age:** Relevant in narrowing Ddx (e.g., GCA unlikely if <50 yo)
- **Ocular history:** Trauma, eye surgery, contact lens use, family ocular hx
- **Symptoms:** Gradual vs. sudden onset, monocular vs. binocular, duration, quality, similar prior episodes, painful vs. painless vision change
- **Associated systemic symptoms:** E.g., HA, fever, rash, arthralgia
- **Medications:** See "Gradual painless decreased vision" below

## Ophthalmologic Exam

- **Visual acuity:** Measure in each eye; if worse than 20/40, re-measure w/ pinhole (refractive error typically improves); if unable to read chart, document as follows: CF (can count fingers at *x* feet) > HM (hand motion) > LP (light perception) > NLP (no light perception)
- **Confrontational visual field:** Assess all 4 peripheral quadrants in each eye separately; field loss can suggest optic nerve pathology or retinal detachment (RD)
- **Pupils:** Symmetry of size & reactivity; test for RAPD w/ "swinging flashlight test": Hold penlight on 1st eye for 2–3 s then rapidly switch to the 2nd; pupil of 2nd eye should stay stable or constrict; dilation indicates afferent defect of 2nd eye ("perceives" less light)

- **Extraocular movements:** Full & conjugate
- **Anterior segment:** Eval w/ penlight for lid changes, conjunctival hyperemia or hemorrhage, corneal opacity or epithelial defect (+ fluorescein staining), anterior chamber (see *"Red Eye"*), iris (irregular shape, obvious defects), lens (visible opacity)
- **Posterior pole:** Direct ophthalmoscopy to assess vitreous clarity (e.g., able to visualize nerve?) & eval for optic nerve edema, cotton wool spots, peripapillary/retinal hemorrhage

## Common Ocular Complaints

**Differential of Common Ocular Complaints**

| | |
|---|---|
| **Blurry vision** | See subsections below |
| **"Flashing lights" or "floaters"** | Retinal detachment or tear: see below, posterior vitreous detachment |
| **Double vision** (see *"Diplopia"*) | Critical to establish whether persists w/ one eye covered<br>*Monocular:* Refractive error, cataract, epiretinal membrane, tear film/ocular surface issues; **nonurgent referral**<br>*Binocular:* Suggests neurologic etiology |
| **Droopy lid** | CNIII palsy, Horner syndrome, MG, age-related muscle dehiscence |
| **Periorbital & lid swelling** | Trauma, preseptal/orbital cellulitis, allergy, stye (see *"Red Eye"*) |
| **"Large" or bulging eye** | Proptosis vs. lid retraction; orbital cellulitis or inflammation (e.g., thyroid, sarcoid, Wegener's), neoplasm, vascular, trauma |

## Acute Painless Vision Loss

- **Requires same-day ophthalmology evaluation;** usually unilateral; n.b. gradual monocular vision loss may be perceived as "sudden" due to inadvertent occlusion of other eye; obtain careful hx
- **Differential diagnosis: GCA/temporal arteritis** (suspect if >50 y w/ new HA or diplopia; ⊕ systemic sx)—p/w amaurosis fugax, diplopia; empiric tx w/ PO corticosteroids & schedule temporal artery (see "PMR")

  **Nonarteritic ischemic optic neuropathy** (Mean age 60, ↑ in vasculopath, PDE5 use) p/w painless vision loss, ⊕ RAPD, sectoral optic disc hemorrhage

  **Central retinal artery occlusion** (Vasculopath, postcardiac surgery, 5–10% assoc w/ GCA)—p/w sudden vision loss, ⊕ RAPD, ± amaurosis fugax → ED for stroke w/u

**Central retinal vein occlusion** (hx PAD, hypercoagulability, hyperviscosity, glaucoma, vasculitis); meds (e.g., OCPs); p/w variably ↓ VA, ± RAPD, + diffuse intraretinal hemorrhages

**Vitreous hemorrhage:** Commonly due to DM or RD/retinal tear; VA variable

**Retinal detachment:** Findings vary, can include flashing lights, floaters, variable VA/visual field loss, abnormal red reflex

## Acute Painful Vision Loss

- **Optic neuritis:** Typically unilateral w/ age <50 y; Etiologies include MS, idiopathic, infectious (e.g., postviral, Lyme), & granulomatous (e.g., sarcoidosis)
  *Hx:* Pain w/ eye movement; ± rash, fever, arthralgia, numbness, & weakness
  *Exam:* VA variable, dyschromatopsia, + RAPD, ± optic disc edema
  *Tx:* **Refer w/in 24 h;** needs MRI, LP, ± steroids, ± lab w/u
- **Also see *"Red Eye"* & *"Eye Trauma"* for further discussion**

## Gradual Painless Decreased Vision

- Uni- or bilateral; routine referral appropriate if loss over months-years
- **Refractive error (improves w/ pinhole):** Myopia, hyperopia, astigmatism, presbyopia (>40 y old)
- **Cataract** (lens opacification): Age-related (most common), metabolic, traumatic, congenital
- **Open-angle glaucoma:** Asx peripheral vision loss often w/ ↑ IOP & ↑ cup:disk ratio; *RF:* ↑ Age, African-American ethnicity, ⊕ FHx, ocular HTN, myopia
  *Screening:* Refer if age >40 & 1st-degree relative w/ glaucoma; progression can be slowed/halted w/ proper tx, so timely referral key
- **Diabetic retinopathy:** Initially asx → leading cause of legal blindness among working-age Americans; *RF:* ↑ Severity of hyperglycemia, ↑ disease duration, HTN, ↑ lipids; *Tx:* Strict BP/glucose control, laser & anti-VEGF Rx if severe
- **Age-related macular degeneration:** ↓ Central vision; most common cause of blindness in US (*Arch Ophthalmol* 2004;122:477); *RF:* **tob,** ↑

age, ⊕ FHx *Tx:* See Ophtho for Amsler grid, AREDs Vits, & anti-VEGF Rx if "wet"

- **Medications:** Cataracts/glaucoma (steroids), optic neuropathy (ethambutol, amiodarone), maculopathy (hydroxychloroquine) (*Drug Safety* 2008;31:127)
- **Idiopathic intracranial hypertension (pseudotumor cerebri):** ♂ > ♂
  *RF:* Obesity, steroid use & cessation, high-dose Vit A, tetracyclines, OCPs
  *Sx:* Transient visual obscuration, diplopia, positional HA, pulsatile tinnitus, N/V
  *Findings:* Variably ↓ VA, ± 6th nerve palsy, bilateral optic nerve edema
  *Tx:* **Referral w/in 24 h;** see "Neurology", *"Headache"* for more details
- **Amblyopia:** Unilateral chronic ↓ VA due to asymmetric childhood cortical visual input; if mild, may not be detected until adulthood *Tx:* Routine ophthalmic referral

## Patient Information

- **Driving guidelines:**
  www.mdsupport.org/library/drivingrequirements.html
- **Patient resources:**
  www.aao.org/practice_mgmt/patient_ed/resource.cfm

# ATTENTION DEFICIT HYPERACTIVITY DISORDER

## Background (*AFP* 2012;85:890; *Am J Psychiatry* 2006;163:716; 1730; 2059)

- **Definition:** Impairment in ≥2 life settings (school, work, home, social) due to persistent sx of inattention, impulsivity, and/or hyperactivity since childhood (age of onset ↑ from 7 to 12 in DSM-5) and sx not caused by another med or Ψ condition; determination of functional impairment is highly dependent upon contextual factors; ∴ dx & indications for tx need to be determined on an individual basis
- **Epidemiology:** 7–9% of children & 4–5% of adults; assoc w/ educational/occupational underperformance; poor relationships w/ peers, family members, & authorities; ↑ traffic violations, accidents, & injuries; ↑ rates of substance misuse
- **Differential diagnosis:** Depression, anxiety, panic, mania/hypomania, substance use/withdrawal; ADHD is distinct in that sx are present since childhood & persist during noncomorbid periods

## Evaluation (*JAMA* 1998;280:1086)

- **History:** Adult ADHD Self Report Scale is a useful screening tool for adults (available online); interview pt & collateral sources about sx in past 6 mos & childhood; screen for RFs for SCD if treatment with stimulants planned (see *"Sudden Cardiac Death"*), substance abuse (see *"Substance Use Disorders"*), & comorbid psych conditions; review steroid, nicotine, caffeine use
- **Labs:** Consider TSH, urine drug monitoring if prescribing stimulants
- **Neuropsych testing:** Helpful for eliciting learning disabilities or cognitive impairments, but not necessary for dx (*Clin Psychol Rev* 2006;26:466)

## Treatment (*JAMA* 2004;292:619; *NEJM* 2005;352:165)

- **General approach:** Treatment should be initiated by providers confident of dx and comfortable with Rx options; **comanagement w/psychiatry** is typical
- **Stimulant treatment:** 1st-line if no contraindicating conditions; greater effect size than nonstimulant treatments (*Med Gen Med*

2006;8:4); long-acting preparations preferred due to ease of dosing & lower likelihood of abuse (*J Am Acad Child Adolesc Psychiatry* 2008;47:21; *Prim Care Companion CNS Disord* 2011;13:pii); avoid w/ MAOI antidepressants; serum levels of some agents may be ↑ by treatments that lower acidity (e.g., PPI)

**Side effects:** Distressing thoughts/feelings, insomnia, anorexia, catecholaminergic effects (↑ HR 3–10 bpm, ↑ SBP 3–8 mmHg, ↑ DBP 2–14 mmHg, & ↑ cardiac contractility) mild in most pts, but monitor VS to screen for outliers

**Risk factors for misuse:** Caucasian, fraternity/sorority membership, lower GPA, immediate-release (vs. ER) (*J Am Acad Child Adolesc Psychiatry* 2008;47:21)

- **Nonstimulant treatment:** Preferred in pts w/ substance use disorders; atomoxetine only FDA-approved member of this class for tx of ADHD, though bupropion has demonstrated efficacy (*Biol Psychiatry* 2005;57:793). Evidence supports off-label use of TCAs (desipramine, imipramine), but may be limited by s/e profile
- **Cardiac considerations:** Risk of sudden cardiac death in both stimulant & atomoxetine tx may be ↑ in pts w/ pre-existing structural heart defects (*Circulation* 2008;117:2407), but little evidence for serious CV events, incl. MI, stroke, & death in healthy pts (*JAMA* 2011;306:2673; *NEJM* 2011;365:1896)

**ADHD Pharmacotherapy**

| Generic (Brand Names), Daily Dose Range | Duration (h) |
|---|---|
| **Stimulants: Amphetamines** | |
| Dextroamphetamine (Dexedrine); 5–60 mg, divided BID-TID | 5 |
| Dextroamphetamine ER (Dexedrine spansules); 5–40 mg, divided QD-BID | 8 |
| Mixed amphetamine salts (Adderall); 5–40 mg, divided BID-TID | 5 |
| Mixed amphetamine salts ER (Adderall XR); 20–60 mg | 12 |
| Lisdexamfetamine (Vyvanse); 30–70 mg | 12 |
| **Stimulants: Methylphenidates** | |
| Methylphenidate IR (Ritalin); 10–60 mg, divided BID | 4 |
| Methylphenidate SR/ER (Metadate CD, ER, Ritalin SR, LA); 10–60 mg | 8 |
| OROS methylphenidate (Concerta); 18–72 mg | 12 |
| Dexmethylphenidate ER (Focalin XR); 10–30 mg | 12 |
| **Nonstimulants:** Atomoxetine (Strattera); 40–100 mg (not a controlled substance) | 24 |

(Adapted from *AFP* 2012;85:890)

- **Initiating/maintaining therapy:** At outset establish specific daily life

tasks that could benefit from Rx & track progress; frequent visits & gradual ↑ in dose (every few d–wks); monitor for s/e, use rating scales to monitor for response (stimulant effects may occur same day, nonstimulant effects may take days–wks)

- **Nonpharmacologic treatment:** Cognitive behavioral & group tx (*Am J Psychiatry* 2010;167:958; *JAMA* 2010;304:875), ADHD coaching, disability accommodations
- **Pregnancy/lactation:** Paucity of evidence; continue Rx only in severe cases; consider referral to perinatal psychiatrist
- **Patient information:** *JAMA* 2013;309:1843; chadd.org

# ALCOHOL USE DISORDERS

## Background (*NEJM* 2013;368:365)

- **Epidemiology:** 60–70% of US adults consume EtOH; EtOH use disorders affect 7–8% Americans, & cause 85,000 deaths/y (*NEJM* 2005;352:596; 2008;359:715)

**1 drink is 12–14 g EtOH (i.e., 12 oz beer, 5 oz wine, 1.5 oz spirits)**

| |
|---|
| **Risky drinking:** ♂ > 15 drinks/wk or > 5 drinks/occasion; ♀ > 8 drinks/wk or > 4 drinks per occasion; for pts >65 y cut-off the same as for ♀; binge drinking is > 5 drinks/occasion |
| **Alcohol use disorder (DSM-V):** Maladaptive pattern of EtOH use → clinically significant impairment or distress, as manifested by **2 (or more) of the following,** occurring w/in a 12 mo period (≥4 considered severe): **(1)** Failure to fulfill roles, **(2)** Use in risky situations, **(3)** Persistent desire/unsuccessful efforts to cut down, **(4)** Use despite known ⊖ impact on med/psych problems, **(5)** E/o tolerance, **(6)** Cravings, **(7)** ↑ doses or ↑ period than intended, **(8)** ↑ time finding, using, recovering, **(9)** E/o withdrawal, **(10)** Abandonment of other pleasurable activities, **(11)** Use despite adverse effects on social/interpersonal fxn |
| **Medical Consequences** |
| **Cardiac:** HTN, nonischemic dilated CMP, AF; EtOH ↑ HDL short-term; ~1–2 drink/d assoc w/ ~30% ↓ risk of CAD & ~18% ↓ mortality in observational studies (*Arch Int Med* 2006;166:2437); initiating moderate drinking not recommended as a CAD preventative strategy given risks/harm of EtOH & absence of randomized trials (*JAMA* 2010;303:2065) |
| **Hematology/oncology:** ↓ HCT, ↓ PLT due to $B_{12}$/folate deficiency, marrow suppression; Macrocytosis; some breast CA risk even at levels as low as 3 drinks/wk (*JAMA* 2011;306:1884); ↑ risk of oral, GI, & liver CA (*Lancet Oncol* 2009;10:1033) |
| **Neuro:** Korsakoff syndrome (memory deficits), Wernicke encephalopathy (encephalopathy, gait ataxia, oculomotor dysfunction), peripheral neuropathy, seizures |
| **Pregnancy:** Abstinence recommended; ↑ risk of stillbirth, low birth weight, fetal EtOH syndrome (growth problems, facial dysmorphia, CNS/cognitive problems) |
| **GI:** Cirrhosis, gastritis, hepatitis, pancreatitis; doubles risk of progression to cirrhosis in pts w/ Hep C (*Am J Gastroenterol* 2002;97:1807) |

## Evaluation

- **Screening: CAGE:** Screening for lifetime abuse/dependence; >1 (+) answer 85% sensitive, 78% specific; Have you ever felt you should **C**ut down on your drinking? Have you been **A**nnoyed by criticism of your drinking? Felt **G**uilty about your drinking or taken an **E**ye opener first thing in the morning? (*J Clin Epidem* 2004;57:30)
  **AUDIT (abbreviated):** "How many times in the past year have you had (5 for men, 4 for women) or more drinks in a day?" >1 episode is ⊕ for unhealthy EtOH use; 82% sensitive, 79% specific for risky drinking (*JGIM* 2009;24:783)
- **History:** Quantify drinking, reasons for drinking, screen for comorbid psych conditions (e.g., depression, trauma hx); sleep disturbances & erectile dysfunction assoc w/ EtOH use; review meds that interact assoc w/ EtOH (sedatives, APAP); assess safety (minors/elders dependent on pt, risk of driving, work hazards); assess readiness to change ("On a scale of 0–10, w/ 10 being completely committed to change, how ready are you to stop drinking? Why did you pick 7?") (*NEJM* 2013;368:365)
  **Family history:** ~50% of susceptibility to alcoholism thought to be genetic, prevalence higher w/ affected 1st-degree relative (*Curr Psych Rep* 2009;11:364)
  **Evaluation of consumption:** # of d/wk EtOH consumed, # of drinks consumed, max # of drinks on an occasion, # of d/mo of heavy drinking (*NEJM* 2013;368:365)
  **Evaluation of patients w/ EtOH use disorders:** Prior tx, other illicits, attempts to quit, duration of episodes of sobriety, environment where drinking occurs, triggers for relapse, consequences of drinking (*NEJM* 2013;368:365)
- **Physical:** Hepatomegaly, neuropathy, asterixis, stigmata of chronic liver disease (spider angiomas, caput medusa, splenomegaly, palmar erythema, ascites, jaundice)
  **Withdrawal:** Diaphoresis, tachycardia, tremors, nausea, hallucinations, seizures, psychoses, anxiety; sx present <6 h after EtOH cessation; delirium tremens develops 48–96 h after cessation; withdrawal unlikely >5 d after cessation
- **Labs:** AST: ALT > 2 typically, CBC w/ macrocytosis; EtOH level, tox

screen

## Treatment (*NEJM* 2005;352:596)

- **Brief interventions:** Counseling (~10–15 min) w/ motivational interview (see *"Patient Counseling"*) ↓ risky drinking, not dependent drinking; consider involving family members; arrange f/u; if pt unwilling to stop drinking, consider harm reduction (e.g., to cut back or not to drink & drive)
  **Show concern, give feedback:** "You are drinking more than is medically safe & most adults drink less than you; my advice is to quit or drink w/in healthy limits; EtOH likely causes your GERD/HTN/fatigue"
  **Engage:** "What do you think about your drinking? How do you feel about cutting back?"
  **Empathy:** "Quitting EtOH is difficult for many people"
  **Options:** "A number of treatments are available including medications, AA, counseling"
  **Anticipate:** "What situations prompt you to drink? How can you avoid them?"
  **Follow-up:** "Let's schedule a f/u visit to track your progress"
- **Counseling:** (findtreatment.samhsa.gov)
  **Cognitive behavioral tx:** Skills to avoid situations that cause heavy drinking
  **12-step:** Alcoholics Anonymous (disease model)
  **Other:** SMART recovery (nonreligious alt to AA); self-help booklets, religious organizations, employee assistance programs
- **Outpatient detoxification:** Requires close supervision by provider, may be safe & effective even in heavy drinkers (*Alcohol* 2000;35:66)
- **Inpatient detoxification:** Hx seizure, detoxes, psych disease, BAL > 150 mg/dL, acute illness, unstable Ψ sx, med comorbidities, >60 y of age, use of other illicits, no sober/responsible adult to care for pt, lack of a safe home environment
- **Dependence Pharmacotherapy:** (not for withdrawal); typical course 3–12 mos; medication combinations do not ↑ efficacy (*JAMA* 2006;295:2003); medication + brief counseling as effective as added behavioral specialist tx (*JAMA* 2006;295:2003); standard of care

includes ongoing counseling

**Acamprosate:** ~50% ↑ in abstinence vs. placebo (*Addiction* 2004;99:811); pts may need to detox first; halve dosage in renal insufficiency (CrCl 30–50 mL/min); use cautiously in pts w/ hx suicidal ideation/attempts

**Disulfiram:** Aldehyde dehydrogenase inhibitor leads to ↑ acetaldehyde → vomiting w/ EtOH consumption; efficacious w/ supervised administration; s/e include risk of fulminant hepatitis, neuropathy, psychosis; contraindicated in CAD, metronidazole use, or rubber allergy

**Naltrexone:** May ↓ craving for EtOH, ↓ frequency & intensity of drinking; useful for controlled consumption; ? effect on abstinence; monthly naltrexone injections (380 mg) ↓ event rate of heavy drinking d in EtOH dependent pts by 25% compared to placebo (*JAMA* 2005;293:1617); depot naltrexone FDA approved in 2006 for Rx of EtOH dependence & showed no e/o hepatotoxicity, even in pts drinking heavily after tx (*Alcoholism* 2008;32:498); Naltrexone is contraindicated in pts on opioids or w/ elevated LFTs; pts must be opioid-free for >7 d & carry wallet card alerting med personnel; GI s/e early in tx, limited risk of hepatotoxicity at standard dose (*NEJM* 2008;359:715)

- **Supportive treatment:** Thiamine 100 mg PO QD, folic acid 1 mg PO QD, multivitamin
- **Harm reduction:** Counseling about driving, firearms, mixing meds w/ EtOH
- **Remission:** Definition requires freedom from consequences of EtOH, not abstinence (*NEJM* 2013;368:365); only 11% of pts w/ EtOH dependence maintain long-term control of their drinking w/o dependence∴ abstinence recommended (*Addiction* 2003;98:1043)
- **Treat comorbid psychiatric conditions:** Many affective sx abate w/ abstinence; however, may use SSRI to treat associated depression (*JAMA* 2004;291:1887)
- **Referral:** Consider consulting an addiction specialist/psychiatrist, esp if complex hx
- **Patient information:** *JAMA* 2005;293:1694

# ANXIETY DISORDERS

## Background (*AFP* 2006;73:1049; *NEJM* 2006;354:2360)

- **Definition:** Anxiety is a state of psychological distress (apprehension, internal conflict), w/ or w/o a specific focus; may be adaptive (e.g., ↑ alertness & performance) or maladaptive (e.g., assoc w/ hypervigilance, ↓ concentration, physical sx, functional impairment)
  **Panic attack:** Discrete, sudden period of intense apprehension, impending doom, & discomfort, usually peaking in ≤10 min; often assoc w/ palpitations, chest discomfort, sweats, shakes, hot flushes, chills, SOB/choking feelings, nausea, abd discomfort, dizziness, paresthesias, derealization, depersonalization, fear of losing control/dying
- **Epidemiology:** 10% prevalence in primary care; often undetected; presents in teens to mid-30s, ↑ risk w/ ⊕ FHx of anxiety d/o; majority of pts w/ GAD have a mood, somatoform, SUD, or (another) anxiety d/o (*BMJ* 2007;334:579); ~50% of pts w/ major depression may have a comorbid anxiety d/o (*JAMA* 2003;289:3095)
- **Differential diagnosis:** Hypoglycemia, hyperthyroidism, pheo, carcinoid, anemia, withdrawal (EtOH, opioids, BZD, antidepressants), SUD, excess caffeine

## Evaluation and Management (*AFP* 2005;71:733; 2009;79:785; *NEJM* 2004;351:675)

- **History:** May include prominent physical sx (palpitations, ↑ HR, SOB, chest/abd discomfort, N/V, diarrhea, HA, dizziness, paresthesias) even in the absence of psychological distress; triggers of anxiety; caffeine use; focused vs. nonfocused anxiety; acute vs. chronic; safety behaviors or avoidance; impairment in work, school, relationships; panic attacks; screen for depression (see *"Depression"*), mania (see *"Bipolar Disorder"*), suicidal ideation (see *"Suicide Risk Assessment"*); prior psych hx; FHx; **Screening Tools:** (available those below on-line)
  **Generalized anxiety disorder:** GAD-7 & GAD-2 both developed/validated in the primary care setting; GAD-2 → 2 question screen scored from 0 (not at all) to 3 (nearly every day)

w/ score ≥3 prompting further eval: Feeling nervous, anxious or on edge? Not being able to stop or control worrying? (*Arch Int Med* 2006;166:1092; *Ann Int Med* 2007;146:317)

**Social anxiety disorder:** Mini-SPIN → 3 question screen scored from 0 (not true) to 4 (extremely true), w/ score ≥6 prompting further eval: (1) Fear of embarrassment; (2) Avoiding being ctr of attention; (3) Worst fears include embarrassment, humiliation (*Prim Care Comp J Clin Psychiatr* 2009;11:231)

**PTSD checklist:** DSM-based, 17-items, military & civilian versions; 4 item version for primary care use (PC-PTSD) (*J Anxiety Disord* 2008;22:337)

**Panic disorder severity scale:** 7 items assessing attacks, anticipatory anxiety, avoidance; can be clinician or self-rated (*Depress Anxiety* 2002;15:183)

- **Workup:** Consider TSH, UTox, fasting glucose based on clinical scenario

## Clinical Features and Treatment of Anxiety Disorders(See *"Depression"* for Specific Properties, s/e of SSRIs, SNRIs)

| |
|---|
| **Generalized anxiety disorder:** Functional impairment/significant distress on more days than not over a 6-month period from excessive, uncontrollable worry about a number of concerns (e.g., finances, health, safety of family & friends); anxiety is assoc w/ ≥3 of: **(1)** Restlessness or feeling on edge; **(2)** Easy fatigue; **(3)** Difficulty concentrating; **(4)** Irritability; **(5)** Muscle tension; **(6)** Sleep disturbance; r/o PTSD, panic, OCD, or other medical dx<br>**Therapy:** CBT (*JAMA* 2009;301:1460), relaxation training; **Rx:** 1st-line → SSRIs (generally, all SSRIs equally effective) or SNRIs; consider benzodiazepine bridge; *Sample Rx:* Paroxetine 10 mg QD; ↑ to 20 mg QD in 1 wk, titrate to 40 mg over 2–6 wks, (± clonazepam 0.25–0.5 mg BID during acute phase/SSRI titration) |
| **Panic disorder:** Recurrent, out-of-the-blue panic attacks w/ concern about the attacks or their implications, & assoc behavior Δ; **agoraphobia** is the most common panic d/o: Anxiety about panic attacks and/or ability to escape from a situation where attack might be difficult or embarrassing (e.g., crowds, queues, stores/malls, restaurants, public transit, appts, cars, planes) leading to avoidance or enduring w/ extreme distress; may also seek presence of reassuring other to accompany pt while in feared situations<br>**Therapy:** CBT incl exposure to feared bodily sensations or places; **Rx:** 1st-line → SSRIs, SNRIs; consider BZD while awaiting response, TCAs (may be s/e limited) (*J Clin Psychiatry* 2010;71:574); *Sample Rx:* Sertraline 25 mg QD; ↑ to 50 mg QD in 1 wk, titrate to 100–200 mg over 2–6 wks; note: Long-term prn BZD are not indicated |

| |
|---|
| **Social anxiety disorder:** Excessive, unreasonable anxiety related to social situations & potential scrutiny of others that causes functional impairment or severe distress; may be *generalized* (experienced in multiple types of interactions such as conversations or social gatherings) or *nongeneralized* (e.g., public speaking) (*NEJM* 2006;355:1029)<br>**Therapy:** CBT, individual or group; **Rx:** *Generalized:* 1st line → SSRIs, SNRIs (venlafaxine) e.g.: Sertraline as above, consider augmentation w/ BZDs; *Nongeneralized:* 1st line → PRN βB |
| **Specific phobias:** Excessive or unreasonable fear about an object or situation → immediate anxiety response, avoidance behaviors or enduring w/ extreme distress<br>**Therapy:** CBT incl exposure therapies (imagined or live exposures); systematic desensitization; **Rx:** Rare PRN benzodiazepine use |
| **Post-traumatic stress disorder:** Exposure to a life-threatening event w/ sx >1 m in 3 clusters: Re-experiencing, avoidance/emotional numbing, & hypervigilance (*AFP* 2003;68:2401; *JAMA* 2002;288:1513); If sx <1 m → acute stress d/o; often comorbid w/ depression, SUD; complex PTSD may involve dissociation, perceptual abnorm; *reclassified as Trauma and Stressor-Related Disorder for DSM-5*<br>**Therapy:** 1st-line → CBT (cognitive processing therapy or prolonged exposure), may consider eye movement desensitization and reprocessing (EMDR) **Rx:** 1st line → SSRIs, SNRIs, prazosin for associated nightmares; BZDs not recommended |
| **Obsessive compulsive disorder:** See *"Obsessive Compulsive Disorder"* |

- **Patient information:** adaa.org; anxieties.com; *AFP* 2003;68:2409 (PTSD); 2005;71:740 (panic); 2006;73:1057; 2010;81:987 (exercise); *JAMA* 2011;305:522; 305:1256; 2012;308:729

# BIPOLAR DISORDER

## Background

- **Bipolar type I:** ≥1 manic episode, usually alternating w/ depressive episodes; prevalence: 1–2% of population
- **Bipolar type II:** Major depressive episode + *hypomanic* episode(s); prevalence: >2%
- **Manic episode:** Abnormally & persistently elevated, expansive or irritable mood, lasting >1 wk (less if hospitalized), **and ≥3 of following** (≥ 4 if mood only irritable): **(1)** Inflated self-esteem or grandiosity; **(2)** ↓ need for sleep; **(3)** Talkativeness/pressured speech; **(4)** Racing thoughts/flight of ideas; **(5)** Distractibility; **(6)** ↑ goal-directed behavior (socially, sexually, at work); **(7)** Psychomotor agitation; **(8)** Excessive involvement in pleasurable activities w/ ↑ potential for painful consequences; two-thirds, of manic episodes have psychotic sx (hallucinations, delusions)
- **Hypomanic episode:** Abnormally and persistently elevated, irritable, or expansive mood that lasts ≥4 days, **with** 3 or more symptoms of

mania, but **without** either significant change in social/occupational functioning or psychotic sx

- **Depressive episode:** "Atypical" symptoms (hypersomnia, hyperphagia) common; psychotic symptoms can also be present
- **Mixed episode:** Features of mania & depression coexist; ↑ risk of suicide
- **Rapid cycling:** ≥4 mood episodes/y, often treatment-resistant; poorer prognosis

## Evaluation (*Arch Gen Psychiatry* 2007;64:543; *Prim Care CNS Disord* 2011;13:10r01097)

- **History:** >50% bipolar pts p/w depressive episode ∴ taking a careful hx for past manic sx important (*Psychiatr Serv* 2001;52:51); *Screening:* "Was there a time when you were feeling so good or hyper that other people thought you were not your normal self, or so hyper that you got into trouble? Was there a time when you got much less sleep than usual & still felt rested?" *Suicide/violence risk assessment:* BPAD pts have >50% lifetime risk of suicide attempt (*J Clin Psychiatry* 2005;66:1456)
- **Workup:** TSH, RPR, UTox, $B1_2$; **Medication monitoring:** CBC, ECG, Chem-12, BMI, waist circumference, lipids, fasting glucose

## Management

- **General principles:** Cautious antidepressant use (if at all) b/c can induce mania (*J Clin Psychiatry* 2008;69:1307); sleep hygiene important; disrupted sleep is a major trigger for mania; individual or group psychotherapy improves outcomes (*Arch Gen Psychiatry* 2007;64:419)

**Overview of FDA-approved Treatments (*J Clin Psychiatry* 2005;66:870)**

| Acute Mania | Bipolar Depression |
|---|---|
| Lithium* | Lamotrigine |
| Valproic acid* | Quetiapine |
| Carbamazepine* | Olanzapine/fluoxetine combination |
| 2nd generation antipsychotics | |

*Serum plasma level monitoring recommended

# DEPRESSION

## Background (*JAMA* 2002;287:1568; 2003;289:3095; *NEJM* 2000;343:1942)

- **Definitions (DSM-IV):**
  **Major depressive episode:** 5/9 sx (see SIGECAPS, below), incl either depressed mood or anhedonia, which must be present every day, nearly all day, for 2 wks
  **Major depressive disorder:** Recurrent major depressive episodes
  **Dysthymia:** 2 y of persistently depressed mood + 2–4 sx (see SIGECAPS)
- **Epidemiology:** Major depression present in 5–13% of primary care pts w/ a lifetime prevalence of ~16% in the general population
- **Differential diagnosis:** y: dysthymia, cyclothymia, adjustment d/o w/ depressed mood, seasonal affective d/o; *Organic:* Meds (antiarrhythmics, steroids, BZD, βB, others), SUD, thyroid (hypo/hyper), Cushing, hypercalcemia, DM, dementia, neuro d/o, infection (mono/flu/HIV/syphilis/Lyme), $B1_2$/zinc deficiency, cancer (classically pancreatic), postsurgical, stroke

## Evaluation

### Screening for Depression (*AFP* 2012;85:139; *Ann Inter Med* 2009;151:784; 2010;152:ITC5–1)

Recommended by USPSTF in practices w/ resources for depression dx & tx
PHQ-2: Over the past 2 weeks how often have you been bothered by: (1) little interest/pleasure in doing things (2) feeling down, depressed, or hopeless?
Any positive response → 96% Se/57% Sp for depression → undergo further eval (below), incl PHQ-9

| Evaluation of Depression | |
|---|---|
| **Symptoms** | Depressed mood/anhedonia & **SIGECAPS** sx: **S**leep (↑/↓), **I**nterest, **G**uilt, **E**nergy, **C**oncentration, **A**ppetite (↑/↓), **P**sychomotor sx, **S**uicidality; ≥5 of 9 sx present nearly every d for ≥2 wks diagnostic |
| **Further hx** | Duration; severity; past episodes; psychosocial factors (precipitants & supports); FHx; **hx of bipolar sx;** psychosis; How sx interfere w/ fxn |
| **Mental status exam: Appearance** (grooming, eye contact, behavior); **Motor activity** (psychomotor retardation/agitation); **Speech** (quantity, rate, volume, fluency, spontaneity, coherence); **Mood** (pt subjective report of internal emotional state) & **affect** (provider's perception of pt expressed emotion); **Thought process & content; Cognition** (i.e., MMSE); **Insight** (self-awareness of problem); **Judgment** (appreciate consequences) | |

- **Ongoing Assessment:** important to review at each visit: symptoms (SIGECAPS, above), severity (various tools, consider PHQ-9, available on-line), suicide (see "*Suicide Assessment*")
- **Workup:** Consider TSH, CBC (anemia)

## Treatment (*AFP* 2006;73:83; 2008;77:785; 2009;80:167; *JAMA* 2006;295:318; *NEJM* 2005;353:1819)

- **Psychotherapy:** Equivalent efficacy to pharmacotherapy & effects of the two are additive (*Arch Gen Psych* 2004;61:714); Psychotherapy ideal for mood sx (sadness, guilt, worthlessness)
  **Supportive therapy:** Effective & can occur in primary care settings; it involves aiding the pt by identifying triggers, explaining sx, & offering support & guidance
  **Cognitive behavior therapy (CBT):** Cognitive tx addresses inaccurate or maladaptive beliefs (*Lancet* 2013;381:375); behavioral tx attempts to improve sx & functioning through exercises & focused counseling
- **Pharmacotherapy:** Counsel pts it may take 1–6 wks to improve sx, RR ~50–60%; Meta-analysis demonstrates no difference in efficacy among agents (*Ann Intern Med* 2011;155:772); different agents have different s/e profiles (table); goal should be to have pt take a drug they can tolerate; ideal for neurovegetative sx (energy, sleep disturbance, appetite Δ, psychomotor Δ ); 2nd gen meds (e.g., SSRIs, SNRIs) are more tolerable than TCAs & less dangerous in O/D; pts should be followed closely after drug initiation
  **Duration of therapy:** Typically at least 6–9 mos w/ a slow taper; pts who relapse are candidates for longer or lifelong Rx
  **Precaution:** ↑ suicidal ideation in young adults (18–24 y) → discuss w/ pt & advise them to call if they have suicidal thoughts
  **Refractory depression:** If no response in 4–10 wks, consider a different agent from the same or another class; confirm medication adherence, r/o organic causes, augment w/ CBT; treat comorbid SUD, personality d/o, or hx physical/sexual abuse (all ↑ refractoriness); if depression persists, refer to psychiatry

**Depression Pharmacotherapy by Class/Agent**

| | Class Characteristics | Drug | Notes |
|---|---|---|---|
| SSRI | Better tolerated, little risk in O/D<br>S/e: Agitation, insomnia, sexual dysfunction, GI upset, wt gain; ↑ bleeding risk w/ ASA, NSAIDs; risk of serotonin syndrome in combination w/ certain drugs | Fluoxetine | More stimulating; long-acting metabolite; Least amount of wt gain among SSRIs; ↑ drug–drug interactions; helpful for anxiety; SD: 10–20 mg; TD: 20–40 mg |
| | | Paroxetine | Helpful for anxiety/OCD; withdrawal sx*; more sedation, sexual dysfunction; ↑ orthostatic HoTn vs. other SSRIs; SD: 10–20 mg; TD 20–40 mg |
| | | Citalopram | Helpful for anxiety; ↓ Na; risk of ↑ QTc; SD: 10–20 mg; TD: 20–40 mg |
| | | Escitalopram | ↓ drug–drug interactions; SD: 10 mg; TD: 10–20 mg |
| | | Sertraline | More diarrhea*; helpful in anxiety/ OCD; stimulating; SD: 50 mg; TD: 50–100 mg |
| TCA | Similar efficacy to SSRIs but more S/E; anticholinergic, arrhythmogenic & possibly **lethal** in O/D; Wt gain | Amitriptyline | Most sedating/anticholinergic; helpful in chronic pain/migraines; SD: 25–50 mg; TD: 100–300 mg |
| | | Imipramine | Oldest TCA; SD: 25–50 mg; TD: 100–300 mg |
| | | Desipramine | Least sedating/anticholinergic SD: 25–50 mg; TD: 100–300 mg |
| | | Doxepin | Mod sedating/anticholinergic SD: 25–50 mg; TD: 100–300 mg |
| | | Nortriptyline | Less sedating/anticholinergic; lower orthostatic HoTN compared to other TCAs; helpful in chronic pain/IBS; SD: 25 mg; TD: 50–150 mg |

## Other Pharmacologic Agents

| Drug | Notes |
|---|---|
| Bupropion | Dopamine & noradrenergic reuptake inhibitor; fewer sexual s/e, not assoc w/ wt gain; stimulating; often used as an adjunct or for smoking cessation; ? helpful in ADHD; ↓ seizure threshold (little risk at low dose); may be fatal in O/D; SD: 50–75 mg BID; TD: 300–450 mg TID |
| Venlafaxine | SNRI; GI upset, withdrawal sx; stimulating; ↑ doses may cause HTN; concern for ↑ CV events; helpful in chronic pain; may be lethal in OD; ↑ drug–drug interactions; SD: 37.5 mg BID; TD: 75–300 mg BID or TID |
| Duloxetine | SNRI; s/e similar to venlafaxine w/ less e/o CV effects; contraindicated in liver disease; may worsen DM2; helpful in chronic pain; SD: 30 mg QHS; TD: 60–120mg† |
| Mirtazapine | Acts on norepinephrine, serotonin; ↓ drug–drug interactions; wt gain, sedation (useful in insomnia); SD: 15 mg QHS; TD: 15–45 mg QHS |
| Trazodone | Serotonin antagonist & partial agonist; sedation, postural HoTN & priapism; SD: 50 mg; TD: 75–500 mg† |
| MAOIs (Tranylcypromine, Phenelzine, Selegiline) | May be fatal in O/D, in drug combinations, or w/ tyrosine-rich food or drink; also cause HoTN, insomnia; rarely initiated by PCPs; demonstrated efficacy in atypical depression & elderly |

SD, Starting Dose; TD, Therapeutic Dose
*S/E differences supported in meta-analysis (*Annals Intern Med* 2011;155:772)
†At lower doses, may be given as a single-dose QHS; otherwise should be divided BID or TID

- **Light therapy:** Conventionally used in seasonal affective d/o (depression that recurs & remits seasonally); *Rx:* 10,000 lux lamp, gradually increasing up to 30–45 min daily; s/e include risk of hypomania
- **Electroconvulsive therapy (ECT):** May be effective in severe, unremitting depression; used more often in the elderly; *s/e:* include prominent retro/anterograde amnesia (less during maintenance tx); even so, overall cognitive function generally improves; ECT may temporarily ↑ cardiopulmonary demands despite anesthesia (*NEJM* 2007;357:1939)
- **Indications for psych referral:** Multidrug Rx, suicidality/thought d/o, depression refractory to first-line Rx, unclear dx, psychotic features, bipolar; Pts may be reluctant to see psychiatrist/counselor, consider saying, "Sx of depression are very common. I want to introduce you to a colleague whom I really like; I think you would like him/her, too, & he/she could help"

## Special Populations (*AFP* 2010;82:926; 2011;84:1149; *NEJM* 2007;357:2269; 2011;365:1605)

- **Pregnancy:** SSRIs, sometimes used in pregnancy, may modestly ↑ risk for birth defects; consider referral to perinatal psychiatry & for CBT; Paroxetine is category D
- **Elderly:** Some sx (poor concentration, energy) may be misinterpreted as dementia (see *"Dementia"*); start pharmacotherapy (SSRIs) at very low doses & avoid TCAs if possible; ECT is an option for refractory sx (*AFP* 2004;69:2375)

  **Geriatric Depression Screen:** Extensively validated; depressive responses to at least 2/5 suggest dx: Are you basically satisfied w/ your life? Do you often get bored? Do you often feel helpless? Do you prefer to stay at home rather than going out & doing new things? Do you feel pretty worthless the way you are now? (*J Am Geriatr Soc* 2003;51:694)
- **Postpartum:** 85% of ♀ experience transient postpartum blues w/ a peak incidence 4–5 d postdelivery; these should not affect function & remit by 2 wks; 5–15% of ♀ develop postpartum depression, likely due to lifestyle changes w/ childbirth (loss of sleep) (*JAMA* 2006;296:2616)
- **Patient information:** *AFP* 1999;60:239; 2006;73:90; 2008;77:795; 2010;82:939; 2011;84:1155; *JAMA* 2008;299:2466; 2010;304:1736

# CARE OF THE "DIFFICULT PATIENT"

## Background (*AFP* 2013;87:419; *Am J Bioeth* 2012;12:18; *BMJ* 1988;297:528; *JAMA* 2001;285:2629)

- **Definition:** Often defined as a pt who engenders a negative reaction from providers (frustration, distress, exasperation), w/ whom it is difficult to establish a therapeutic relationship, or who fails to assume the "pt role" → clinical errors, boundary violations, & lawsuits; known in the United Kingdom as "heartsink" or "black hole" pts; in the United States known as "problem" pts
- **Characteristics:** More likely to have a psych d/o (esp anxiety, SUD, or personality d/o), >5 somatic sx, more severe sx, poor functional status, unrealistic expectations, ↓ satisfaction w/ care, & ↑ use of health services (*Arch Intern Med* 1999;159:1069; *JGIM* 1996;11:1); socioeconomic environment of medical practice may also contribute

(*Ann Intern Med* 2004;141:126)

**Provider factors:** Poor attitude for psychosocial aspects of pt care, working >55 h/wk; depression/anxiety; age <40; ↑ number of pts w/ psychosocial problems or SUD (*BMC Health Serv Res* 2006;6:128); lack of understanding/empathy re: the pt role, loneliness, different socioeconomic backgrounds, or what it means to be ill or in pain (*NEJM* 2012;367:1284); labeling a pt as "difficult" can allow providers to dismiss or even blame the pt; **no evidence for correlation:** Provider gender, ethnicity, years of experience (*Arch Intern Med* 1999;159:1069)

- **Epidemiology:** Prevalence in primary care ~15–30% of encounters; families may also be experienced as difficult; no evidence for association with pt demographic characteristics or type of physical illness (*JGIM* 1996;11:1)

## Management (*AFP* 2005;72:2063; *J Am Board Fam Med* 2006;19:533; *JAMA* 2011;306:94)

- **Provider training & factors:** (1) ↑ awareness/compassion for pt psychosocial context, enhance communication skills (*Arch Intern Med* 1999;159:1069); (2) Dx & treat comorbid psych illness; (3) Focus on provider well-being (balanced lifestyle, respect work hours for trainees), (4) Restore collaboration by prioritizing pt concerns, using a nonjudgmental attitude; (5) Set limits & boundaries—being firm but compassionate; (6) Mindfulness: awareness & acknowledgment of providers' own emotional responses when caring for difficult pts

  **Empathic interactions:** Naming/validating pt emotion ("I can see you are upset"); active listening ("tell me why X is so upsetting;" "I hear you're telling me…"); shared decision-making ("I think the best way to help your shortness of breath is to quit smoking; what are your thoughts?"); engage pt ("What may we do to help you feel better?")
- **Patient factors:** Get more info about the pt & family (may help relieve clinical insecurity) (*BMJ* 1988;297:528)

### Strategies for Successful Care

| Classical description | Management Recommendation |
|---|---|
| "Dependent clinger" (needy) | Professional behavior, boundaries (i.e., when to call/page), shared decision-making, regular f/u, reassure pt they will not be abandoned; set small, achievable goals; enlist family if pt willing; schedule longer visits; address one concern/visit |
| "Entitled demander" (demanding) | Mindfulness, address specific pt emotion; advise pt they are entitled to good med care & team is working in their best interest; apologize for legitimate grievances (i.e., wait times) |
| "Manipulative help rejecters" (nothing works) | Engage by sharing disappointment at poor results; realistic expectations; focus on sx control rather than cure |
| "Self-destructive denier" | Realistic expectations; celebrate small successes; examine cause of noncompliance; motivational interviewing (see *"Pt Counseling"*) |

(*AFP* 2005;72:2063; *NEJM* 1978;298:883)

# DOMESTIC VIOLENCE

## Background (*AFP* 2011;83:1165; *JAMA* 2011;306:513; *NEJM* 1999;341:886)

- **Definition:** Intimate partner violence (IPV) involves psychological, emotional, physical, & sexual abuse
- **Epidemiology:** 25–33% of women experience domestic violence in their lifetime; ♂ → ♀ most common, but may be found in any relationship
- **Obstacles to leaving an abusive relationship:** Fear, threats, financial dependence, lack of knowledge, family/societal pressure, love, children
- **Complications of abusive relationships:** Death, disability, HIV/STIs, poor pregnancy outcomes, lost work days, loss of housing, chronic disease, PTSD/depression/anxiety

## Evaluation (*Ann Intern Med* 2013;158:478; *NEJM* 2012;367:2071)

- **Clinical pearls:** Maximize pt sense of control (e.g., does pt want door open/closed), engage (shared decision-making) & educate about what to expect (e.g., labs); emphasize that it is not patient's fault & he/she is not alone; acknowledge how difficult it is to be in an abusive relationship & that he/she does not deserve this
- **History:** Severity, frequency, type of abuse (incl forced sex); screen for comorbid psych disease, SUD; safety of others in household; assess immediate safety

**Screening:** USPSTF recommends screening ♀ of childbearing age; **always screen pt alone**—ask partner to leave room; **suggested approach:** "Domestic violence is a common problem & affects people's health, so I ask all my pts about it. Do you feel safe at home? Does anyone in your life make you feel scared or intimidate you?" HITS: "Does your partner **H**urt, **I**nsult, **T**hreaten, or **S**cream at you?"

- **Exam:** Bruises at different stages of healing, around neck (choking), rib Fx, "baby zone" injuries (breasts/abdomen), inner thigh bruising (sexual trauma); photograph injuries
- **Workup:** STI, HIV testing

## Management (*JAMA* 2003;289:589; 601)

- **Contraception:** Self-empowering methods (i.e., ring, IUD, ♀ condom, diaphragm, hormone injection)
- **Referrals:** Psychiatry, social work, financial services
- **Pre-exposure HIV prophylaxis:** Controversial; consider in high-risk situations
- **Emergency resources:** Provide contact info pt can use in an emergency
- **Mandatory reporting:** Abuse of a child (<18), disabled person (physical or mental), elder abuse; injury involving a firearm or knife may be reportable in some states; Not mandated to report domestic violence in an adult woman who is not disabled
- **Create a safety plan:** Call 911 if immediate danger, have a back-up friend/neighbor to call 911, teach kids to call 911, go over safety plan w/ kids & have place for them to go (neighbors, closet); emergency kit w/ important documents, money, keys, emergency place to stay; know where local police precinct is
- **Signs of escalation:** Perpetrator is violent outside the home, gun in home, violence toward children, escalating threats, forced sex, drug/EtOH abuse by partner, choking, use of weapon or threats w/ weapon, stalking behavior, abusive during pregnancy
- **Patient information:** ncadv.org, thehotline.org, 1–800–799-SAFE, *AFP* 2011;83:1173; *JAMA* 2010;304:596; futureswithoutviolence.com, instituteforsafefamilies.org

# EATING DISORDERS

## Background (*Arch Gen Psych* 2000;57:659; *Int J Eat Dis* 2002;31:151; *JAMA* 1998;279:1992)

### Classification of Eating Disorders (*AFP* 2003;67:297; *Mayo Clin Proc* 2010;85:746)

| |
|---|
| **Anorexia nervosa:** ↓ food intake → significant ↓ wt (<85% expected wt); fear of gaining wt despite being underweight; body image disturbance; *Restrictive type:* No binging/purging in past 3 mos; *Binge eating/purging type:* ⊕ binge eating or purging in 3 mos; Lifetime prevalence: 0.9% in ♀; 0.3% in ♂; fatal in 8–16% of pts |
| **Bulimia nervosa:** Recurrent binging (consuming large amounts of food in a discrete time period) followed by inappropriate compensatory behavior to prevent wt gain (e.g., purging, exercise, fasting, laxatives, diuretics) which occurs, on avg, ≥1×/wk for 3 mos; *in contrast to anorexia, most pts are near-nl wt*; lifetime prevalence 1.5% in ♀, 0.5% in ♂; 70% of pts in partial/full remission at mean f/u of ~12 y |
| **Binge eating disorder:** Episodic binge eating w/o purging, exercising or dietary behaviors to prevent wt gain; at least 3 of the following present: (1) Eating more rapidly than nl; (2) Eating until uncomfortably full; (3) Eating large amounts when not hungry; (4) Eating alone b/c of embarrassment of how much one is eating; (5) Feeling disgusted, depressed, or guilty from overeating; must occur ≥1×/wk for ≥3 mos; assoc w/ lack of control & distress over eating; lifetime prevalence: 3.5% in ♀; 2% in ♂ |
| **Eating disorder NOS:** Aberrant eating patterns & wt mgmt not meeting above criteria; prevalence: 3–5% of women age 15–30 y |

- **Differential diagnosis:** IBD, celiac disease, achalasia, hyperthyroidism, Addison's, hypopituitarism, DM1, cancer, HIV, TB, depression, SUD, medication effect

## Evaluation (*Ann Intern Med* 2012;156:ITC4–1; *JAMA* 1999;282:1737; *NEJM* 1999;340:1092)

- **History:** Wt & exercise hx, motivation for Δ, past response to Rx, s/sx of malnutrition (e.g., amenorrhea) (*Ped Rev* 2011;32:511); screen for comorbid psych d/o, e.g., anxiety (see *"Anxiety Disorders"*), OCD (see *"Obsessive Compulsive Disorders"*), SUD (see *"Substance Use Disorders"*), depression (see *"Depression"*) & suicide (see *"Suicide Assessment"*, 17% prevalence of attempts in anorexia); FHx (↑ prevalence in pts w/ first-degree relative w/ alcoholism or eating d/o); Social hx: hx dieting, sports w/ weight limits or where leanness emphasized (ballet, wrestling, running) or scoring is subjective (gymnastics, skating); OCP use

  **Body image:** "What percent of the day are your thoughts occupied w/ food, eating, body size or shape? How often do you weigh

yourself? Are you satisfied, dissatisfied, or distressed with your current body weight ?"

**Eating history:** Ask about vomiting, spitting, use of laxatives, diuretics, diet pills, syrup of ipecac, or ruminating (regurgitating/rechewing); "Do you restrict calories or avoid certain foods?"

**SCOFF questions:** "Yes" to ≥2 or more questions = 100% Se & 87.5% Sp for diagnosis of an eating d/o (*BMJ* 1999;319:1467): (1) Do you make yourself **S**ick because you feel uncomfortably full? (2) Do you worry you have lost **C**ontrol over how much you eat? (3) Have you recently lost more than **O**ne stone (14 lbs) in a 3 mos period? (4) Do you believe yourself to be **F**at when others say you are too thin? (5) Would you say that **F**ood dominates your life?

- **Exam:** *Gen:* Emaciated, lack of ♀ fat distribution; *VS:* BMI, ↓ HR, hypothermia, HoTN; *HEENT:* dental enamel erosion, enlarged parotid glands; *CV:* MVP murmur; *Ext:* Russell sign (callous over knuckles from purging), ankle or pretibial edema; *Derm:* xerosis, hypercarotenemia, lanugo, thinning scalp hair
- **Workup:** ECG (↑ QTc), Mg, Phos, Chem-12 (↓ K, metabolic alkalosis), CBC, TSH, CK (↑ if excessive exercise), U/A, amylase (↑ if purging, lipase nl); labs can be nl even in anorexic pts w/ severe malnutrition (*Clin Ter* 2011;162:401); Bone densitometry

## Treatment (*AFP* 2008;77:187; *Lancet* 2005;365:79; *NEJM* 2003;349:875; 2005;353:1481; 2009;360:500)

- **Indication for hospitalization:** HR < 40, BP < 90/60, sx hypoglycemia, K < 3 mM, T < 97°F, dehydration, orthostatic, CV abnormalities, wt < 75% expected, failure of outpt tx, rapid wt loss, requiring NG feeding, poor motivation/insight, abusive home environment, suicidal, serious comorbid psych conditions
- **General principles:** Interdisciplinary care (psychiatrist, therapist, nutritionist, & PCP)

  **Goals:** Attain & sustain nl BMI; stop abnl eating behaviors; replace cognitive distortions w/ capacity for emotional & behavioral self-regulation; improve coping skills
- **Anorexia:** 1st-line tx is wt restoration w/ nutritional rehab + psychotherapy (*AJP* 2006;163:4); pt may safely gain 0.5–2 lb/wk

outpt; meal plans start at 1500 cal/d, ↑ by 500 cal/d q3–4d prn; vitamin supplementation; monitor for refeeding syndrome (potentially fatal shifts in fluids & electrolytes [↓ K, ↓ Phos, ↓ Mg]) in malnourished pts

**Psychotherapy:** CBT, family tx for younger pts (Maudsley – intensive outpt tx involving parents) (*Br J Psych* 2001;178:216, *AJP* 2006;163:4)

**Medical therapy:** No FDA-approved meds (*JAMA* 2006;295:2605); treat comorbid psych d/o; some data suggests atypical antipsychotics (olanzapine) may target cognitive distortions, insomnia, & wt; zinc gluconate 100 mg/d & cyproheptadine 32 mg/d possibly helpful for more rapid wt restoration (*Int J Eat Disord* 1994;15:251; *Clin Evid* 2003;9:986)

- **Bulimia nervosa:** CBT is best evidenced-based form of psychotherapy (*Int J Eat Disord* 2007;40:95; *Lancet* 2010;375:583); Rx + psychotherapy better than either alone

  **Nutrition:** Structured, consistent meals (e.g., 3 meals + 2 snacks/d) (*Am J Psych* 2006;163:4)

  **Medical therapy:** SSRIs 1st-line (fluoxetine 60 mg QD); 2nd-line tx is another SSRI (citalopram, fluvoxamine, & sertraline); 3rd-line tx, in order of preference: Topiramate, TCAs, trazodone, or MAOI; avoid bupropion due to ↑ seizure risk (*Am J Psych* 2006;163:4)
- **Binge eating:** Psychotherapy more effective than behavioral wt loss therapu or pharmacotherapy (*Am Psychol* 2007;62:1999)

  **Psychotherapy:** 1st-line; proven effective therapies include CBT, self-help CBT, interpersonal tx, & dialectical behavioral tx (*Int J Eat Dis* 2010;43:205)

  **Medical therapy:** Sertraline (50–200 mg/d) & fluvoxamine (50–300 mg/d) ↓ binge frequency (*Am J Psych* 1998;155:1756; 2000;157:1004); topiramate (50–600 mg/d) to ↓ sx (*Am J Psych* 2003;160:612; *Arch Gen Psych* 2003;60:1109)
- **Patient information:** *AFP* 2003;67:311; 2008;77:196; 78:223; anad.org nationaleatingdisorders.org

# OBSESSIVE-COMPULSIVE DISORDER

## Background (*AFP* 2009;80:239; *Lancet* 2009;374:491)

- **Obsessions:** Recurrent thoughts, impulses (e.g., to harm someone for no reason) or images (e.g., violent scenes) that cause marked anxiety or distress, are experienced as intrusive, go beyond excessive worry about real-life problems, & are not related to another mental disorder
- **Compulsions:** Repetitive activities (e.g., hand-washing, ordering, checking) or mental acts (e.g., counting) in response to an obsession; acts aimed at preventing or reducing distress; pt usually recognizes as excessive or unreasonable (ego-dystonic)
- **Obsessions/compulsions** are time-consuming (>1 h/d), cause marked distress or interfere w/ a person's daily routine, occupation or social functioning, or lead to avoidance; may involve cleaning, symmetry/order/counting, forbidden thoughts (i.e., sexual), harm to self/others, or hoarding
- **Epidemiology:** Lifetime prevalence 2–3% in the general population; bimodal age of onset at ~10 y & ~21 y; mean age of onset: ~20 y; ♂:♀ 1:1; same incidence across cultural boundaries, monozygotic > dizygotic twins (*Arch Gen Psychiatry* 1988:45:1094)

## Evaluation and prognosis (*JAMA* 2001;285:2121; *NEJM* 2004;350:259)

- **History:** *Screening questions:* Do you have repetitive thoughts that make you anxious & that you cannot get rid of regardless of how hard you try? Do you keep things extremely clean or wash your hands frequently? Are there certain behaviors that you feel compelled to repeat? Do you check things to excess? (*NEJM* 2004;350:259)
- **Natural history:** Two-thirds of pts improve over a decade w/o tx, but full remission in only 20%; suicide attempts reported in 10% of pts (*Arch Gen Psych* 1999;56:121)

## Treatment (*J Clin Psychopharm* 2002;22:309)

- Treatment should be initiated by providers confident of dx and comfortable with Rx options; comanagement w/ psychiatry is typical
- **Pharmacotherapy:** SSRIs & clomipramine lead to improvement in 40–60% pts; on average, pts experience 20–40% ↓ in sx w/ meds alone, but best in combination w/ CBT (*J Clin Psych* 1999;60:101)
  **SSRIs:** No difference in efficacy w/in class, choice is determined by

which pt will tolerate best (*Cochrane Database Syst Rev* 2008:CD001765); maximum tolerated dose is usually most effective; requires 8–12 wks for adequate trial & titration: sertraline (50–200 mg), paroxetine (10–60 mg), fluoxetine (20–80 mg), fluvoxamine (50–300 mg); see "*Depression*" and "*Psychotropic Medications*" for specific SSRI properties & s/e

**TCAs:** Clomipramine 25–250 mg; monitor for anticholinergic s/e

**Antipsychotics:** Consider if partial response w/ SSRI/clomipramine

- **CBT:** Exposure & response prevention (most effective behavioral intervention); graded exposure to anxiety-provoking stimuli; cognitive restructuring; pt & family psychoeducation; 83% of pts responded to exposure-based CBT (>30% sx reduced); 76% show ↓ sx long-term (*J Consult Clin Psychol* 1997;65:44)
- **Surgical treatment options:** Anterior cingulotomy, deep brain stimulation can be effective in refractory cases (*Am J Psych* 2002;159:269)
- **Patient information:** *JAMA* 2011;305:1926; ocfoundation.org

# PSYCHOTIC DISORDERS

## Background (*AFP* 2007;75:1821; *NEJM* 2003;349:1738)

- **Definition:** Disturbance in perception of reality (hallucinations, delusions, thought d/o)

  **Schizophrenia:** Chronic/recurrent psychosis w/ impaired social/occupational functioning

  **Schizoaffective disorder:** Schizophrenia + mood disorder

  **Brief psychotic d/o:** Psychosis in stressful situation; resolves w/ removal of stressor

  **Postpartum psychosis:** Typically presents 2 wks after childbirth in 0.1–0.2% postpartum ♀; assoc w/ ↑ risk of suicide, infanticide
- **Differential diagnosis: Primary psychotic disorders** (schizophrenia; schizoaffective d/o; delusional d/o); **Mood d/o** (bipolar or major depressive d/o w/ psychotic features); **Personality d/o** (schizotypal personality d/o); **Substance or medication-induced psychosis** (intoxication w/ or withdrawal from EtOH/illicits); steroids, pseudoephedrine, stimulants, anesthetics, analgesics; **Psychosis 2/2 a**

**medical condition** (delirium, dementia, stroke, CA, heavy metals, demyelinating disease, seizures, autoimmune, infections, endocrinopathies, nutritional deficiencies, metabolic d/o; neuropsychiatric d/o (Wilson's, Huntington's, etc)

## Evaluation (*Arch Gen Psychiatry* 2005;62:247; *Early Interv Psychiatry* 2009;3:10; *JAMA* 2002;287:3249)

- **History:** Mental status exam, MMSE, FHx of Ψ problems
  **Positive sx:** Hallucinations (auditory, visual, tactile, olfactory, gustatory); delusions, esp paranoid; disorganized speech & thought pattern
  **Negative sx:** Blunted or flattened effect; anhedonia; alogia (poverty of speech); avolition; asociality or isolation; impaired self-care
  **Cognitive symptoms:** Impaired executive function, working memory, attention
  **Screening questions:** Do you ever hear voices you're not sure other people can hear? Do you feel like your mind plays tricks on you? Do you feel like people are trying to harm you or that there is a plot against you? Have you ever felt that people try to insert or control thoughts you have? Have you ever felt that the television, radio, or internet communicates special messages meant just for you?
- **Workup for first episode of psychosis:** CBC, Chem-12, ESR, ANA, serum & urine tox, TSH, HIV, ceruloplasmin, folate, $B1_2$, ✓ syphilis; Brain MRI; EEG if clinically indicated
  **Safety:** Screen for suicidality (lifetime risk of 4.8%) & homicidality

## Management (*JAMA* 2003;290:2693; *NEJM* 2005;353:1209)

- **General principles for antipsychotic prescribing:** Start low, ↑ dose slowly
  **Monitoring:** Baseline & follow-up wt, BMI, waist circumference, lipids & glucose
  **Adverse effects:** Extrapyramidal sx (dystonia, pseudoparkinsonism, akathisia); neuroleptic malignant syndrome; tardive dyskinesia; ↑ wt, HLD, DM2, ↑ QTc
  **Anticholinergic coprescribing:** Benztropine frequently given w/

first-generation antipsychotics to prevent dystonic reactions/EPS (but ↑ cognitive s/e)

**Antipsychotic Pharmacotherapy**

| Medication | Considerations |
|---|---|
| **Aripiprazole** | Long half-life; ↑ risk of akathisia |
| **Clozapine** | Agranulocytosis, requires weekly ANC; ↑ sedation; ↑ metabolic s/e; used in refractory cases, not first-line |
| **Olanzapine** | ↑ sedation; ↑ metabolic s/e, ↑ wt; ↓ rate of discontinuation in chronic schizophrenia compared to other 2nd-gen antipsychotics |
| **Quetiapine** | Wide dosing range (≥200 mg likely for maintenance); orthostatic HoTN; ↑ sedation; ↑ metabolic s/e; [↑] PRL |
| **Risperidone** | Hyperprolactinemia; ↑ risk of EPS at higher doses compared to other atypicals; ↑ risk metabolic s/e |
| **Chlorpromazine, haloperidol, perphenazine:** "Typical" antipsychotics; ↑ sedation; risk of TD; extrapyramidal symptoms common; hyperprolactinemia | |

- **Tardive dyskinesia:** A potentially permanent & debilitating s/e; track involuntary movements using Abnormal Involuntary Movement Scores (AIMS) scale w/ all pts; can be reduced w/ slow dose ↓ or using clozapine (*Am J Psychiatry* 1980;137:900)
- **Patient information:** *AFP* 2007;75:1830

# PSYCHOTROPIC MEDICATIONS

**Reactions Requiring: Immediate Medical Attention (i.e., ED referral)**

| |
|---|
| **Acute dystonic reaction:** From antipsychotics; painful muscle spasms, posturing |
| **Lithium toxicity:** Level > 1.2 mM → tremor, vomiting, diarrhea, confusion |
| **Clozapine agranulocytosis or myocarditis:** Incidence 0.05–2% (*Schizophr Bull* 1995;21:579) |
| **Stevens–Johnson syndrome:** 2/2 rapid dose ↑ of lamotrigine (incidence 0.1–0.8%) (*Clin Neuropharmacol* 2011;34:39) |
| **Neuroleptic malignant syndrome:** From antipsychotics; incidence up to 2.4% for typical antipsychotics (*J Clin Psych* 2004;65:464); fever, akinesia, muscular rigidity, altered mental status, autonomic dysfunction → rhabdomyolysis, DIC, respiratory & CV failure |
| **Serotonin syndrome:** From serotonergic agents alone or in combination: Fever, diarrhea, myoclonus, hyperreflexia, altered mental status, agitation (*AFP* 2010;81:1139) |
| **Common Adverse Effects Requiring Outpatient Medical Attention** |
| **Antidepressant discontinuation syndrome:** Dizziness, light-headedness, insomnia, fatigue, anxiety/agitation, HA, flu-like sx, sensory disturbance (e.g., shock-like sensations); seen in up to 85% of pts; most common w/ paroxetine, venlafaxine; distinguished from depression relapse by presence of sensory disturbance, coincidence w/ tapering antidepressant, & resolution in 1–2 wks; **Management:** Pt education re: avoiding abrupt d/c of med; gradual taper (*AFP* 2007;74:449) |
| **Metabolic syndrome & antipsychotic use:** ↑ insulin resistance, altered appetite from meds; Incidence ↑ w/ olanzapine & clozapine, ↓ w/ aripiprazole & ziprasidone; **Management:** Measure at baseline & at f/u: waist circumference (annually), BP, fasting glucose (at 4–6 wks, then annual), fasting lipids (at 4–6 wks then q5y) (*Diabetes Care* 2004;27:596) |
| **↑ QTc:** May occur w/ any antipsychotic or antidepressant; incidence 8% in Ψ pts; ↑ w/ haloperidol, thioridazine, ziprasidone, citalopram; **Management:** ✓ ECG, K & Mg at initiation, w/ each dose escalation, & q6months (*Curr Drug Safety* 2010;5:97) |
| **Hyponatremia:** Any SSRI, AP, mood stabilizer may cause SIADH; ↑ risk w/ carbamazepine, oxcarbazepine, citalopram; **Management:** Baseline Na before starting med, q1–6 mos thereafter, r/o psychogenic polydipsia; see "*Sodium Disorders*" |
| **Lithium-induced nephrogenic DI:** ADH resistance in up to 40% of pts on chronic lithium; **Management:** Monitor for polyuria, water restriction test to establish dx; if DI present stop lithium if feasible in conjunction w/psychiatrist; amiloride if lithium Rx necessary (*NEJM* 1985;312:408); see *"Diabetes Insipidus"* |
| **Lithium-induced hypercalcemia:** 4–6 fold ↑ incidence of hyperparathyroidism, up to 80% pts w/ some rise in Ca; **Management:** If sx, stop lithium ± cinacalcet; see *"Calcium Disorders"* |

## Special Populations (*AFP* 2012;85:483)

- **Cardiovascular disease:** Many meds interact w/ warfarin; significant cardiotoxicity w/ thioridazine, disulfiram; SSRIs are first-line for post-MI depression; Venlafaxine, bupropion may raise BP; hx arrhythmia/prolonged QTc: avoid ziprasidone, citalopram (*Mayo Clin Proc* 2012;87:1042); ↑ QTc potential for any antipsychotic/antidepressant; aripiprazole is only atypical antipsychotic not assoc w/ HL
- **Liver disease:** Most psychotropics metabolized by liver & are highly protein-bound; start w/ low doses, monitor closely, adjust gradually; BZDs of choice in liver disease: Oxazepam, lorazepam, temazepam, (require only glucuronidation, not oxidative metab)

- **Kidney disease:** May → accumulation of drugs/active metabolites, start low, monitor closely, go slowly; Lithium relatively contraindicated
- **Women:** PCOS common in pts treated w/ valproate before age 20; incidence of hypothyroidism w/ lithium higher in ♀
- **Elderly:** Typical & atypical antipsychotics ↑ risk of death in older pts w/ dementia; BZD may have a paradoxical reaction, esp in the elderly
- **Pregnancy:** Paroxetine is category D; valproate, carbamazepine teratogenic; consider referral to perinatal psychiatry
- **Asian & South Asian Indians:** Prior to carbamazepine Rx, HLA-B*1502 allele testing due to 5% incidence of Steven–Johnson syndrome (*Nature* 2004;428:486)

## Significant Drug–drug Interactions

| Psych med | Interacting agent & effect | Management |
|---|---|---|
| **BZD** (CYP3A4) | Azole antifungals, clarithromycin, grapefruit ↑ levels | Consider ↓ of BZD dose by 50% |
| **Antipsychotics** (CYP1A2) | Smoking ↓ med levels, adjust dose w/ quitting or resuming smoking | |
| **Antipsychotics** | ↓ efficacy of oral hypoglycemics, statins | Dose adjustment |
| **SSRIs** | Triptans, MAOIs/TCAs, linezolid, meperidine, tramadol, ↑ risk of serotonin syndrome | Avoid combination if possible |
| **Lithium** | ACEIs, thiazides, furosemide, NSAIDs inhibit renal clearance, ↑ risk of lithium toxicity | Avoid combination, close monitoring, dose ↓ |
| **Carbamazepine/ Valproic acid** | Warfarin ↓ INR (CYP2C9) | Monitor INR, dosing |

(*Curr Psychiatry Rep* 2012;14:376)

| Medication | Therapeutic Concentration | Labs to Monitor |
|---|---|---|
| Lithium | 0.6–1.2 mEq/L (12 h trough) | BMP, TSH, Ca (& PTH if abnl) |
| Valproic acid | 50–125 μg/mL (12 h trough) | LFTs, $NH_3$ |
| Carbamazepine | 4–12 μg/mL | BMP, LFTs q6–12mos |
| Clozapine | 300–500 ng/mL | CBC w/ diff |
| Nortriptyline | 50–150 ng/mL | BMP |
| SSRIs | N/a | BMP |
| Other antipsychotics | N/a | Fasting glucose, lipids, prolactin |

*Trough levels drawn in the morning prior to first dose of the day

## Common Side Effects

| Side Effect | Meds | Notorious Culprit | Management |
|---|---|---|---|
| Nausea | SSRI<br>SNRI | Sertraline | Wait, lower dose, typically improves in <2 wks |
| Sedation | SSRI, SNRI<br>Typical AP<br>Atypical AP<br>Mood stabilizer | Fluvoxamine<br>Mirtazapine<br>Quetiapine Olanzapine | Switch dosing to bedtime if possible, look for drug–drug interactions |
| Insomnia | SSRIs<br>SNRIs<br>Stimulants<br>Bupropion<br>Aripiprazole | Fluoxetine | AM dosing, 2nd dose no later than 4 pm if BID dosing, augmentation w/ sedating agent |
| Weight gain | SSRI<br>SNRI<br>TCA<br>APs<br>Mood stabilizer | Paroxetine<br>Mirtazapine<br>Amitriptyline<br>Olanzapine<br>Valproic acid | Studies suggest metformin may be of benefit, diet/ exercise counseling |
| Weight loss | Some mood stabilizers<br>Stimulants | Topiramate<br>Lamotrigine<br>Bupropion | Monitoring |
| Sexual s/e | SSRIs<br>APs | Paroxetine<br>Sertraline<br>Venlafaxine | Sildenafil, Yohimbine, augmentation/switch |
| Extrapyramidal effects | Typical APs<br>Atypical APs | Haloperidol<br>Risperidone | Anticholinergic agents, dose reduction/switch |
| Anticholinergic effects | SSRIs<br>TCAs<br>APs | Nortriptyline | Lower dose, pharmaco-mgmt of dry mouth/constipation |
| Hyperhidrosis | SSRIs<br>SNRIs | Venlafaxine | Lower dose, switch, topical meds |
| Akathisia | APs<br>Antidepressants | Aripiprazole<br>Risperidone | βB, BZD, lower dose/ switch |
| Priapism | Trazodone<br>APs | Trazodone | Emergent medical care if occurs → educate pt |
| ↑ prolactin | Antipsychotics | Haloperidol<br>Risperidone | Consider head imaging |
| Rash | Any | Lamotrigine (10%) | D/c, monitor for SJS |

(*Stahl's Essential Psychopharmacology, Cambridge University Press*, 2009)

# INSOMNIA AND SLEEP DISORDERS

## Background (*AFP* 2013;88:231; *BMJ* 2004;329:724; *JAMA* 2013;309:706)

- **Insomnia:** Difficulty initiating/maintaining sleep, waking too early, or chronic nonrestorative sleep, despite adequate opportunity for sleep → functional impairment, not better explained by another disorder; clinical dx

**Epidemiology:** Most common sleep disorder; ~30% of adults have sx, 10% meet criteria for insomnia disorder (*Sleep Med* 2006;7:123); incidence ↑ w/ age, 2:1 ♀:♂

**Ddx:** Psych (anxiety, depression, mania/hypomania, adjustment disorders, PTSD), substance abuse, chronic pain, CHF, OSA, COPD, asthma, hyperthyroidism, menopause, BPH, restless leg syndrome, meds (steroids, stimulants, levothyroxine, albuterol, BZD/EtOH withdrawal, caffeine, tobacco), high altitude

**Forms of Insomnia** (*ICSD*-2 2005, *DSM-V* as proposed)

| Type | Clinical Features |
|---|---|
| Acute | <3 mos duration, related to a stressor (Δ in bedroom setting, background noise/lighting), life events (work/school stress, divorce/ relationship conflicts, bereavement), acute illness, drugs/substances, hospital admission → improves w/ adaptation or stressor resolution |
| Inadequate sleep hygiene | Habits not conducive to restful sleep: daytime naps, irregular bedtimes, use of bed/bedroom for nonsleep activities (work, sex, TV, eating), exercise/EtOH/tobacco/caffeine before bed |
| Primary | Learned and ? genetic sleep-disruptive behaviors (hyperarousal, sleep state misperception, anxiety about sleep loss, inability to relax, racing thoughts, worry about impact of sleeplessness) → chronic insomnia |
| Paradoxical | Persistent complaints of ↑ latency & ↓ sleep times, w/ nl PSG/sleep times; pts misperceive sleep time & overestimate degree of insomnia |
| Idiopathic | Persistent difficulty falling/staying asleep, beginning in childhood |

- **Narcolepsy:** Chronic daytime somnolence & in some, cataplexy (transient muscle weakness triggered by emotion), hypnagogic hallucinations (vivid visual or auditory phenomena likely reflecting intrusions of REM sleep into wakefulness), & sleep paralysis (transient inability to move after awakening)
- **Circadian sleep disorders:** Shift work, jet lag (*NEJM* 2010;362:440)
- **Nightmare disorder:** Recurrent awakenings w/ recall of intensely disturbing dreams (usually provoking fear, anxiety, or other dysphoric emotions), w/ full alertness on awakening, & delayed return to sleep; assoc w/ anxiety, stress, other Ψ disorders

## Evaluation (*NEJM* 2005;353:803)

- **History:** Daytime somnolence, ↓ energy, impaired concentration or function in work/school/social interactions, depression, anxiety, irritability, HA; sleep log

**Sleep history:** Acute vs. chronic; bedtime (regularity & timing); quantity & quality of sleep, what wakes pt up; how long to fall asleep; timing of nocturnal & final awakening; daytime naps; pre-bedtime behavior (tobacco, EtOH, caffeine, vigorous activity); bedroom environment (light, noise, TV, use for nonsleep activities such as work, sex); stressors, snoring, restless legs, parasomnias (unusual sleep behavior)

- **Workup:** Polysomnography (PSG or "overnight sleep study") if concern for another sleep disorder (see *"Obstructive Sleep Apnea"*); multiple sleep latency testing for narcolepsy

## Treatment (*AFP* 2007;76:517; *Am J Med* 2010;123:1087)

- **Insomnia: Sleep hygiene counseling:** First-line tx along w/ CBT (below); regular sleep schedule, do not remain in bed longer than 20 min if unable to sleep, avoid naps, sleep as long as needed to feel refreshed the next day but not more, preserve bedroom comfort (light, sound, & temperature), reserve the bed for sleep, exercise regularly but not close to bedtime, avoid mentally or emotionally challenging activities before bedtime, avoid caffeine/tobacco 4–6 h before bed (*Sleep Med Rev* 2003;7:215)

  **Psychotherapy:** CBT, relaxation techniques, sleep restriction Rx (limiting total time in bed to improve sleep efficiency) (*AFP* 2009;79:125; *JAMA* 2009;301:2005)

  **Pharmacotherapy:** Pts w/ difficulty in sleep onset may receive short-acting Rx (lorazepam, ramelteon, triazolam, zaleplon, zolpidem); pts w/ difficulty staying asleep should receive long-acting Rx (doxepin, eszopiclone, temazepam, zolpidem ER); counsel pt to use caution in driving, combination w/ sedating medications/ETOH, and document conversation; caution re: s/e profile of hypnotics and BZDs (see below)

**Pharmacotherapy for Insomnia (*Sleep Med Rev* 2009;13:265)**

| Type | Features |
|---|---|
| **Benzodiazepines**<br>Risk of **tolerance, dependence, impairment** in attention, concentration, memory | *Long-acting:* **Flurazepam, quazepam** (↑ likelihood of daytime impairment); avoid diazepam 2/2 metabolite accumulation<br>*Intermed-acting:* **Lorazepam, temazepam**<br>*Short-acting:* **Triazolam** |
| **Sedative hypnotics**<br>Eszopiclone & zolpidem ER eval in trials for up to 6 mos use; zaleplon for up to 12 mos (*Sleep* 2007;30:959; 2008;31:79; *Sleep Med* 2005;6:107) | **Zolpidem:** Short-acting form most useful for sleep initiation; ER more effective for sleep maintenance; ↓ dose by 50% in elderly; max dose 5 mg in women (*JAMA* 2013;309:2203)<br>**Eszopiclone:** Effective for sleep-onset & maintenance (*AFP* 2005;71:2359); **Zaleplon:** Effective for sleep initiation & nocturnal awakenings; ultra-short half-life |
| **Antidepressants**<br>Options in several classes, consider in pts w/comorbid depression (*AFP* 2011;84:1) | **Trazodone:** 25–50 mg QHS (can ↑ to 200 mg); limited published efficacy data but well-tolerated, often used first-line<br>**Doxepin:** 3–6 mg QHS; FDA approved for insomnia (*AFP* 2011;84:453); **Mirtazapine:** 7.5–15 mg QHS (*AFP* 1999;59:159) |
| **Antipsychotics**<br>Consider where indicated for 1° mood or psychotic disorder | *Often used off-label despite lack of RCT data*<br>**Quetiapine:** 12.5–100 mg QHS<br>**Olanzapine:** 2.5–10 mg QHS |
| **Antihistamines**<br>(Risk of oversedation the next day, anticholinergic s/e) | **Diphenhydramine** (25–50 mg), **doxylamine** (25 mg), **hydroxyzine** (25–50 mg) |
| **Melatonin agonists**<br>Ramelteon eval in clinical trials for up to 6 mos use (*Sleep* 2009;32:351) | **Melatonin** (1–10 mg), several hours before bedtime; effective in circadian rhythm disorders (jet lag, ? shift work)<br>**Ramelteon** (8 mg) ↓ sleep onset latency, ↑ sleep time; Approved in US but not Europe due to lack of efficacy; only sedative-hypnotic that is not a DEA-controlled substance; fewest s/e among sedative-hypnotics, not habit forming |

- **Narcolepsy:** Strategic daytime naps; modafinil (1° pharmacotherapy); methylphenidate or dextroamphetamine second-line (limited by ↑ BP, ↑ risk SCD; venlafaxine & other SNRIs effective for REM suppression; counsel about driving
- **Nightmare disorder:** CBT, desensitization, relaxation, image rehearsal (document nightmares, Δ narratives to be ⊕, rehearse rewritten dream); prazosin for PTSD-related nightmares
- **Jet lag:** Melatonin, optimize light exposure, Δ sleep schedule in advance, short-acting sleep aids, hydration, use EtOH, caffeine judiciously; see "*Travel Medicine*"
- **Patient information:** *AFP* 2007;76:527; 2009;79:131; *JAMA* 2012;307:2653; 2013;309:733

# SOMATOFORM DISORDERS

## Background (*Lancet* 2006;367:452; *JAMA* 1997;278:673; 2009;302:550; *NEJM* 2001;345:1395)

- **Definition:** Psychosocial & emotional problems manifest primarily through physical symptoms
- **Epidemiology:** Disproportionately affects pts w/ low socioeconomic status, fewer years of education, unemployed; common comorbidities include mood, anxiety, SUD, & personality disorders
- **Common complaints:** Limb pain, insomnia/low energy, nausea/abdominal pain/distention

### DSM-IV Diagnostic Criteria for Specific Disorders

| |
|---|
| **Somatization disorder:** Onset before age 30 y; sx unexplained by a medical condition; excessive impairment; requires (over time) physical complaints in multiple domains: 4 painful sx, 2 nonpainful GI sx, 1 nonpainful sexual sx, 1 non-organic neuro sx |
| **Conversion disorder:** Sx/deficit affecting voluntary motor/sensory function (blindness, paralysis, deafness, seizure); assoc w/ psychological conflict or stressor; **not intentional** *Predisposing factors:* Prior med illness/psych dx, exposure to others w/ specific sx; *Workup:* Thorough investigation so that dx is confident; *Ddx:* Myasthenia gravis, movement disorders, stroke, epilepsy, nerve entrapment; single sx distinguishes from somatization d/o |
| **Pain disorder:** Pain in ≥1 anatomical sites → significant distress or impairment; psychological factors thought to play important role; *Presentation:* Pain out of proportion to exam; severe disability & impaired ability to work; frequently w/ comorbid major depression |
| **Hypochondriasis:** Persistent fear of having a particular disease despite med w/u indicating the contrary; misinterpretation of benign s/sx; >6 mos duration |
| **Body dysmorphic disorder:** Preoccupation w/ imagined physical defect, or excessive distress about slight defect; frequently seeks consultation w/ plastic surgeon/derm |

## Evaluation (*AFP* 2007;76:1333)

- **History and exam:** Thorough evaluation w/o invalidating pt concerns; relation of sx to pt emotions & social situation; hx physical/sexual abuse, domestic violence
- **Workup:** Rating tools available on-line: Patient Health Questionnaire 15, Somatic Symptom Index, somatization subset of Symptom Checklist-90

## Treatment (*JAMA* 2004;291:1464)

- **History and exam:** Antidepressants are the mainstay of tx; TCAs for pain disorder, SSRIs for other somatoform disorders (*J Psychosom Res*

2004;56:455)

- **Follow-up:** Regular appts; avoid urgent appts, diagnostic tests, surgery unless indicated; communicate w/ involved specialists; reassure pt serious conditions are ruled out
- **Continue to validate patient complaints:** "It must be difficult/frustrating to have recurrent abdominal pain," or "Tell me more about why this is distressing you"
- **Reattribution training:** Short consultations aim to normalize pt interpretations of sx, modify beliefs about sx causes, & treat underlying depression (*Psychosomatics* 2002;43:394)
- **Behavioral/cognitive therapy:** (*Psychother Psychosom* 2000;69:205) *Relaxation:* Yoga, meditation, diaphragmatic breathing, progressive muscle relaxation; *Behavioral activation:* ↑ pt engagement in pleasurable activities w/ aim to perform activities even when physical or emotional barriers exist; *Cognitive restructuring:* aims to alter ⊖ thinking & correct distortions

# SUBSTANCE USE DISORDERS

## Background (*AFP* 2003;68:869; 2004;69:2619; 2013;88:113; *NEJM* 2003;349:975)

### Diagnostic Criteria for Substance Use Disorders (DSM-V)

| A maladaptive pattern of substance use leading to impairment/distress, manifested by ≥2 of the following over a 12-month period: | |
|---|---|
| • Failure to fulfill roles<br>• Use in risky situations<br>• Persistent desire or unsuccessful efforts to cut down<br>• Use despite known ⊖ impact on med/psych dx<br>• Tolerance<br>• Cravings | • ↑ doses or ↑ period of use than intended<br>• ↑ time finding, using, recovering<br>• E/o withdrawal<br>• Abandonment of other pleasurable activities<br>• Use despite adverse effects on relationships |

### Risks Associated with Drug Use

| Drug | Potential Consequences |
|---|---|
| **IV cocaine** (*Drug Alcohol Depend* 2011;116:64) | Short half-life → frequent injection + vasospasm → ↑ risk abscess/cellulitis |
| **Cocaine** (*Clin Toxicol* 2012;50:231) | ~69% of cocaine mixed w/ levamisole (chemo) → leucopenia, vasculitis, thrombotic vasculopathy; cocaine-related chest pain |
| **Opioids** | May be cut w/ fentanyl (↑ risk of OD); injection → risk of HIV, HCV, abscess, osteomyelitis, endocarditis |
| **Benzodiazepines** | High risk of OD when mixed w/ EtOH or opioids |
| **Synthetic cathinones** ("Bath Salts") (*J Med Toxicol* 2012;8:33) | Intoxication → agitation, psychosis, tachycardia, myoclonus, mydriasis, HTN, ↑ CPK, hypokalemia, & death |
| **Inhalants** (glue, aerosols) | Teratogen; memory loss, psychosis, arrhythmia, death |
| **Oxymorphone ER** ("Opana") | Crushing & injecting → TTP (*JAMA* 2013;309:1338) |
| **Marijuana/cannabis** (*Lancet* 1998;352:1611) | ↑ potency → concern w/ excess use, esp in adolescence; *Aspergillus* risk in immunocompromised |
| **Phencyclidine** ("PCP") | Psychosis, rhabdomyolysis, seizures, hypoglycemia, coma |
| **Synethetic cannbinoids** ("Spice", "K2") | Intoxication → tachycardia, psychosis, seizures, acute kidney injury; MI & death reported |
| **Stimulants: methamphetamines, MDMA** ("ecstasy"/"Molly") (*Prim Care* 2011;38:41) | Used in binge–abstinence cycles; psychosis in up to 25–50% of chronic users; risk of MI, arrhythmia, CMP, pHTN, stroke, rhabdomyolysis, bowel infarction, movement disorders, dental decay ("meth mouth"), risky sexual behavior |

## Evaluation (*AFP* 2010;81:635)

- **History:** The 5 A's (Ask, Advise, Assess, Assist, Arrange):
  **Ask:** "In the past y, how many times have you used illegal drugs or Rx drugs for nonmedical reasons?" It may help to establish rapport/trust to first ask about legal substances (caffeine, nicotine, EtOH)
  **Ask:** Lifetime use of: Cocaine/crack, Rx stimulants (ritalin, adderall), methamphetamine, cannabis, inhalants (nitrous, glue), hallucinogens (LSD, PCP, special K, ecstasy) synthetic cannabinoids (K2, spice), cathinones (bath salts), Rx sedatives (BZD), Rx opioids, street opioids (heroin); route of administration, time of last use, $ spent/d, FHx SUD; determine risk level based on frequency of use & craving, consequences (med, social, legal, financial), failure to fulfill roles, failed prior attempts to quit or cut down, & hx injection drug use

**Checklist:** drugabuse.gov/sites/default/files/pdf/nmassist.pdf
**Advise:** Provide med advice, **assess** readiness to change, **assist** (offer help), **arrange** (refer to tx if necessary)

- **Workup:** HIV, Hep A/B/C, TB/screening, UTox, serum tox (ask pt permission—requirement for pt permission varies by state)
- **Exam:** Needle puncture sites ("Track marks", IVDU), dentition (crystal meth), perforated nasal septum (cocaine); beware of retained needle fragments in IVDU pts

## Management (*AFP* 2001;63:2404; 2003;68:1971; *NEJM* 2003;348:1786)

- **Motivational interviewing:** Effective, empathic, nonjudgmental approach; empowers pt & helps identify discrepancies btw future goals & current behavior; discuss pros & cons of using drugs; Emphasize pts free choice; help develop optimism; "What encourages you to think you can change?" See "*Counseling Patients*"
- **Treatment options:** Pharmacotherapy (below), individual & group counseling, behavioral Rx, residential tx, intensive outpt programs, contingency mgmt, religious associations, & peer support groups (12-step, SMART recovery) Successful tx requires continual evaluation and modification; detox alone not effective
- **Opioid dependence pharmacotherapy:** Opioid full & partial agonists, antagonists; opioid withdrawal sx include craving/anxiety (3–4 h after last dose), diaphoresis, stomach pain, rhinorrhea (8–14 h), tremor, chills, vomiting, diarrhea, tachycardia (1–3 d)
  **Methadone:** (Full agonist) available through federally regulated clinics; pts must be >18 y & have 1 y of opioid dependence; higher doses (60–100 mg) more effective (*Coch Data Syst Rev* 2003; (3):CD002208)
  **Buprenorphine:** (Partial agonist); may be prescribed by any MD w/ special training; compared to methadone, ceiling effect of partial agonist ↓ risk of OD, less severe withdrawal, & less abuse potential (*AFP* 2006;73:1573); at a dose of 8–16 mg less effective than methadone 60–120 mg (*Cochrane Database Syst Rev* 2008;2:CD002207)
  **Naltrexone:** (Antagonist) long-acting injectable form ↓ opioid use compared to placebo, likely inferior to agonist Rx (*Lancet*

2011;377:1506)

**Supportive care: Clonidine:** ↓ withdrawal sx; discontinuation requires taper; **Dicyclomine:** Treats abdominal cramps; **Hydroxyzine:** Controls agitation

- **Cocaine & stimulants:** No FDA-approved Rx; antipsychotics & anticonvulsants ineffective; Bupropion, dextroamphetamine, & modafinil of modest benefit
- **Toxicology screens:** Essential part of tx; false ⊕ & ⊖ common so must interpret cautiously & discuss w/ toxicology lab (kap.samhsa.gov)
- **Contingency management:** Vouchers w/ monetary value provided for ⊖ tox screens; most effective w/ opioids & cocaine (*Addiction* 2006;101:1546)
- **Harm reduction:** ↓ ⊖ consequences of drug use; pt-centered, nonjudgmental

  **Safer injecting strategies:** Clean, fresh needles, sterile water, clean cotton, skin prep, clean, individual cookers; direct pt to needle exchange

  **Overdose prevention tips:** Pt should know dealer, use test shot, don't mix drugs, don't use alone; highest risk of OD after abstinence due to low tolerance

  **Naloxone:** Rapidly acting, opiate antagonist; tx of choice for reversing respiratory depression due to opioid overdose (anypositivechange.org)

  **Vaccination:** Consider HAV, HBV & meningococcal

  **Contraception:** Educate about risk to fetus & ensure access to contraception
- **Patient information:** *AFP* 2006;73:1580; *JAMA* 2013;309:2055; drugabuse.gov; samsha.gov; clubdrugs.org; streetdrugs.org

# SUICIDE RISK ASSESSMENT

## Background (*Mayo Clin Proc* 2011;86:792; *JAMA* 2005;294;2064; 2013;309:2432)

- **Epidemiology:** Suicides account for >1% of all US deaths annually (10th leading cause of death, more than car accidents); PCPs write most antidepressant prescriptions & are the group most likely to see pts the month before suicide (*Psychiatr Serv* 2009;60:1167; *Am J Psych*

2002;159:909); 83% of people who commit suicide have had contact w/ a PCP w/in a year & up to 66% w/in a month of their death (*Acta Psychiatr Scand* 2000;102:126)

**Warning Signs and Risk Factors for Suicide (*JAMA* 2000;283:2693)**

| | |
|---|---|
| **Warning signs** (Transient, often modifiable) | Talking, writing, or planning for suicide; hopelessness, rage, anger, seeking revenge; impulsive or reckless actions, feeling trapped, ↑ EtOH/drug use, withdrawing from others, anxiety or agitation; Δ in sleep, mood; no purpose or reason for living |
| **Risk factors** (Often static, difficult to modify) | White; ♂; hx suicide attempt (↑ risk if recent); FHx of suicide; psych dx; firearms access; hx physical or sexual abuse; hx Ψ admission; older age (♂ > 50, ♀ > 60); poor physical condition; hallucinations (esp command auditory hallucinations); financial stress |

## Evaluation (*AFP* 2003;68:1814; 2006;74:1159; 2012;865:602)

- **History:** Depression, EtOH, & SUD screening (see *"Depression"*, *"Alcohol Abuse"*, *"Substance Use Disorders"*); suicidal thoughts/behaviors should be assessed in all pts w/ depression or hx depression, using a step-wise approach: Thoughts of death → suicidal ideation → plan for suicide → means available (incl firearms) → intent (*J Clin Psychiatry* 1998;59:58); ensure safety of others; **Inquiring about suicide does not ≠ likelihood a pt will make an attempt;** sample questions include, "Have you ever felt so down that you thought life wasn't worth living?" "Do you think about hurting yourself? Do you have a plan?"

## Management

- **General principles:** Treat comorbid mental illness, including depression (see *"Depression"*), EtOH/SUD (see *"Alcohol Use Disorders"* and *"Substance Use Disorders"*), anxiety (see *"Anxiety Disorders"*)

**SAFE-T Risk Assessment Model**

| | Low Risk | Moderate Risk | High Risk |
|---|---|---|---|
| Symptoms | No specific plan or intent to commit suicide; no hx suicide attempts | Suicidal ideation + plan, but no intent or behavior | Serious thoughts of suicide; plan and/or intent; prominent agitation, impulsivity, psychosis; recent attempt |
| Treatment | Outpt f/u, remove obvious means of self-harm (firearms, large quantities of meds); consider safety contract; provide suicide hotline (1–800–273-TALK) | Urgent referral to a psychiatrist vs. ED | Constant observation & monitoring until transfer for psych eval/hospitalization |

- **Patient information:** *AFP* 2006;74:1165; 2012;85:610; *JAMA* 2004;291:1158; 2005;293:2558

# ASTHMA

## Background (*NAMCS* 2010, cdc.gov/nchs/ahcd; NHLBI 2007, nhlbi.nih.gov/guidelines/asthma)

- **Definition:** Chronic inflammatory disease of airways → episodes of airflow limitation → classic triad of sx (wheezing, cough, & dyspnea); over time can → airway remodeling (fibrosis, smooth muscle hypertrophy) → fixed obstructive component
- **"Asthma-plus" syndromes:** *Atopy* (asthma + allergic rhinitis + atopic dermatitis), *Samter's Triad* (asthma + ASA sensitivity + nasal polyps), *Allergic Bronchopulmonary Aspergillosus* (*ABPA*) (asthma + pulm infiltrates + allergic reaction to aspergillus), *Churg–Strauss* (Asthma + eosinophilia + granulomatous vasculitis) (*Lancet* 2002;360:1313)
- **Pathophysiology:** Genetic (predisposition for IgE-mediated/$Th_2$ response) & environmental factors (pollution, tobacco, allergens) → altered immune response → airway hyperresponsiveness & obstruction
- **Epidemiology:** Affects 8% of US adults, ♀ > ♂; African-American > Caucasian > Hispanic; onset in majority of pts occurs by age 40 y
- **Risk factors:** Atopy, smoking, obesity, occupational exposure (adult onset), dust mite exposure (childhood onset); rural upbringing protective (thought to be 2/2 ↑ diversity of microbial exposure) (*NEJM* 2013;369:549)
- Common complaint in primary care; primary dx in >1% of all outpt visits in US

## Evaluation (*NEJM* 2001;344:350)

- **General approach:** *For pts w/o asthma diagnosis:* (1) Establish dx, determine comorbid conditions & potential exacerbating factors based on hx/PE & spirometry; (2) Assess disease severity/control to determine initial tx
- **History:** *Classic sx:* Intermittent episodes of dyspnea, wheezing, frequently w/ identifiable triggers (below), often nighttime or early-AM coughing

*PMHx:* Atopy (atopic dermatitis, allergic rhinitis), GERD, CHF
*Meds:* ASA/NSAIDs (use or hx sensitivity), βB, morphine, ACEI
*FHx:* Asthma, atopy, other pulm diseases
*Social hx:* Tobacco exposure, occupational & home exposures

- **Asthma history:** If previously diagnosed, assess age of onset, hx exacerbations, ED visits, hospitalizations, intubations, need for systemic steroids, albuterol use, peak flows

**Potential Asthma Triggers (cdc.gov/asthma/healthcare)**

| | |
|---|---|
| Allergens | *Persistent:* Dust mites, cockroaches, dogs/cats,<br>*Seasonal:* Trees (spring), grass (summer), weed pollen (fall) |
| **Occupational** | Smoke, irritants, mold |
| **Meds/toxins** | Tobacco smoke exposure, perfumes, ASA, NSAIDs, βB, morphine |
| **Infections** | Rhinovirus/URI |
| **Other** | Stress, cold air, exercise, hard laughing/crying |

- **Exam:** Often unremarkable exam if not in acute exacerbation; HEENT (nasal polyps, allergic "shiners" or rhinitis), skin (AD), full chest & pulm exam
- **Spirometry:** Recommended in all pts in whom asthma is considered; documents *obstruction* (FEV1/FVC < 70%) & its potential *reversibility* (FEV1 ↑ by 200 mL & 12% w/ bronchodilator); however, spirometry can be nl in mild disease btw episodes; pts may fail to show reversibility if asthma very poorly controlled
- **Peak flow:** Used to assess control (comparing current test against personal best), but improvement by 20% w/ bronchodilator can be used to support dx
- **Labs:** Not routinely indicated; if prominent allergic component suspected → serum IgE, skin testing, RAST (typically by allergy/immunology specialist)
- **Other:** *Methacholine challenge:* Induced bronchospasm demonstrates airway hyperresponsiveness; occasionally used if PFTs nl and/or cough-variant asthma suspected; Se > 90% (*ARJCCM* 2000;161:309), trial of empiric tx typically preferred; *Sputum:* >3% eosinophils has Se 86%, Curschmann spirals (mucous casts), Charcot–Leyden crystals (eosinophil lysophospholipase); CXR if indicated by Ddx
- **Differential diagnosis:** COPD, CHF, PE, mechanical airway

obstruction (tumor), ABPA, med-induced cough (ACEI), vocal cord dysfunction (see "Hoarseness")

## Nonpharmacologic therapy (*NEJM* 2009;360:1002)

- Indicated for all pts, often multifaceted approach beneficial
- **Allergen avoidance:** *Dust mites:* Use bedding encasements, wash sheets weekly in hot water, avoid down, HEPA vacuum or air filter, no carpet in bedroom; *pets:* ↓ pet exposure (pet-free home or at least keep out of bedroom); eliminate mold/moist conditions when possible (↓ indoor humidity); *Cockroach:* Extermination, no exposed food or garbage; *Pollens* (indoors w/ windows closed during peak season)
- **Irritant avoidance:** Avoid outdoor exercise during periods of ↓ air quality, avoid exposure to wood stoves, tobacco smoke
- **Smoking:** Smoking & 2nd-hand smoke may ↓ response to asthma medication, ↓ lung function, & can trigger exacerbations; counsel all pts & family members to quit (see *"Tobacco Use"*) & ask housemates to smoke outside (*AJRCCM* 2007;175:783)
- **Immunizations:** Influenza & PSV23 recommended; see *"Immunizations"*
- **Patient education:** Key to trigger avoidance, effective inhaler use; see "Tip Sheets" at www.nhlbi.nih.gov/health/public/lung/asthma/asthma_tipsheets.pdf & inhaler how-to videos at www.cdc.gov/asthma/inhaler_video/default.htm
- Patients & providers should establish an asthma action plan, using sx or peak flow: sample at www.nhlbi.nih.gov/health/public/lung/asthma/asthma_actplan.pdf

## Pharmacotherapy (*NEJM* 2009;360:1002)

- **Inhaled agents:** Myriad forms exist, require proper use to be effective; see below

**Inhaled Medication Delivery Systems (nhlbi.nih.gov)**

| | |
|---|---|
| **Metered-dose inhaler (MDI)** | Aerosolized Rx; must be "primed" (discarded sprays) before 1st use; requires coordination of actuation & breath<br>Deep slow breath × 3–5 s, then hold × 10 s; repeat after 1 min if dose is "2 puffs" |
| **Spacer** | Used w/ MDI; turns aerosol into finer droplets for ↑ delivery to lungs; ineffective if pt exhales into spacer; requires separate Rx; often recommended especially for medium-high dose ICS |
| **Valved holding chamber (VHC)** | Similar to spacer but prevents pt exhaling into device, may be more expensive; requires Rx |
| **Dry powder inhaler (DPI)** | Powdered Rx drawn into lungs w/ inhalation; can clump w/ ↑ humidity; use fast, deep breath & hold for 10 s |
| **Nebulizer** | Requires nebulizer machine to deliver Rx; no more effective at Rx delivery, but does not require pt effort/ coordination |

- **Two categories:** (1) "rescue" or "quick-relief" Rx; (2) "controller" Rx, long-actig agents which reduce freq/severity of episodes (*not* useful in acute episode)
- **"Quick-relief" therapy:** short-acting bronchodilators offer relief of sx or used before anticipated exposure (e.g., exercise); short-acting beta agonists (SABA) are mainstay and **should be prescribed for all pts;** onset <5 min, peak 30–60 min, duration 4–6 h; *s/e:* Tremor, tachycardia, anxiety, palpitations
  *Alt:* short-acting anticholinergics (ipratropium) used as less-effective *alternative* in pts w/ mild sx who do not tolerate SABA or as *adjunct* in pts w/ severe sx; not FDA-approved

**Long-term Agents for Asthma Control**

| Class | Example/Dosing | Notes |
|---|---|---|
| **Inhaled corticosteroid (ICS)** | *Low-dose:*<br>Beclomethasone 40 µg/puff MDI: 1–3 puff BID<br>*Medium-dose:*<br>Budesonide 180 µg/inh DPI: 2–3 inh BID<br>Fluticasone 110 µg/puff MDI: 2 puff BID<br>*High-dose:*<br>Fluticasone 220 µg/puff MDI: 2 puff BID | Suppresses airway inflammation & nonspecific bronchial hyperresponsiveness → fewer asthma sx, increased lung function, improved QoL, fewer exacerbations & ↓ mort (*JAMA* 1997;277:887; *NEJM* 2000;343:332)<br>*S/e:* Hoarseness, sore throat, oral candidiasis; rinse mouth after use, use MDI w/ spacer or VHC; can → systemic s/e in ↑ doses (e.g. >1000 µg beclomethasone/d) |
| **Long-Acting Beta Agonist (LABA)**<br>Adjunct to ICS | Fluticasone/Salmeterol 100 µg/50 µg DPI: 1 inh BID<br>110 µg/21 µg MDI: 2 puff BID | In conjunction w/ ICS → sustained improvement in lung function, ↓ in sx, exacerbations, ICS dose (*Cochrane Database Syst Rev* 2010;4:CD005533)<br>*S/e:* Usually mild; muscle cramps, ↑ HR<br>**Always used w/ ICS;** LABA alone may ↑ risk of asthma-related deaths (*Chest* 2006;129:15) |
| **Antileukotriene agents**<br>(Adjunct or alternative to ICS) | *Leukotriene Receptor Antagonists (LTRA):*<br>Montelukast: 10 mg PO QD<br>(*AJRCCM* 2007;175:783; *AJRCCM* 2006;173:379; *JACI* 2012;130:535)<br>*Inhibits leukotriene formation:*<br>Zileuton extended release 1200 mg BID | Also effective for AR; may be preferred to ICS in pts w/ mild sx & allergic component<br>Also consider in obese, smokers, ASA hypersensitivity; additive benefit to ICS in EIB;<br>*Onset:* hours, peak few days<br>*Dosing:* PM preferred<br>*S/e:* Hepatitis (zileuton 2–4%, requires LFT monitoring), possible mood/behavior sx |
| **Tiotropium Adjunct to ICS ± LABA** | 2 inh (18 µg) QD | Not FDA-approved for asthma; adding tiotropium superior to doubling ICS dose re: ↑ asthma control days, PEF, & ↓ daily sx (*NEJM* 2010;363:1715)<br>Can ↓ exacerbation freq when added to pts w/ sx despite LABA/ICS (*NEJM* 2012; 367:1257) |
| **Other**<br>(Typically Rx'ed by specialist) | Omalizumab<br>*Given SC q2–4 wks* | Used for mod–severe disease if poor control despite ICS, LABA, leukotriene modifier; $$$ (>10K/y) (*Allergy* 2004;59:701; *JACI* 2001;108:184)<br>Pt must have ↑ IgE w/ documented sensitization to perennial aeroallergen (e.g., dust mite, pet)<br>*S/e:* Local reaction, anaphylaxis (rare) |
| | Theophylline | Can be useful in refractory disease; narrow therapeutic window (can → arrhythmia, N/V, HA, sz) |
| | *Mast-cell Stabilizer:*<br>Cromolyn sodium<br>Nedocromil | Specific benefit for ASA-sensitive pts or exercised-induced asthma; few s/e (*AJRCCM* 2002;165:9; *Ann Intern Med* 2000;132:97) |

- **Initiating treatment:** For pts not currently treated, determining which

"step" to start on determined by severity assessment (below); pt category determined by most severe sx

### Classification of Asthma Severity

| | | Persistent | | |
|---|---|---|---|---|
| | **Intermittent** | **Mild** | **Mod** | **Severe** |
| **Sx frequency** | ≤2 d/wk | >2 d/wk | Daily | Daily |
| **Nighttime awakenings** | ≤2×/mo | 3–4×/mo | >1/wk | Nightly |
| **SABA use for sx control** | ≤2 d/wk | >2 d/wk | Daily | Several times/d |
| **Interference w/ nl activity** | None | Minor | Some | Extreme |
| **Spirometry (% predicted)** | Nl btw exacerbations | Nl btw exacerbations | $FEV_1$: 60–80% $FEV_1/FVC$: ↓ 5% | $FEV_1$: <60% $FEV_1/FVC$: ↓ >5% |
| **Exacerbations** | <2/y | ≥2/y | ≥2/y | ≥2/y |
| **Initial Tx** | **Step 1** | **Step 2** | **Step 3** | **Step 4 or 5** |
| **Asthma Treatment Steps** | | | | |
| **Step** | **Controller Medication** | | | |
| **Step 1** | None indicated (should receive SABA prn) | | | |
| **Step 2** | **Low-dose ICS,** consider allergen immunotherapy<br>*Alt:* Antileukotriene, theophylline, cromolyn | | | |
| **Step 3** | **Low-dose ICS & LABA**<br>*Alt:* Medium-dose ICS, low-dose ICS + (LTRA, theophylline, or zileuton); consider adjunct tiotropium, allergen immunotherapy | | | |
| **Step 4** | **Med-dose ICS & LABA,** specialist referral<br>*Alt:* Med-dose ICS & (LTRA, theophylline, or zileuton); consider adjunct tiotropium, allergen immunotherapy | | | |
| **Step 5, 6** | High-dose ICS + LABA ± oral corticosteroids, consider omalizumab if allergic asthma → specialist referral | | | |

- **Follow-up/Patients already on treatment:** Assess control; step up, down or maintain as indicated; pt & provider judgment of tx efficacy should be guide; if asthma not well-controlled, assess inhaler adherence & technique before modifying tx

### Assessing Control in Treated Asthmatics: Well-controlled Pts should have

| | |
|---|---|
| Daytime sx ≤ 2 d/wk | No limitation of activities |
| Reliever/rescue tx ≤ 2 d/wk | No nocturnal sx/awakenings |
| PEF or $FEV_1$ nl | Validated survey indicating control (see below) |

- **Patient survey:** E.g., Asthma Control Test, qualitymetric.com/act; score > 20 indicates control
- **Well-controlled** (all above criteria met): Maintain current regimen; consider step-down if controlled × 3 mos; reassess in 1–6 mos
- **Partially controlled** (any of above criteria not met): Step up 1 step, reassess in 2–6 wks
- **Poorly controlled** (≥3 above criteria not met): Step up 1–2 steps; consider short course PO corticosteroids (40–60 mg QD × 3–10 d), reassess in 2 wks

## When to Refer

- Patients with "asthma-plus" syndromes; pts w/ mod–severe asthma or poorly controlled/frequent exacerbations despite escalation of Rx; dx uncertain, prior hospitalization for asthma → specialist (pulm or allergy/immunology)
- Patients with /prominent allergic component → allergy/immunology for allergy testing, consideration of allergen immunotherapy

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# EXACERBATIONS

- **Definition:** Acute onset/worsening of asthma symptoms (*AFP* 2011;84:40)
- **Presentation:** *hx:* Cough, wheeze, chest tightness, some limitation of activity *Exam:* ↑ work of breathing on exam, wheezing, tachypnea; *Peak Flow:* <80% (<50% consistent w/ severe exacerbation)
- **Red flags:** Severe SOB, failure for peak flow to improve after quick-acting rx used, sx not improving 24 h after step-up → **severe exacerbation Æ ED**
- **Management of mild–mod exacerbation:** (Some limitation of activity, peak flow 50–80% personal best): SABA 2–6 puff (or neb) now then Q2– 4 h prn; step up to next level of care; low threshold for short-course oral corticosteroids (40–60 mg prednisone QD × 3–10 d), esp if sx fail to improve w/ initial rescue Rx; may prevent full exacerbation if quadruple ICS dose for 1–2 wks when PEF ↓ by 30% over 24–48 h (*AJRCCM* 2009;180:598)

# CHRONIC OBSTRUCTIVE PULMONARY DISEASE

## Background (*NEJM* 2010;362:1407, *GOLD* 2011 Report, goldcopd.org, NHAMCS 2010, cdc.gov)

- **Definition:** COPD is a chronic, progressive pulmonary disease w/ systemic effects, characterized by airway inflammation & progressive airflow obstruction that is only partly reversible
- **Pathophysiology:** Genetic predisposition + toxic inhalants → parenchymal destruction and/or airway inflammation, mucus hypersecretion → flow limitation, loss of elastic recoil → hyperinflation, hypoxemia, hypercapnia, pHTN (*Lancet* 2012;379:1341)
- **Etiology:** Most cases assoc w/ smoking (cigarette, cigar, pipe, marijuana); biomass fuels (wood, coal, or dung stoves) & occupational exposures (dusts, gases, fumes) also contributors; genetics (α1-antitrypsin deficiency accounts for 1–2% of cases)
- **Epidemiology:** 6.3% of US adults report COPD dx; >50% of pts w/ mild–mod cases underdiagnosed (*MMWR* 2012;61:938; *Arch Intern Med* 2000;160:1683); more common in pts aged 65–74 y, Caucasians, ♀, hx asthma, ⊕ FHx; accounts for >5% of US outpt visits

## Evaluation (*NEJM* 2010;362:1407, *GOLD* 2011)

- **General approach:** Clinical diagnosis, confirmed w/ spirometry; distinguished from asthma by smoking/exposure hx & incomplete bronchodilator reversibility
- **History: Cough, DOE or Ø exercise tolerance, ≠ sputum production;** ± wheezing, frequent chest infections; wt loss/anorexia in advanced disease; ↑ suspicion in current/former smokers >35 y
  *Meds/Toxins:* Smoking hx: Calculate cumulative pack-years (packs/d × number of years smoked); occupational exposure to dusts/chemicals
  *PMHx:* Comorbidities—anxiety, depression, CAD, FHx; hx asthma or atopy
- **For patients with known COPD:** *COPD hx:* Exacerbation freq, prior hospitalizations
  *Sx assessment:* CAT (COPD Assessment Test) validated, at

catestonline.org

- **Exam:** Can be nl in mild disease; varied presentation can include ↑ AP diameter, cachexia, pursed-lip breathing, tripod position, ↓ breath sounds, prolonged expiratory: inspiratory ratio, wheezing, hyperresonance; clubbing *not* sign of COPD
- **Spirometry:** Obtained at dx, may be used to track disease progression; for dx, should show obstructive deficit (FEV1/FVC < 0.7);
  *FEV*1 used to classify deficit: *mild* >80% predicted; *mod* 50–80%; *severe:* <50%
  *Bronchodilator response:* Often minimal; marked response → FEV1/FVC > 0.7 suggests asthma (see *"Asthma"*)
  *Other studies*, if obtained: ↑ RV, ↑ FRC ("air trapping"), ± ↑ TLC ("hyperexpansion"); ↓ $DL_{CO}$
- **Other:** Obtain baseline CXR & ECG; consider α1-antitrypsin testing in pts <45 y, ⊕ FHx, upper lobe predominance
- **Differential diagnosis:** Asthma, bronchiectasis, ILD, CHF, lung CA

## Nonpharmacologic therapy (*NEJM* 2010;362:1407; *GOLD* 2011; *Eur Respir J* 2004;23:932)

- **Smoking cessation:** ↓ FEV1 decline & ↓ **all-cause mortality** (*JAMA* 1994;272:1497; *Ann Intern Med* 2005;142:233); *see "Tobacco Use"*
- **Supplemental oxygen:** If $PaO_2$ < 55 mmHg or $SpO_2$ ≤ 88% for goal $SpO_2$ > 90%; ↓ **all-cause mortality** by 20% (*Ann Intern Med* 1980;93:391; *Lancet* 1981;1:681); recommended ≥18 h/d; counsel re: home $O_2$ safety (fire hazard, tubing can be fall risk)
  *Air travel or altitude:* $PaO_2$ > 70 mmHg likely OK, see *"Pre-flight assessment"*
- **Vaccines:** Influenza, pneumonia (see *"Immunizations"*)
- **Pulmonary rehabilitation:** ↑ functional capacity & QoL (*Cochrane Database Syst Rev* 2006;4:*CD*003793)
- **Goals of care:** Discussion indicated for all pts w/ mod–severe disease; explore/document preferences including intubation, tracheostomy, ICU; see *"End-of-Life"*

## Pharmacotherapy (*NEJM* 2010;362:1407, *GOLD* 2011)

- No Rx proven to alter the long-term decline in lung function; used to ↓ sx, ↓ exacerbation severity/freq, improve functioning;
- **Short-acting bronchodilators:** β2-agonist albuterol & anticholinergic ipratropium; combination of both ↑ bronchodilation but may not improve sx (*Chest* 1994;105:1411)
  *Nebs vs. MDI:* Generally equivalent; see "Inhaled medications" in *"Asthma"*
- **LABA:** ↑ FEV1 (but does not change rate of FEV1 decline) ↓ sx, 25% ↓ in exacerbations;
- **Tiotropium:** ↑ FEV1 (but does not change rate of FEV1 ↓ ); ↓ exacerbations, compared w/ LABA, 11% ↓ freq & severity of exacerbations (*NEJM* 2011;364:1093)
- **ICS:** Added to LABA or tiotropium to ↓ exacerbations; *not* recommended as monotherapy (*NEJM* 2007;356:775); s/e include thrush, dysphonia (rinse mouth after use, use spacer w/ MDI—requires Rx); systemic toxicity possible w/ ↑ dose
- **LABA + ICS + tiotropium:** When compared w/ LABA + ICS alone, may ↓ mortality, PO glucocorticoid use, & hospitalizations, but prospective RCT lacking (*Chest* 2012;141:81)
- **Other:** Roflumilast (PDE5 inhibitor) or theophylline used as adjunct, typically in severe disease & usually Rx'd by specialists
- **Azithromycin ppx:** 250 mg QD → ↓ exacerbation frequency by 27%, long-term effects unknown; concern for abx resistance, ↑ QTc, ototoxicity (*NEJM* 2011;365:689; *NEJM* 2012;367:340)

**Initial Approach to Therapy of Stable Disease (*GOLD* 2011)**

| GOLD Category | Regimen |
|---|---|
| **A** (FEV 50–80% predicted, mild sx [e.g., CAT score < 10], <2 exacerbations/y) | PRN SABA or ipratropium<br>*Alt:* LABA, tiotropium, SABA, & ipratropium |
| **B** (FEV 50–80% pred, sx not well-controlled [e.g., CAT ≥ 10], <2 exacerbations/y) | LABA or tiotropium<br>Alt: Tiotropium & LABA |
| **C** ($FEV_1$ < 50% pred, mild sx, ≥2 exacerbations/y) | ICS & (LABA or tiotropium)<br>Alt: Tiotropium & LABA |
| **D** ($FEV_1$ < 50% pred, sx not well-controlled, ≥2 exacerbations/y) | ICS & (LABA or tiotropium)<br>Alt: ICS & LABA & tiotropium, ICS & LABA & PDE5 inhibitor |

- **When to refer:** Dx uncertain, severe/refractory disease, onset <40 y

consideration of add'l agents, frequent exacerbations/hospitalizations, transplant eval (5 y median survival) or lung volume reduction surgery (may ↓ mortality & ↓ sx) (*Eur Respir J* 2004;23:932; *J Heart Lung Transplant* 2006;25:75; *NEJM* 2003;348:2059)

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## Acute Exacerbation

- **Definition:** Change in SOB, cough, and/or sputum production beyond baseline variation
- **Etiology: 50–70% infectious; of these, ~50% viral, 50% bacterial** (*H. influenzae* > *S. pneumoniae*, *M. catarrhalis* > *P. aeruginosa* esp in advanced disease > atypicals) though hard to distinguish colonizer vs. pathogen; noninfectious environmental insults (smoke, air pollution) also precipitants (*NEJM* 2008;359:2355; *Thorax* 2006;61:250)
- **Diagnostics:** Obtain CXR; consider sputum culture, ECG
- **Differential diagnosis:** CHF, PNA, PE may be more common causes of death in COPD exacerb than resp failure (*Chest* 2009;136:376)
- **When to refer:** Failure of outpt tx, uncertain dx, impaired ADL's, worsening gas exchange or SOB, AMS, poor home care → ED/admit (*Eur Respir J* 2004;23:932)

### Management (*NEJM* 2010;362:1407; *GOLD* 2011; *Eur Respir J* 2004;23:932)

#### Pharmacologic Management

| Medication | Comment |
|---|---|
| Oxygen | Target $SpO_2 \geq 90\%$; caution w/ ↑ $PaCO_2$ |
| Bronchodilators | SABA + ipratropium; nebs vs. MDI; review inhaler technique<br>Consider adding long-acting bronchodilator or ICS |
| Glucocorticoids | ↓ recovery time, ↓ risk of early relapse, ↑ $FEV_1$ & $PaO_2$<br>30–40 mg QD × 5–14 d; no difference between 5 d vs. 2 wk or 2 vs. 8 wk course; (*NEJM* 1999;340:1941; *JAMA* 2013;309:2223)<br>Consider PCP ppx if prolonged steroid course (see *"PCP Prophylaxis"*) |
| Antibiotics | Outpt data lacking but likely ↓ tx failure, possibly ↓ mortality; consider if ↑ sputum production/purulence (*Thorax* 2007;62:29);<br>Consider resistance patterns, ± pseudomonal coverage in adv disease |

# CHRONIC COUGH

## Background (*NEJM* 2000;343:1715)

- **Definitions:** *Subacute cough:* 3–8 wks; *Chronic cough:* >8 wks
- **Epidemiology:** Cough is common symptom-based visit complaint (*NHAMCS* 2010*, cdc.gov*)
- **Pathophysiology:** Cough receptors found in airways, lung parenchyma, tympanic membranes, esophagus & pericardium; cough is reflex w/ cortical control (may be suppressed or initiated voluntarily); cough mechanism involves diaphragm, glottis, & muscles of expiration
- **Etiology:** Varies by duration, can include airway (upper airway cough syndrome [UACS]), HEENT, GI, & CV causes

## Evaluation (*Chest* 2006;129:*S*1; *AFP* 2011;84:887)

- **General approach:** Hx/exam to screen potential etiologies; if none discovered, → trial of empiric tx for either UACS, asthma, or GERD
- **History:** Often nonspecific; ask about onset (post-URI), duration, triggers (after meals—GERD, allergens—asthma); R**ed flags:** Wt loss, hemoptysis, systemic sx
  *Assoc sx:* Postnasal drip, sinusitis, hoarseness, reflux sx
  *PMHx:* Atopy, GERD, CHF, immunocompromise, CA, TB exposure/RF
  *Meds/toxins:* ACEI, βB, smoking status/exposure, occupational exposures
- **Physical exam:** *VS*: Incl $SaO_2$, *HEENT:* Auditory canal foreign body, nasal polyps (asthma), cobblestoning (UACS); *Pulm:* wheezes, crackles; *Cardiac:* volume overload, valvular disease; *Extremities:* clubbing
- **Diagnostics:** If dx not suggested by above (e.g., ACEI) → **CXR;** given that most chronic cough 2/2 GERD, UACS, or asthma, may be deferred in nonsmokers until failure of 1st-line empiric tx; further studies (PFTs, CBC, sinus films) as per Ddx (below)

## Differential Diagnosis (*Arch Intern Med* 1996;156:997; *NEJM* 2000;343:1715)

- **Subacute cough:** Postinfectious cough, bacterial sinusitis, asthma;

(*NEJM* 2006;355:2125)

*Postinfectious cough:* Respiratory tract infection → postnasal drip, tracheobronchitis; resolves w/o tx; average duration of bronchitis-associated cough is 24 d

*Bacterial sinusitis:* See *"Sinusitis"*

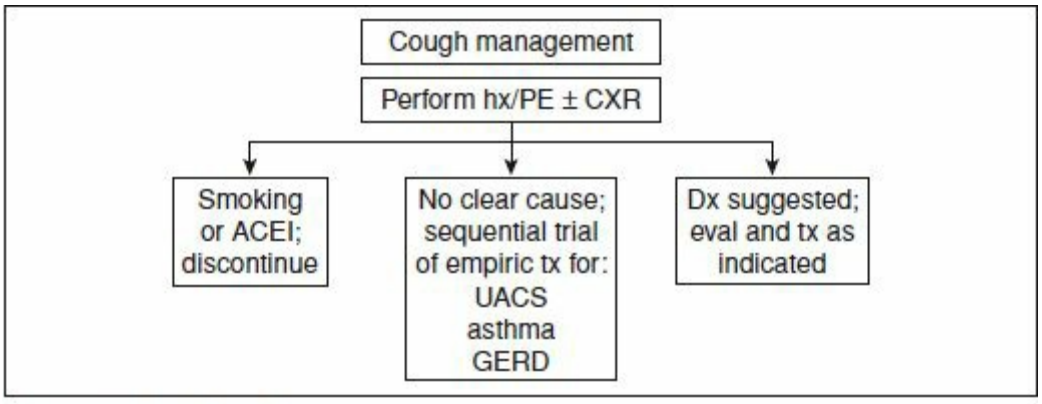
- **Chronic cough:** Often multifactorial; may require tx of multiple causes

**Selected Causes of Chronic cough**

| Etiology | Management/Notes |
|---|---|
| Smoking | Tx: Smoking cessation; see *"Tobacco Use"* |
| ACEI | Sx can occur 1 wk–6 mos after starting Rx; cough resolves w/in 2 wks of discontinuation of Rx |
| UACS (34%) | Allergic or nonallergic rhinitis, sinusitis<br>Tx: Nasal ICS; see *"Allergic Rhinitis"* |
| Cough-variant asthma (28%) | Dx: PFTs (for cough, may start w/ trial of empiric SABA tx)<br>Tx: See *"Asthma"* |
| GERD | Dx/Tx: Empiric trial of PPI; see *"Gastroesophageal Reflux Disease"* |

- **Other:** COPD, Eosinophilic bronchitis (dx'ed w/ induced sputum, rx w/ ICS), *B. pertussis* (see *"URI and Influenza"*), CHF, ILD, allergic alveolitis, bronchogenic CA, lung abscess, sarcoidosis, TB, habitual cough

## Management




(Adapted from *Chest* 2006;129:S1)

**Figure 12-1 Chronic cough management**

## When to Refer

- If red flags present or sx persist despite empiric tx for common

problems, referral to pulm for consideration of bronchoscopy/further studies

# DYSPNEA

## Background (*NEJM* 1995;333:1547)

- **Definition:** Subjective experience of breathing discomfort
- **Pathophysiology:** Likely multifactorial; potential mechanisms include blood gas derangements, ↑ airway resistance, metabolic work of breathing, ↑ effort of resp muscles, pulm receptors (irritant or pressure-responsive), or CNS perception
- **Etiologies:** Vary by onset/duration
  *Acute dyspnea:* Often due to sudden ↑ LVEDP, bronchospasm, PNA, or PE
  *Chronic dyspnea:* Often 2/2 asthma, COPD, ILD, CHF, obesity/deconditioning

**Etiologies of Dyspnea by Category**

| Pathologic Category | Specific Causes |
|---|---|
| Obstructive | Asthma, COPD, tumor, foreign body, bronchiectasis |
| Lung Parenchyma | ILD (incl sarcoid), ARDS |
| Vascular | PE, pHTN, vasculitis, hepatopulmonary syndrome |
| Infectious | PNA (bacterial, viral, fungal), bronchitis |
| Mechanical | *Pleural:* Effusions, fibrosis;<br>*Chest wall:* Edema, obesity, kyphoscoliosis, ascites, pregnancy<br>*Diaphragm:* Muscular, neuromuscular junction, or nerve d/o |
| Cardiovascular | CHF (w/ or w/o pulm edema), angina/ACS, valvular disease, pericardial effusion/constriction; deconditioning |
| Metabolic/hematologic | Anemia, metabolic acidosis, hypoxemia, CO poisoning, methemoglobinemia, pregnancy (multifactorial) |
| Psychological | Anxiety, panic attack, somatization |

(*Harrison's Principles of Internal Medicine, 17th ed; AFP* 2005;71:1529)

## Evaluation

- **General approach:** Categorize likely origin as *pulmonary, cardiac, both, or neither;* causes often coexist (e.g., 20% of pts w/ CHF also have COPD) (*JACC* 2007;49:171)
- **History:** Distinguish from fatigue, asthenia; assess chronicity, onset,

quality, assoc sx (chest pain, wheezing, tightness, fever, cough, sputum, hemoptysis, PND, orthopnea, leg swelling, recent illness); assess comorbidities

- **Exam:** *VS:* BMI, inc resting & ambulatory $SpO_2$, *pulm:* wheezing, consolidation, *cardiac:* murmurs, gallops, JVD, *Ext:* clubbing, edema
- **Labs:** CBC (anemia), chem-7 (acid/base, CKD); **BNP or NT-proBNP;** BNP > 100 pg/mL Se/Sp 90/76% for CHF as cause of dyspnea (*NEJM* 2002;347:161); NT-proBNP < 300 essentially rules out CHF (NPV 98%) (*Eur Heart J* 2006;27:330); both can be falsely ↑ in ESRD & falsely ↓ in obesity
- **Diagnostics: ECG** & **CXR;** if unrevealing → spirometry; consider CBC
- **Further testing:** Consider ABG, chest CT (PE, early ILD) full PFTs w/ lung volumes & diffusing capacity, TTE

# HEMOPTYSIS

## Background and evaluation (*AFP* 2005;72:1253; *Chest* 1997;112:440)

- **Definition:** Blood (mixed w/ sputum or pure blood) expectorated from airway; "massive hemoptysis" defined variably but generally >600 cc/24 h → ED
- **General approach:** Determine source & amount of blood; hx/PE to guide w/u
- **History:** Ask about onset; attempt to quantify blood (frank blood vs. blood-tinged sputum)

*Assoc sx:* Fever, SOB, cough, respiratory infection, nosebleed, vomiting, epigastric pain

*Consider pseudohemoptysis:* ENT (*epistaxis*), oropharynx, GI (*hematemesis*)

*PMHx;* COPD or other lung disease, immunocompromise, autoimmune disease, CHF, coagulopathy (anticoagulants, liver disease) TB exposure/risk factors, smoking hx, malignancy (lung or other primary), travel hx

- **Labs:** Consider CBC, coags, further labs as dictated by eval
- **Imaging:** Chest CT; further studies as dictated by eval

**Selected Differential Diagnosis of Hemoptysis** (*AFP* 2005;72:1253)

| |
|---|
| **Airway disease: Bronchitis** (most common, 26%), bronchiectasis (i.e., CF)<br>*S/sx:* Chronic/subacute cough & sputum which turned bloody/blood-streaked<br>*Dx:* Consider resp viral panel, bronchiectasis w/u |
| **Neoplasm: Primary lung cancer** (23%), metastasis to lung (melanoma, breast, colon, RCC), bronchial carcinoid, Kaposi sarcoma<br>*S/sx:* Smoking hx, elderly, wt loss, dry cough, known nonlung malignancy, HIV+<br>*Dx:* Consider sputum cytology, referral for bx |
| **Infection: PNA** (10%, often staph, pseudomonas, aspergillus), lung abscess, **TB** (8%),<br>*S/sx:* Cough w/ purulent sputum, fevers, chills, wt loss, HIV+, immunosuppression<br>*Dx:* Sputum gs/culture (± AFB), fungal markers, likely referral for bronchoscopy; suspicion of TB requires resp isolation during w/u (see *"Tuberculosis"*) |
| **Pulm/CV:** PE, CHF, mitral stenosis<br>*S/sx:* Dyspnea, hypoxemia, cardiac hx, high risk for DVTs<br>*Dx:* See *"DVT/PE"*, likely → ED/inpt |
| **Inflammatory/vasculitic:** Vasculitis or pulm-renal syndromes (granulomatosis w/ polyangiitis, Behçet, Goodpasture, SLE pneumonitis), diffuse alveolar hemorrhage (ARDS, cocaine, idiopathic pulm hemosiderosis)<br>*S/sx:* As per syndrome: Systemic sx, renal failure, sinus sx, autoimmune hx<br>*Dx:* ANCA, anti-GBM, *UA/urine sediment*, BUN/Cr, ANA, anti-dsDNA, anti-Smith, tox screen; referral for bronchoscopy w/ BAL vs. → ED/inpt |
| **Other:** Vascular (AVM, bronchovascular fistula; usually p/w massive hemoptysis); trauma, FB, postprocedure; typically → ED |

## Management

- **Treatment:** Aimed at underlying etiology
- Reverse any existing coagulopathy if there is no contraindication
- **Referral:** Massive hemoptysis, hemodynamic instability, or new hypoxemia → ED; any other persistent or chronic hemoptysis, abnl chest CT, or dx uncertain → pulm

# PULMONARY NODULES

## Background (*Chest* 2013;143:*s*93)

- **Definitions:** *solitary pulmonary nodule* (SPN): Radiologically defined as an intraparenchymal lung lesion < 3 cm in diameter not assoc w/ atelectasis or adenopathy; often characterized by size, density, & surrounding characteristics (e.g., ground glass); *Indeterminate:* Nodules which radiographically are not clearly benign
- **Size:** Nodules < 8 mm have lower likelihood of malignancy (*Chest* 2007;132:108*S*); lesions larger than 3 cm are termed "lung masses," presumed malignant (*Chest* 2003;123:89*S*)
- **Epidemiology:** >20% prevalence w/ healthy volunteers (*Lancet* 1999;354:99) higher in other populations (*AJRCCM* 2012;185:363)
- **Malignancy risk factors:** *Nodule:* Diameter, spiculation, upper lobe location;
  *Patient:* ↑ age, smoking hx (highest: current smokers; pts who quit >7 y ago now low-risk), hx extrathoracic CA >5 y before nodule detection, asbestos exposure
- **Etiology:** *Benign:* Nonspecific granuloma > hamartoma, infectious granuloma (aspergillosis, Cocci, Cryptococcus, Histo, TB); *Malignant:* Adenocarcinoma (47%), squamous cell (22%), undifferentiated NSCLC (7%), small cell (4%), bronchioloalveolar cell (4%), metastases (8%)

## Evaluation (*NEJM* 2003;348:2535)

- **General approach:** For solitary nodules 8–30 mm in size, assessment of malignancy risk as well as surgical candidacy & pt preference dictate surveillance strategy
- **Nodule history:**
  **Is it real?** If visualized on CXR, confirm w/in-slice CT
  **Is it new?** Review prior imaging—if stable for >2 y, no further w/u needed
- **Probability of malignancy:** Should be calculated w/ validated tool, such as Mayo Clinic model (*Arch Intern Med* 1997;157:849); n.b. this may underestimate risk at low values & test characteristics improved

by adding PET (*Chest* 2005;128:2490); clinical calculator online at: http://reference.medscape.com/calculator/solitary-pulmonary-nodule-risk

- **Surgical risk:** See *"Perioperative Evaluation"*

## Management

- Management options include careful observation, further diagnostic testing, or surgery
- **Shared decision-making:** Discussion of risk/benefits of different strategies appropriate, esp for pts of intermed probability where risks/benefits less certain

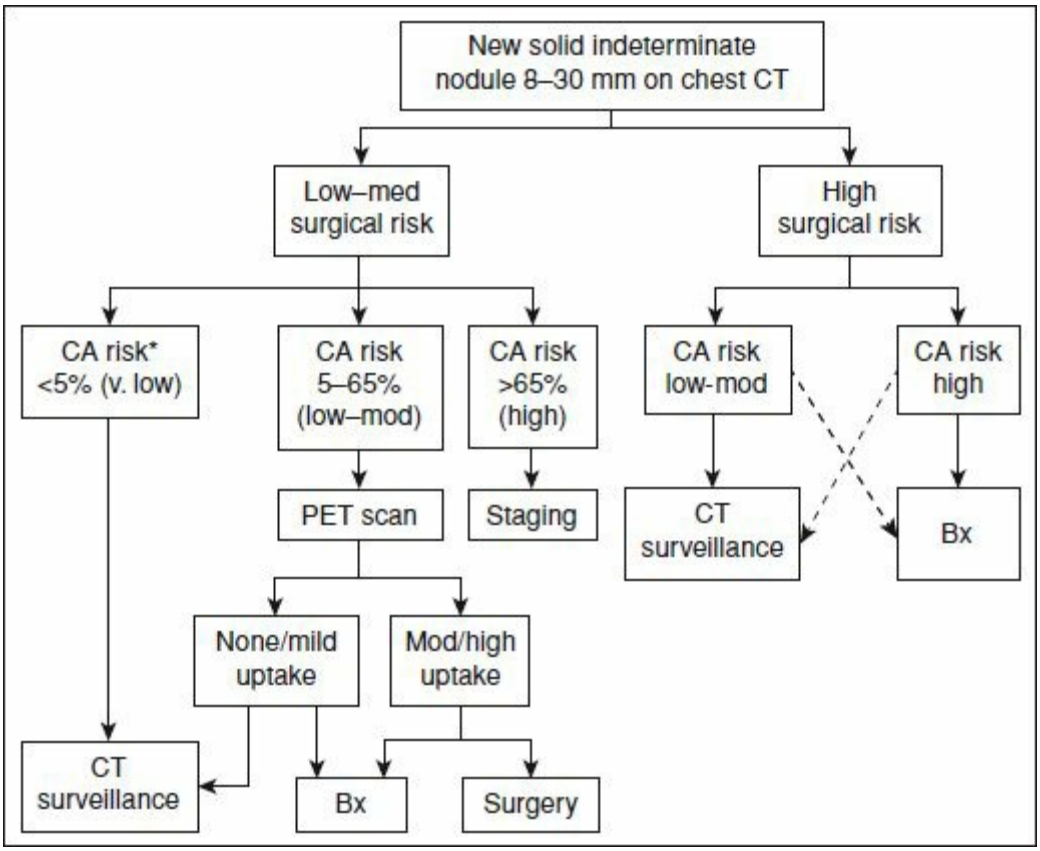



Figure 12-2 Management of solid indeterminate nodules

*CA risk based on validated model (i.e. Mayo Clinic Model)

(Adapted from *Chest* 2013;143:s93)

- **Surveillance:** Done w/ repeat chest CT; dependent on presence or absence of RF (above); generally indicated if pretest probability is **low**

**Fleischner Criteria for Pulmonary Nodule Surveillance** (*Rad* 2005;237:395)

| Nodule Size | Low Risk | High Risk |
|---|---|---|
| <4 mm | Not indicated | 12 mos |
| 4–6 mm | 12 mos | 6–12 mos, then at 18–24 mos |
| >6–8 mm | 6–12 mos, then 18–24 mos | 3–6 mos, then 9–12 mos, then 24 mos |
| >8 mm* | 3, 9, 24 mos | VATS; excision of lesions |

*At nodule size (8 mm; assess if low, intermediate, or high risk (*Chest* 2003;123(1 *Suppl*):89S

- **Further diagnostics:** Generally indicated if pretest probability is **intermediate**
  *PET Imaging:* Se/Sp 87/83 for malignancy, Nodules < 1 cm cannot accurately be evaluated by PET (*Lung Cancer* 2004;45:19)
  *CT-guided FNA* (90% Se, 4–18% risk of PTX, best for peripheral lesions);
  *Bronchoscopy* (best for central lesions) (*AJRCC* 2012;185:363–372)
- **Surgical diagnosis/treatment:** Generally indicated if pretest probability for CA is **high** VATS, traditional thoracotomy, lobectomy
- **Multiple pulmonary nodules:** If lesions > 1 cm, likely to represent malignancy (often mets); if <5 mm likely benign process (infection, inflammatory, pulm AVM, pneumoconiosis); may require tissue sampling

# OBSTRUCTIVE SLEEP APNEA (OSA)

## Background (*Lancet* 2002;360:237)

- **Definitions:** *Sleep apnea:* Disorder in which pts experience *apneas* (cessation of breathing) or *hypopneas* (shallow breathing) often assoc w/ daytime hypersomnolence
  ***Obstructive:*** Due to upper airway collapse/closure; *central:* Due to ↓ respiratory drive; *mixed:* Central event → resumption of resp effort against relaxed/closed upper airway
- **Epidemiology:** 2–4% of the general population has OSA (*Proc Am Thor Soc* 2008;5:136) but prevalence up to 26% in high-risk populations
- **Risk factors:** Obesity, ♂ sex, age > 50 (*Arch Intern Med* 2002;162:893), EtOH use, tobacco use, African-American descent
- **Pathophysiology:** Sleep-induced relaxation of pharyngeal dilator

muscles → repetitive pharyngeal collapse during sleep → apnea (≥10 s) or hypopnea (30% ↓ airflow × ≥10 s) → recurrent arousals & desaturations

- **Complications:** *CV:* ↑ risk HTN (*NEJM* 2000;342:1378), CAD (*Eur Respir J* 2006;28:596), stroke (*NEJM* 2005;353:2034), & death (*Lancet* 2005;354:1046); *Neurocognitive:* ↓ cognitive performance, ↓ QoL, ↑ MVC & work accidents (*NEJM* 1999;340:847)

## Evaluation

- **General approach:** Suspicion based on hx/exam, confirmed w/ sleep study
- **History:** Snoring, witnessed apneas/gasping,
  *Daytime sx:* Daytime hypersomnolence (most common sx in OSA, can use validated survey to track, e.g., Epworth Sleepiness Scale), cognitive dulling, morning HA,
  *PMHx:* Poorly controlled HTN, CHF, stroke, DM, unexplained pHTN, polycythemia, ↑ $PaCO_2$, poorly controlled HTN
  *Meds/Toxins:* Respiratory depressants (opiates, sleep aids, EtOH), tobacco
- **Exam:** *Vitals:* BP, BMI, $SaO_2$; *HEENT;* septal deviation, turbinate hypertrophy, enlarged tonsils or uvula, macroglossia, retrognathia, ↑ Mallampati score (obscured view of soft palate/uvula), ↑ neck circumference; *CV* (cor pulmonale, LVH); *Pulm:* Full lung & chest wall exam
- **Sleep study:** Either lab-based polysomnography (PSG) or in select pts w/ a high pretest probability, a home-based study (HST); can be used in diagnosis and/or for titration of optimal CPAP Rx
  *Mechanism:* PSG records sleep stages using EEG, EMG, & eye movements; evaluates for respiratory events (≥10 s); & calculates apnea-hypopnea index (AHI) = sum of apneic & hypopneic episodes/h of sleep
  *Dx:* OSA diagnosed when AHI shows at least 5 events/h (mild = AHI 5–15, mod = AHI 16–30, severe = AHI > 30)
- **Differential diagnosis:** 1° snoring (see *"Snoring"*), hypothyroidism, med effects/sedatives

## Management

- **Behavioral:** ( ↓ wt; avoid EtOH, tobacco, sedatives), positional Rx to avoid supine sleep, dental/oral appliance
- **Positive pressure ventilation:** CPAP or BiPAP
  *CPAP:* Generally first-line for OSA; ⊕ pressure "stents" upper airway open & prevents collapse; has been shown to ↓ BP & improve metabolic syndrome (*NEJM* 2011;365:2277), ↓ sleepiness/↑ performance (*AJRCCM* 2001;164:608) ↓ fatal & nonfatal CV events (*Lancet* 2005;354:1046) & ↑ EF in pts w/ CHF (*NEJM* 2003;348:1233)
  *BiPAP:* Can be tried in pt intolerant of continuous ⊕ pressure; more expensive & not shown to ↑ adherence; first-line for central sleep apnea, may be helpful if concomitant hypoventilation (e.g., COPD or obesity hypoventilation)
- **Surgery:** Of limited benefit; consider referral in refractory disease, nonobese young pts w/ severe disease (*Chest* 1997;111:265; *Sleep* 2007;30:461)

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## Obesity Hypoventilation Syndrome (OHS)

- **Definition:** OHS is a disorder in which obese individuals (BMI > 30 kg/m$^2$) demonstrate awake alveolar hypoventilation ($PaCO_2$ > 45 mmHg) that cannot be attributed to other conditions
- **Epidemiology:** All pts w/ OHS are obese; 85–90% have coexisting OSA (*Chest* 2007;131:1678)
- **Typical presentation:** S/sx: Similar to OSA + *Dyspnea on Exertion* (*Chest* 2000;117:205); may have s/sx of pHTN and R-sided HF, ± plethoric complexion from polycythemia; labs may include ↑ serum bicarb, ↑ HCT
- **Eval:** ABG, PFTs, sleep PSG, CXR (r/o diaphragmatic paralysis), ECG (RAA, RVH), TTE (RVH) ± RHC (pHTN) (*Am J Med* 2004;116:1)
- **Treatment:** High assoc mortality if untreated: OSA **behavioral tx** (wt loss, avoiding sedatives, treating comorbid conditions); **BiPAP** (CPAP okay if maintains adequate ventilation); surgical intervention (incl bariatric surgery; see *"Obesity"*)

# NOTES

# CHRONIC KIDNEY DISEASE

## Background (*Am J Kidney Dis* 2002;39:S1; *NEJM* 2006;354:2473; 2008;359:1477)

- **Definition:** ≥3 months w/ GFR < 60 mL/min/1.73 m² **or** signs of kidney damage: proteinuria/albuminuria, pathology on renal biopsy/imaging
  **Estimated GFR (EGFR):** Measure of filtration of all glomeruli; used to classify CKD; ↓ w/ age; Estimated w/ Cockroft–Gault, CKD-EPI, or MDRD equations; CKD-EPI is best for pts w/ GFR near nl (*JAMA* 2012;307:1941); Cockroft–Gault tends to overestimate GFR; calculators available on-line: kidney.org/professionals/kdoqi/gfr_calculator.cfm
  **Proteinuria:** Spot urine albumin:Cr ratio >30 mg/g); spot urine protein:Cr ratio >0.2 g/g or 24 hour excretion >0.3 g/d
  **Nephrotic syndrome:** Proteinuria >3.5 g/d w/ minimal to no hematuria, no RBC casts ± edema, HLD
  **Nephritic syndrome:** RBC in urine ± proteinuria, RBC casts; Ddx includes IgA nephropathy, lupus nephritis, ANCA vasculitis, postinfectious GN, thin basement membrane disease, hereditary nephritis, mesangial/MPGN, RPGN, fibrillary GN
  **Medications that interfere w/ serum Cr assay:** TMP-SMX, cimetidine, cefoxitin
- **Pathophysiology:** Diabetes mellitus (45%), HTN/renal artery stenosis (27%), glomerular (10%), interstitial (5%), polycystic kidney disease (PKD) (2%).
- **Epidemiology:** CKD affects 16.8% of US adults (*JAMA* 2007;297:1767); prevalence among US adults, by stage: 1: 1.8%, 2: 3.2%, 3: 7.7%, 4: 0.35%, ESRD: 2.4% (*JAMA* 2007;298:2038)
- **Risk factors:** DM, HTN, CVD, HLD, obesity, age >60 y, tobacco, malignancy, congenital urinary tract abnormalities, FHx (CKD, PKD, Alport, medullary cystic disease), myeloma, HIV, HCV, autoimmune disease, recurrent UTIs, drugs (NSAIDS, aminoglycosides, tacrolimus, CsA), ethnicity (African ancestry, Native American, Asian-Pacific Islander, Hispanic), hx AKI
- **Prevention:** Glycemic control in DM, **BP control,** avoid nephrotoxins including IV contrast, NSAIDs (*NEJM* 1993;329:977; *Lancet*

1998;352:837)

## Evaluation (*AFP* 2011;84:1138)

- **History:** Variety of presentations, from asx to edema, HTN, *uremia* (nausea, pericarditis, anorexia, neuropathy, altered MS), hematuria, flank pain
- **Exam:** Carotid/renal bruits in addition to regular exam
- **Workup:** Exam of urine microscopy & sediment, Chem-7, Ca, $PO_4$, PTH, lipids, serum albumin, CBC, urine protein:creatinine ratio (UPCR), urine albumin:creatinine ratio (UACR); ✓ lipids & TG; *Consider*, HbA1c, hepatitis serologies, HIV, RPR, based on clinical suspicion; *Can usually defer to specialist:* 24 h urine protein, ESR, CRP, C3, C4, ANA, ANCA, anti-GBM, cryoglobulins, serum/urine immunofixation for amyloid, light chains

  **Renal biopsy:** Consider in nephrotic syndrome/acute kidney injury of unknown cause, acute nephritic syndrome

  **Screening for CKD:** Indicated in pts w/ CKD risk factors (above); ✓ serum Cr, UA, urine albumin; USPSTF found insufficient evidence to recommend screening asx adults (excluding those w/ HTN, DM2) (*Ann Intern Med* 2012;157:567)

  **Monitoring:** Chem-7 q1–3mos; CBC, vit D, PTH, $PO_4$ q6mos; annual urine microalbumin:creatinine ratio in DM (see "*Diabetes*")

## Management (*AFP* 2007;75:1487; 2010;81:27; 2012;86:749; *JAMA* 2004;291:1252; *NEJM* 2010;362:56)

### Chronic kidney disease: A clinical action plan (KDOQI Guidelines)

| Stage | Description | GFR (mL/min/1.73 $m^2$) | Actions |
|---|---|---|---|
| | At ↑ risk | ≥90 + CKD risk factors | Screening, risk reduction |
| 1 | Kidney damage w/ nl or ↑ GFR | ≥90 + persistent albuminuria | Dx/Rx underlying condition, comorbidities, CVD risks |
| 2 | Kidney damage w/ mild ↓ GFR | 60–89 + persistent albuminuria | Est progression, optimize CVD risk reduction |
| 3 | Mod ↓ GFR | 30–59 | Eval & treat complications, nephrology referral |
| 4 | Severe ↓ GFR | 15–29 | Prepare for RRT |
| 5 | Kidney failure | <15 or dialysis | Dialysis if uremic, ↑ fluid |

- **Correct reversible causes:** Dehydration, meds (diuretics, NSAIDs, ACEI, aminoglycosides), infection, urinary obstruction
- **Lifestyle modification:** Smoking cessation (see "*Tobacco use*"), BMI $<25$, waist circumference $<102$ cm ♂, 88 cm ♀; mod exercise 30–60 min 4–7 d/wk
- **Nephrology referral:** For stage 3 CKD, any diabetic w/ microalbuminuria; consider for urine albumin:Cr ratio $\geq 300$ mg/g, etiology unknown cause, rapidly ↓ GFR, complications of CKD requiring medical Rx (i.e., Epo, phosphorous binders, Vit D), hyperkalemia, resistant HTN, recurrent nephrolithiasis, suspicion of hereditary CKD
- **Slowing CKD progression:**
  **ACEI or ARB:** Renoprotective in proteinuric CKD; tolerate 25% ↑ in Cr w/ use; ACEI + ARB combo likely no benefit (*Lancet* 2008;372:547), BP goal $<130/80$ (proteinuric CKD, proteinuria $>500$ mg/d), $<140/90$ (nonproteinuric CKD, proteinuria $<500$ mg/d) (*Circ* 2011;124:1727); For HTN uncontrolled by ACEI/ARB alone, add loop diuretic; diltiazem & verapamil ↓ proteinuria in contrast to amlodipine which does not (*Kidney Int* 2004;65:1991)
  **Nutrition:** Low salt, low protein (0.8 g/kg/d) diet (very low protein diet may ↑ death in stage 4 CKD) (*Cochrane Database Syst Rev* 2009;8:CD001892), glycemic control in DM, consider low K & $PO_4$ (800–1000 mg/d); nephrocaps (vit B complex + vit C)
  **Treatment of hyperlipidemia:** May slow kidney damage
  **Correction of metabolic acidosis:** ↓ GFR → ↓ acid excretion → ↓ $HCO_3$ → osteopenia, ↑ PTH, ↑ inflammation, muscle wasting, progressive CKD; treat w/ Na bicarbonate or citrate to $HCO_3$ goal of 23–29 mEq/L (*Kidney Int* 2010;78:303; *J Am Soc Nephrol* 2009;20:2075); citrate contraindicated in pts on aluminum-containing medications, e.g., antacids, buffered ASA, sucralfate, or some phosphate binders due to ↑ aluminum absorption → intoxication & osteomalacia
- **CV risk reduction:** BP control, lipids & TG at goal (*Ann Int Med* 2012;157:251)
- **Renal replacement therapy:** Includes hemodialysis (HD), peritoneal dialysis (PD), transplant

**Indications:** Clinical decision; pericarditis, uremic encephalopathy/bleeding, fluid overload, uncontrolled HTN, persistent electrolyte disturbances, uncontrolled N/V, malnutrition; consider for cognitive problems, itching/restless legs, fatigue; Consider when eGFR 5–10 **&** sx of uremia/fluid overload (*CJASN* 2011;6:1222)

**Preparation for HD:** For stage 4 CKD, avoid BP measurement & venipuncture in nondominant arms, avoid subclavian or PICC lines; refer to vascular surgeon when serum Cr >3.5 or 3 in DM; 1° AV fistulas take mos to mature; synthetic grafts mature in wks, but have ↑ thrombosis/infections

**Timing of HD initiation:** No mortality benefit to early initiation of dialysis & no difference in CV events, infection, HD complications (IDEAL, *NEJM* 2010;363:609)

**Peritoneal dialysis:** Catheter may be used ~2 wks after placement

**Transplant:** Refer to transplant center when GFR <30 in appropriate candidates and if pt willing to consider

- **Vaccines:** PSV23 and influenza; if on HD, add PCV13 and HD (see "*Immunizations*")
- **Care after transplant:** ✓ Chem-7, urine protein/albumin/Cr, BK virus (if ↑ Cr), lipids, A1c, Vit D, PTH, immunosuppressant troughs (if applicable); Avoid live virus vaccines
- **Patient information:** *JAMA* 2007;298:1244

## Complications of CKD & Management (*NEJM* 2010;362:56; 1312)

- **Anemia:** ↓ renal Epo production → fatigue, lethargy; correct iron deficiency (i.e., transferrin saturation <20% + ferritin <100 ng/mL in CKD pts, 200 ng/mL in HD pts) before using ESA; consider ESAs in CKD & ESRD when Hgb <10 w/ a target of 11–12 (*Am J Kidney Dis* 2007;50:476); higher Hgb targets (i.e., Hgb >13) assoc w/ ↑ risk of stroke/CHF/mortality (*NEJM* 2009;361:2019); ESA s/e include HTN, HA, myalgias, pure red cell aplasia (rare); ESA contraindicated in hx stroke, malignancy; darbepoetin has a longer half-life than Epo w/ similar s/e profile; peginesatide is a synthetic agonist of the EPO receptor (*NEJM* 2013;368:387)

  **Iron repletion:** Goal transferrin saturation 20–50%, ferritin >100 (*AJKD* 2007;50:471)

- **Bone disease:** ↓ GFR (usually <30) →↑ $PO_4$ →↑ PTH, ↓ calcitriol → renal osteodystrophy (osteitis fibrosa, osteomalacia, adynamic bone disease) (*NEJM* 1995;333:166); PTH goal varies by CKD stage: **3:** 35–70 pmol/L, **4:** 70–110, **<15 or HD:** 150–300 (*Am J Kidney Dis* 2003;42:S1); For CKD stages 3–5, check Ca, $PO_4$, 25OH Vit D, PTH; ↑ PTH is a surrogate for renal osteodystrophy & is targeted by therapies below:
  **Ergocalciferol or cholecalciferol:** If 25OH Vit D <30 ng/mL
  **Calcitriol (= 1,25-dihydroxyvitamin D):** Used to treat 2° hyperparathyroidism; Analogues include doxercalciferol, paricalcitol; Use when 25OH Vit D levels >30 & PTH levels exceed target; Stop if ↑ Ca (*Arch Int Med* 2008;168:397)
  **Cinacalcet:** Parathyroid calcium-sensing receptor agonist used to treat hyperparathyroidism; ↓ PTH, ↓ Ca, ↓ $PO_4$
- **Hyperphosphatemia:** Goal $PO_4$ is the normal range (*Kidney Int Suppl* 2009;76:S1) for pts not on HD, 3.5–5.5 for pts on HD (*Am J Kidney Dis* 2003;42(4 Suppl 3):S1); Use low $PO_4$ diet (800–1000 mg/d, no processed foods or colas); phosphorus binders w/ meals
  **Ø Ca (<8.4 mg/dL):** Use Ca acetate (PhosLo) or carbonate (Tums)
  **Intermediate Ca (8.4–9.5):** Ca acetate/carbonate; If bone disease, vascular calcification, or ↓ PTH then sevelamer or lanthanum
  **≠ Ca (>9.5 mg/dL):** Use sevelamer or lanthanum (non-Ca based); Sevelamer carbonate as effective as sevelamer HCl at reducing $PO_4$, yet has less of a lowering effect on $HCO_3$
  **≠ ≠ $PO_4$:** Use aluminum hydroxide short-term (<4 wks)
- **Volume overload/edema:** <2 g/d Na restriction + diuretics
- **Hyperkalemia:** Avoid potassium-rich foods, NSAIDs

# HEMATURIA

## Background (*AFP* 2006;73:1748; *BMJ* 2009;338:a3021; *NEJM* 2003;348:2330)

- **Gross hematuria:** Red or brown urine (~1 mL blood/L urine enough to change urine color); 25% of pts will have urologic CA, 34% other

urologic disease

- **Asymptomatic microscopic hematuria (AMH):** ≥3 RBCs/HPF on consecutive UA (clean catch, fresh void, midstream w/o menstruation); ⊕ dipstick should be followed by microscopy since concentrated urine, hemoglobinuria, & myoglobinuria may cause a false ⊕; AMH found in 9–18% of adults; 1–10% of these will have urologic CA, 8–10% will have no cause identified (but 1–3% of this group will later be diagnosed with malignancy) (*Cleveland Clin J Med* 2008;75:227)

**Differential diagnosis of hematuria**

| | |
|---|---|
| **Renal** | *Glomerular* (urine RBC casts, dysmorphic RBC, i.e., acanthocytes): IgA nephropathy, thin basement membrane disease, Alport syndrome, postinfectious GN, rapidly progressive glomerulonephritis, SLE, vasculitis, loin pain hematuria syndrome, Goodpasture, HSP<br>*Non-glomerular:* PKD, RCC, ruptured hemangioma, renal AVM, nutcracker syndrome (L renal vein compressed btw aorta & SMA), infarct/papillary necrosis, renal TB, TMA, sarcoid, thrombosis |
| **GU tract** | BPH, infection (UTI, pyelonephritis, prostatitis, urethritis, viral infection, sickle cell, stones, GU malignancy, hydronephrosis, vesico-ureteral reflux, fistula, hemorrhagic cystitis (cyclophosphamide), recent urologic procedure |
| **Other** | Exercise ("march hemoglobinuria"), trauma, over-anticoagulation, Foley; endometriosis of urinary tract (cyclic hematuria); Sex, DRE, Meds |
| **False ⊕** | Gyn source, supratherapeutic anticoagulation, myoglobinuria, semen, pH >9, dilute urine (leading to osmotic cell lysis) |
| **AUA Risk Factors for Malignancy** (*Urology* 2001;57:604) | |
| Age >35, tobacco use, analgesic abuse (phenacetin), pelvic XRT, alkylating agents (i.e., cyclophosphamide), occupational (dyes, benzene, aromatic amines), irritative voiding sx/chronic cystitis, gross hematuria, repeated UTIs, chronic indwelling foreign body | |

## Evaluation (*AFP* 2008;78:347; *NEJM* 2003;348:2330; *Urology* 2001;57:604)

- **History:** Transient vs. persistent hematuria, fevers, pain, medications, trauma, pyuria, dysuria; blood clots; lower urinary tract sx; recent URI (postinfectious glomerulonephritis/IgA nephropathy) or sexual activity; personal/FHx of renal disease, malignancy, bleeding d/o; occupational exposures, travel hx

  **Medications & food associated w/ red urine:** Ibuprofen, iron sorbitol, nitrofurantoin, food coloring, chloroquine, rifampin, beets, blackberry, rhubarb

  **Medications Æ hematuria:** Aminoglycosides, amitriptyline, analgesics, anticonvulsants, ASA, diuretics, OCPs, PCN (extended

spectrum), warfarin OD (*AFP* 2006;73:1748)

- **Exam:** Urethral exam, pelvic exam in ♀, DRE to assess for BPH in men; ✓ BP
- **Workup:** UA, UCx, microscopic urine eval (to confirm ⊕ urine dipstick), serum Cr; 24 h urine protein may be estimated by multiplying random urine protein:Cr ratio (mg/mmol) by 10 (*BMJ* 2009;338:a3021); pts w/ microscopic hematuria & e/o a UTI should have a repeat UA 6 wks later to confirm resolution of hematuria
  **Urine cytology:** *Cannot* r/o bladder Ca (Se 40–76%), but ⊕ cytology diagnostic of urothelial Ca; urine cytology & urine markers NOT recommended as part of routine eval of AMH, but may be useful if workup otherwise ⊖ (*Cancer* 1987;60:1423)
  **CT urography of kidney, ureters:** Preferred for pts w/ gross or microscopic hematuria without e/o infection, glomerular bleeding; MRI urography or U/S in pregnant pts
  **Cystoscopy:** Visualizes prostate, bladder, urethra; *Indications:* gross hematuria without e/o glomerular disease or infection, **all pts w/ blood clots;** pts w/ asymptomatic microscopic hematuria without e/o glomerular disease, infection, or other known cause of hematuria, & who have a malignancy risk factor (above)
  **Nephrology referral:** Glomerular hematuria (RBC casts, dysmorphic urine RBC, *absence* of blood clots), consider for ↑ Cr, eGFR <60, new HTN, proteinuria (>500 mg/24 h; see "*Proteinuria*")
  **Pts on anticoagulation:** Should undergo eval similar to pts who are not anticoagulated; therapeutic anticoagulation does not ↑ risk of hematuria (*Arch Intern Med* 1994;154:649)
  **Screening for bladder cancer in the general, asymptomatic population:** USPSTF finds insufficient evidence to screen for bladder CA (U/A, urine cytology, urine biomarkers) (*Ann Intern Med* 2011;155:246)
- **Follow-up for asymptomatic hematuria:** In pts with negative workup but malignancy risk factors, check annual U/A; If ⊖ for 2 consecutive y, then annual U/As may be discontinued
- **Patient information:** *AFP* 2005;71:135; 2006;73:1759

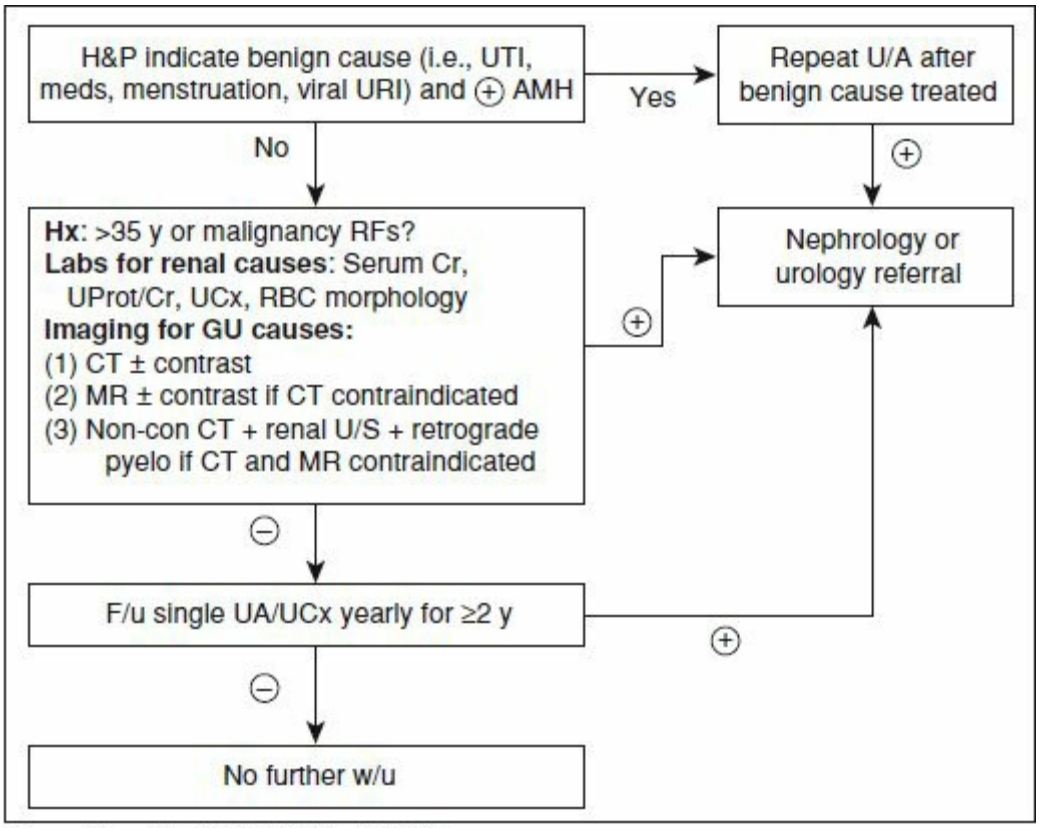


Figure 13-1 Hematuria Workup Algorithm

# NEPHROLITHIASIS

## Background (*J Urol* 2005;173:848; *NEJM* 1992;327:1141; 2010;363:954; 2012;367:50)

- **Epidemiology:** Affects 10–12% of US adults (7% of ♀, 13% of ♂)
- **Risk factors:** ⊕ FHx, sedentary/immobilized, IBD, UTI w/ urease ⊕ organism (i.e., *Proteus*), CKD, bone disease, hyperparathyroidism, CAD, HTN, DM2, chronic diarrhea, gout, pregnancy, RTA
  **Prior stone:** ↑ risk of recurrence: 50–60%/5 y, 50–75%/10 y
- **Pathophysiology:** Supersaturated urine w/ stone-forming salts + localized predisposing metabolic factors (↓ urine volume; ↓ pH; ↑ urinary Ca, ↑ oxalate, or ↑ urate; ↓ citrate)
  **Staghorn calculi:** Form in renal pelvis & branch to fill renal calyces

### Stone Types and Characteristics (*J Clin Endocrinol Metab* 2012;97:1847)

| Stone Composition | Common Causes | Urine pH |
|---|---|---|
| **Ca Oxalate > phosphate** (most common, 80%) | Dehydration, diet (↑ animal protein & salt), IBD, CKD, distal RTA, hyperparathyroidism, sarcoidosis, obesity, gastric bypass | Variable |
| **Uric acid** (5–10%) (Pure uric acid stones are radiolucent on radiograph) | Volume depletion, diet (high animal protein), gout, neoplastic disease w/ chemotherapy, TLS, obesity, myeloproliferative d/o; more common in hot, dry areas | <5.5 |
| **Struvite** (magnesium ammonium phosphate) | Urease-splitting UTIs (*Proteus, Klebsiella*) → staghorn stones; indwelling catheters | >7.5 |
| **Cystine** | Autosomal recessive d/o → cystinuria | ↓ |

## Evaluation (*AFP* 2011;84:1234; 2013;87:441; *JAMA* 2005;293:1107)

- **History:** Pain ranging from mild to acute colic ± nausea; sharp flank or abdominal pain ± radiation to groin/penis depending on location of stone; microscopic or gross hematuria (80% of pts); irritative sx (freq, urgency, dysuria) occur w/ distal ureteral stones or UTI; fluid intake, diet (salt, animal protein, spinach/nuts [↑ oxalate]); pts may be asx & the stone may be an incidental finding on CT done for other reasons

  **Medications:** Vit C (metabolized to oxalate), triamterene, protease inhibitors (Indinavir), furosemide (↑ Ca excretion), sulfadiazine, acyclovir
- **Exam:**

  **Full abdominal exam:** Pts w/ renal colic writhe in pain (vs. acute abdomen → lie still)
- **Workup:** UA (+RBCs, +WBCs), CBC (WBC >12 indicates systemic infection), Chem-7, UCx; Noncontrast CT scan **or** KUB + U/S to identify stone (*Eur Urol* 2002;41:351)

  **Urine strainer:** Strain all urine & save passed stone for analysis

  **24-h urine:** Two 24 h collections to measure composition & excretion of Ca, uric acid, citrate, oxalate & guide prevention in pts w/ recurrent stones; may be necessary to monitor response to lifestyle & medication

  **Noncontrast CT:** 3 mm cuts *gold standard* (97% sens, 96% spec) (*AJR* 2008;191:396); low-dose CT for BMI <30; IV contrast not needed

  **KUB radiograph:** 57% Se, 85% Sp: Inexpensive, minimal radiation; cannot detect stones <2 mm or radiolucent stones (uric acid, cystine, indinavir); serial imaging by KUB + US to assess for hydronephrosis & monitor stone location if pt is asx & does not

return w/ stone in hand after 40 d

**Ultrasound:** 61% Se, 97% Sp: Excellent for children, pregnant women, contrast allergy, serial studies; difficult to detect small stones but can visualize hydronephrosis

**After stone is passed:** W/u for d/o that predispose to stone formation (hyperparathyroidism, hyperuricemia/gout, distal RTA)

- **Prognosis:** Diet, medical Rx prevent recurrence in 75% of pts, ↓ new stones in 98%; 68% of stones ≤5 mm pass in 40 d; ↓ passage w/ ↑ size or location in UV junction

  **Asymptomatic stones:** ~50% risk of developing sx over next 5 y (*J Urol* 1992;147:319)

## Treatment (*AFP* 2011;84:1234; *Ann Intern Med* 2013;158:535; *J Urol* 2007;178:2418; *NEJM 2004*;350:684)

- **Nonurgent treatment options:**

  **Surveillance + medical expulsive Rx:** 4 wks of tamsulosin reasonable if nl renal function, pain well controlled, no infection, good fluid intake, stone <10 mm; Reimage in 4 wks if stone not spontaneously passed

  **Oral hydration:** ≥2.5 L of fluid/d, esp $H_2O$ or lemonade; goal is >2 L urine/d

  **Pain:** NSAIDs 1° line (avoid in preg, CKD, GI bleed, age >65); narcotics; APAP

  **aB:** Tamsulosin (↑ stone passage, ↓ time to passage by 2–4 d, ↓ pain)

  **CCBs:** Nifedipine not as effective as αB, not recommended

  **Cystine stones:** Hydration, ↓ dietary Na & protein, urinary alkalinization (below)

- **Asymptomatic, nonobstructing stones:** May be followed w/ U/S q6m
- **Surgical options:** (*Uro Clin N Am* 2008;35:441)

  **Extracorporeal shock wave lithotripsy:** Noninvasive, delivers energy pulses through fluid & body tissues into stone; 60–80% successful for ureteral & some renal stones <2 cm; ineffective for cystine & hard stones (*NEJM* 2012;367:50)

  **Percutaneous nephrolithotomy:** Creates an access tract into the renal collecting system to break & remove stone via nephroscopy; 70–95% successful (may require multiple procedures); for large

stone burden >2 cm, staghorn calculi

**Ureteroscopy:** Allows retrograde visualization of collecting system using a semi-rigid or flexible endoscope; gold standard for mid-distal ureteral stones; >95% successful in some studies, removal techniques include laser lithotripsy & basket extraction

- **Prevention of calcium stones:** >2.5 L of fluid intake/d (water or lemonade), low Na (<3 g/d), low oxalate (avoid nuts, spinach), low fructose/sucrose, avoid carbonated beverages (acidify urine); low animal protein (1 g/kg/d; ↓ protein → ↓ serum circulating acid → ↓ bone resorption & ↑ renal reabsorption of Ca → ↓ calciuria); avoid high doses of vit C & D, moderate Ca intake
- **Medications for prevention (prescribed based on 24 h urine studies):**

  **Potassium citrate:** Alkalinizes urine as citrate is metabolized to bicarbonate; Useful for Ca or UA stone formers, staghorn calculi prevention, cystine stones, urine pH <6, RTA, or if urine citrate is low; 10 mEq PO TID & titrate to urine pH 6.1–7; follow serum K; potassium bicarbonate may also be used

  **Thiazide diuretics:** HCTZ or chlorthalidone ↓ urinary Ca excretion, useful in ↑↑ Ca

  **Allopurinol:** Hyperuricemia & recurrent stones despite ↑ fluids & urine alkalinization

  **Tiopronin:** For pts w/ cystine stones; penicillamine also may be helpful; measurement of urine cystine assists in titration of dose

  **Ca supplements:** If urine oxalate is high

**Indications for Urology Referral**

| |
|---|
| Stone >10 mm, refractory pain, N/V, urosepsis, renal failure, hydronephrosis, DM, renal transplant or single kidney, recurrent UTIs |
| Any staghorn calculus |
| Failed surveillance: Pain, no progression of stone, systemic or end-organ effects |
| Pt desires intervention or occupational requirement (airline pilots, truckers, bus drivers) |
| Hx previous stones: Requires metabolic eval |
| Stone analysis & comprehensive metabolic eval (by PCP, urologist, or nephrologist) |

- **Patient information:** *AFP* 2006;74:99; 2011;84:1243; *JAMA* 2012;307:2557

# POTASSIUM DISORDERS

## HYPOKALEMIA (*NEJM* 1998;339:451)

### Causes of Hypokalemia (*Ann Int Med* 2009;150:619)

| General Mechanism | Specific Etiologies |
|---|---|
| Pseudohypokalemia | CML, CLL (WBC $>10^5/\mu L \rightarrow$ leukocyte uptake $\rightarrow$ falsely $\downarrow$ K) |
| Intracellular shift (most common) | $\uparrow$ Insulin (including hyperalimentation), $\beta_2$-agonists, caffeine, thyrotoxicosis, familial periodic paralysis, $\uparrow$ hematopoiesis (esp AML, megaloblastic anemia), alkalemia |
| GI loss | Vomiting, chronic diarrhea (laxative abuse, bowel diversion) |
| Renal loss | $\uparrow$ Aldosterone activity (1° hyperaldosteronism, renovascular disease, Cushing's, licorice, chewing tobacco)<br>Metabolic acidosis (proximal & some distal RTAs)<br>Hypomagnesemia (alcoholism, prolonged PPI) |
| Medications & substances | Diuretics (thiazides [10–40% of treated pts]), laxatives, PCN (esp in high doses), theophylline intoxication, chemotherapy, EtOH, caffeine, cola (>3 L/d) |

## Evaluation (*AJKD* 2005;45:233)

- **History:** Episodic vs. persistent, PMHx (esp eating d/o), FHx, GI fluid loss, TPN, diet, substance use, medications (including OTCs & wt loss remedies); sx typically occur only when K $<3$ mEq/L, & include muscle weakness, cramping, constipation, fasciculations, tetany, rhabdomyolysis; paralytic ileus $\rightarrow$ N/V
- **Exam:** BP, dental erosion, calloused knuckles, renal bruit, stigmata of Cushing's
- **Workup:** First r/o intracellular shifts; consider repeat ✓ K if reported as hemolyzed or suspect lab artifact; ✓ Mg, CK, plasma renin:aldosterone if HTN present
  **ECG changes:** May not correlate w/ level; QT prolongation, T wave flattening, U waves $\rightarrow$ PACs, PVCs, tachyarrhythmias, 2nd- or 3rd-degree AVB, VF

## Treatment

- **Potassium supplementation:** May also need to replete magnesium, although severe $\downarrow$ Mg ($<1.2$ mEq) hard to replete orally
  **Liquid/powder potassium:** Inexpensive, rapid, many pts dislike

taste

**Slow-release K:** Wax/microencapsulated formulation. ? a/w GIB; Expensive

**K-sparing diuretics:** Spironolactone, eplerenone

**K-rich foods:** See below; 1 avocado ~40 mEq, 1 banana ~10 mEq

- **Potassium-sparing diuretic:** May consider if pt hypertensive and idiopathic ↓ K persistent; consider hyperaldosteronism as above
- **When to refer:** K <2.5 mEq/L → ED, esp if pre-exisiting CV disease or ECG changes; consider referral to renal/endocrine if [↓] K persistent and/or cause unclear in spite of initial w/u; for hyperaldosteronism, see *"Hypertension"*

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## HYPERKALEMIA (*AFP* 2006;73:283; *NEJM* 2004;351:585)

### Causes of Hyperkalemia

| General Mechanism | Specific Etiologies |
|---|---|
| Pseudohyperkalemia | Gross hemolysis of sample, massive ↑ WBC or PLT, exercise (incl fist pumping during blood draw), clotted blood specimen |
| Extracellular shift (most common) | Acidemia/metabolic acidosis, ↓ insulin (esp diabetic w/ CKD), massive necrosis (rhabdo, tumor lysis, hemolysis, ischemic bowel), periodic paralysis, hyperglycemia, ↑ serum osmolarity |
| ↓ Renal secretion | Advanced CKD (GFR <15), CHF/cirrhosis, tubulointerstitial disease (DM, sickle cell, SLE, amyloid), hypoaldosteronism, Addison disease, congenital adrenal hyperplasia, type IV RTA, adrenal insufficiency (in assoc w/ ↓ Na) |
| Medications & substances | NSAIDs, ACEIs/ARBs (occurs in ~10% of pts), K-sparing diuretics, βB, TMP-SMX, digoxin, heparin, pentamidine, calcineurin inhibitors, transfusions, CsA |

### Evaluation (*Am J Med* 2009;122:215)

- **Risk factors:** ↓ GFR rather than ↑ Cr a better indicator of pts treated with/ ACEI/ARBs/aldosterone antagonists who are at risk for hyperkalemia
- **History:** Sx include muscle weakness, nausea, paresthesias; timing in relationship to insulin & meals (esp diabetic pts), hx tissue damage, PMHx (esp CHF, cirrhosis, HTN, DM, hx kidney disease), diet, medications
- **Workup:** Recheck K, especially if reported as hemolyzed or suspect lab artifact

**ECG:** Usually K >6 mEq/L: Peaked T waves, PR & QRS prolongation, P waves flattening → cardiac arrest (can occur in the absence of ECG changes)

## Management

- **Dietary management:** Nutrition referral, kidney.org/atoz/content/potassium.cfm
- **Medication review:** In advanced CHF, high mortality benefit of ACEI/ARB & aldosterone antagonists → K level (4–5.5) is acceptable (*Expert Opin Pharmacother* 2011;12:2329); If K ↑ to ≤5.5 on ACEI/ARB/aldosterone antagonist, ↓ dose or implement measures below; If on combination, d/c 1 & recheck dose; If K ↑ to ≥5.5 despite intervention, discontinue med; Spironolactone dose should not >25 mg when combined w/ ACEI/ARB; Avoid NSAIDs, COX-2 inhibitors, or other medicines which ↑ K

**Potassium-rich Foods**

| | |
|---|---|
| Fruits | Apricot, avocado, banana, cantaloupe/honeydew, dates, figs, grapefruit, kiwi, mango, nectarine, orange, papaya, pomegranate |
| Vegetables | Artichoke, beans, broccoli, brussel sprouts, cabbage, carrots, greens, lentils, legumes, mushroom, okra, parsnips, potatoes, pumpkin, spinach, squash, tomatoes |
| Other | Bran, chocolate, granola, milk/yogurt, molasses, certain nutritional supplements, nuts & seeds, peanut butter, salt-free broth, salt substitutes, snuff/chewing tobacco |

- **Diuretics:** Thiazides (GFR >30) or loop (GFR <30) diuretics ↓ K
- **Correct metabolic acidosis:** Na bicarbonate in pts w/ CKD
- **Polystyrene sulfonates (i.e., Kayexalate):** Binds K in GI tract; s/e include N/V, constipation, diarrhea, hypermagnesemia, hypercalcemia, bowel necrosis (esp age >60, predisposing GI pathology, use w/ caution in elderly pts) (*AJKD* 2012;60:409)
- **Diuretics:** Esp loop diuretics: Enhance Na delivery to distal tubules →↑ K secretion

# PROTEINURIA

## Background (*AFP* 2000;62:1333; 2009;80:1129; *JABFM* 2008;21:569)

- **Normal physiology:** Kidney filters 180 L ultrafiltrate/day, w/ approx 1 mg/dL albumin in Bowman space; majority of protein (albumin, low molecular wt protein) reabsorbed in the proximal convoluted tubule (PCT); healthy individuals secrete <150 mg/d of protein/day

### Quantification of Proteinuria (*AFP* 2009;80:1129; *NEJM* 1983;309:1543)

| | Albuminuria | Albumin:Cr | Proteinuria | Protein:Cr |
|---|---|---|---|---|
| Physiologic | <30 mg/d | <30 mg/g | <150 mg/d | <0.2 mg/mg |
| Microalbuminuria | 30–299 mg/d | 30–299 mg/g | — | — |
| Macroalbuminuria | ≥300 mg/d | ≥300 mg/g | — | — |
| Nephrotic range | — | — | >3.5 g/d | >3.5 mg/mg |

- **Pathophysiology:** Secretion of >150 mg/d of protein
  - **Overflow proteinuria:** ↑ production of nonalbumin protein, exceeding PCT reabsorption capacity (i.e., monoclonal gammopathy, leukemia, MM w/ Bence Jones proteinuria, amyloid)
  - **Tubular proteinuria:** Impaired absorption of nonalbumin protein at the PCT; 2/2 tubulointerstitial disease (i.e., HTN nephrosclerosis, Fanconi syndrome, AIN, heavy metals, sickle cell disease, NSAIDs, abx)
  - **Glomerular proteinuria:** Most common; loss of permeability barrier of GBM via ↑ size of GBM pores or loss of ⊖ charge of proteoglycans leads to albumin loss
  - **Postrenal proteinuria:** UTI (inflammation), malignancy, kidney stones
- **Risk Factors:** HTN, DM, obesity, exercise, CHF, UTI, fever, dehydration

### Differential Diagnosis of Glomerular Proteinuria

| |
|---|
| **1° glomerulopathy:** Minimal change disease, membranous nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, IgA nephropathy, fibrillary-immunotactoid, mesangial proliferative GN, transplant rejection |
| **2° glomerulopathy:** DM, SLE, amyloid, cryoglobulinemia, infection (HIV, HBV, HCV, poststreptococcal, syphilis, malaria, endocarditis), GI/lung cancer, lymphoma |
| **Medications associated w/ proteinuria:** NSAIDs, heroin, lithium |

### Specific Causes of Proteinuria

| | |
|---|---|
| **Diabetic nephropathy** | ↑ risk in DM1; DM2 constitutes majority of ESRD; Generally global glomerulosclerosis at time of dx; prevention w/ glycemic & BP control (*JAMA* 1990;263:1954) |
| **Nephrotic syndrome** | Heavy or nephrotic-range proteinuria (>3.5 g/d), hypoalbuminemia, edema, hyperlipidemia & lipiduria; 1° or 2° glomerulonephropathy |
| **Isolated proteinuria** | NI renal function, urinary sediment, & BP; generally <2 g/d; Likely ↑ risk of renal failure compared to same EGFR w/o proteinuria (*Ann Intern Med* 2011;154:12) |
| **Transient proteinuria** | Seen in dehydration, emotional stress, fever, heat injury, inflammatory process, intense activity, most acute illness; no further w/u indicated |
| **Orthostatic proteinuria** | Reproducible proteinuria which occurs in the upright position & resolves when supine; excellent prognosis over 25 y period w/o progression to persistent proteinuria or renal disease |

## Evaluation (*AFP* 2005;71:1153; *JABFM* 2008;21:569)

- **History:** Foamy or cola-colored urine; Δ in UOP; Fatigue, edema, wt Δ, swelling; *PMHx:* DM, CHF, autoimmune disease, post-strep infection; *Meds:* (esp NSAIDs); *FHx:* Alport syndrome
- **Exam:** BP, weight, periorbital or dependent edema, ascites, palpation of kidneys, heart & lung exam
- **Workup:** Assess w/ urinalysis & dipstick testing (value correlates to quantity of protein in urine: 1+ → 30–100 mg/dL, 2+ → 100–300 mg/dL; 3+ → 300–1000 mg/dL); Chem-7, serum albumin, CBC, urine protein:creatinine ratio (UPCR), urine albumin:creatinine ratio (UACR), urine microscopy, SPEP, UPEP; ✓ lipids & TG (commonly ↑ in nephrotic syndrome); *Consider;* HbA1c, hepatitis serologies, HIV, RPR, based on clinical suspicion; Consider renal U/S to r/o reflux or PKD; *Can usually defer to specialist:* 24 h urine protein, ESR, CRP, C3, C4, ANA, ANCA, anti-GBM, cryos, ASO, renal bx

  **Dipstick:** Measures albumin concentration via colorimetric reaction; false ⊖ if nonalbumin proteinuria, false ⊕ if urine pH >7.5, SG >1.1015, hematuria, mucus, semen, leukocytes, or recent IV contrast exposure

  **Urine sediment:** May help to establish glomerular proteinuria (i.e., presence of RBCs, WBCs, eosinophils, casts)

  **Spot urine protein:creatine ratio:** Acceptable for screening (vs. 24-hour collection; proteinuria underestimated in muscular pts & overestimated in cachectic pts); Urine protein excretion varies

throughout day; Generally, ratio is equiv to grams of protein excreted in urine/d (*AFP* 2000;62:1333)

**Orthostatic proteinuria:** Have pt void before going to sleep at night & ✓ urine protein:Cr in sample after awakening; Uncommon in pts >30 y

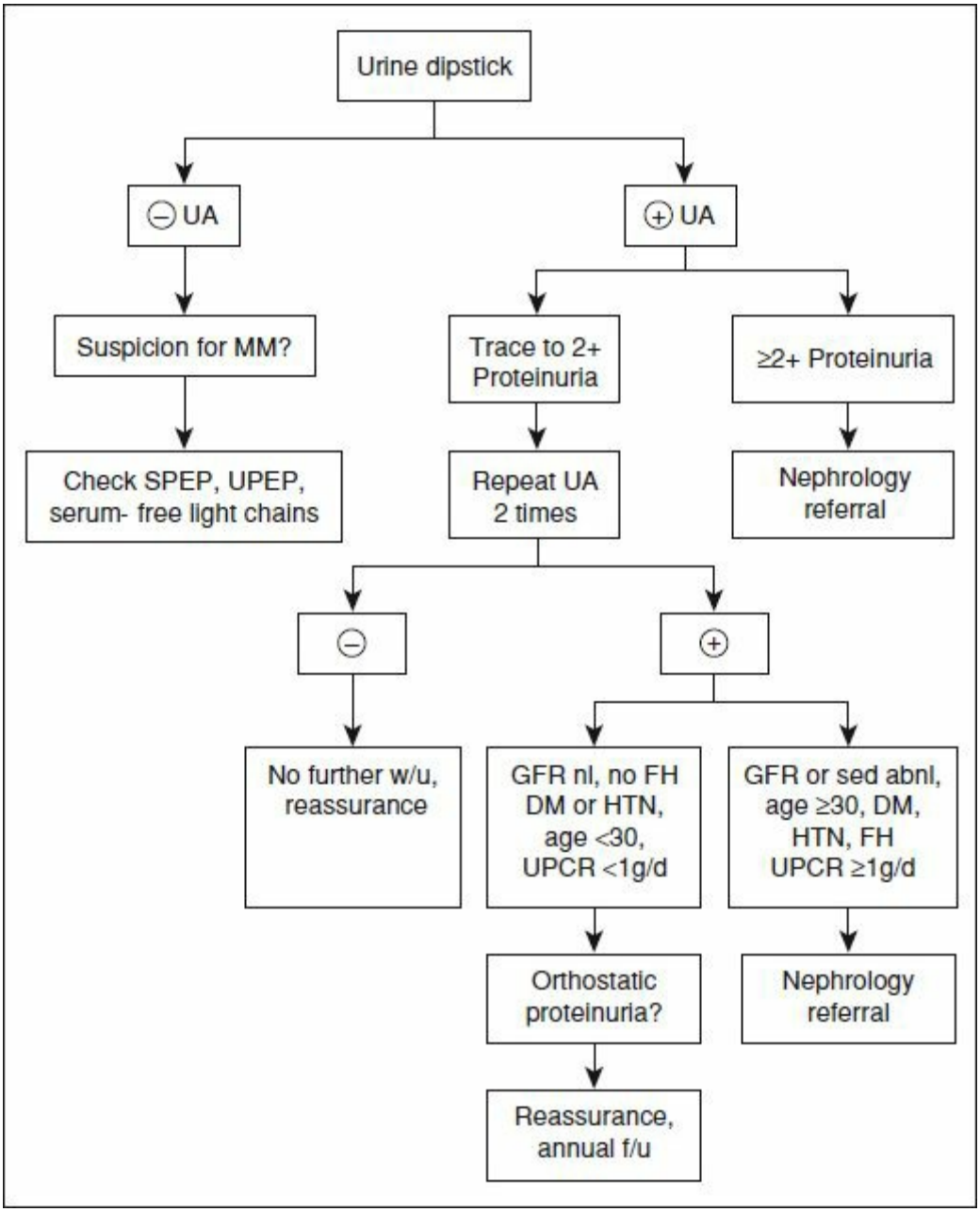


Figure 13-2 Proteinuria Evaluation

(Adapted from *J Am Board Fam Med* 2008;21:569)

## Management (*AFP* 2009;80:1129)

- **General principles:** Varies by etiology; treat underlying disease & factors that predict CKD progression
- **Prevention of CKD progression:** Wt loss, BP control (<130/80), glycemic control
  **ACEI & ARB:** ↓ proteinuria & ↓ risk of progression of renal disease; start w/ ACEI & switch to ARBs if unable to tolerate (*NEJM* 2004;351:1952); likely no benefit to combo Rx (*Ann Intern Med* 2008;148:30; *Circulation* 2011;123:1098)
  **Other antiproteinuric agents:** βB, statin, aldosterone antagonist; use based on comorbidities
- **Edema:** Dietary Na restriction (2 g/d) & diuretics
- **Hypercoagulability:** ↑ incidence of VTE w/ nephrotic syndrome; no consensus regarding anticoagulation
- **Diabetic nephropathy:** Glycemic & BP control (goal BP 130/80), use of ACEI or ARBs
- **When to refer to nephrology:** ↑ Cr, unexplained proteinuria, DM w/ microalbuminuria, abnl urine sediment, >1 g/d proteinuria
- **Information for patients:** *JAMA* 2010;303:470

## Proteinuria in Pregnancy (*Int J Gynaecol Obstet* 2002;77:67)

- **Pathophysiology:** In nl pregnancy, urinary protein excretion ↑ due to ↑ GFR & ↑ permeability of the GBM; nl up to 250 mg/d in third trimester
  Abnormal level of proteinuria: >300 mg/d anytime during gestation based on 24 h urine collection (correlates w/ 1+ on urine dipstick)
  Onset *prior to 20 wks* gestation: Suggestive of pre-existing renal disease
  Onset *after 20 wks* gestation: Must exclude pre-eclampsia

# SODIUM DISORDERS

## Background (*Am J Med* 2013;126:256)

- **Definition:** Dysnatremias are d/o of regulating total body $H_2O$, not total body Na
  **Osmolality:** Solute (mmol) in 1 kg of plasma or urine = 2×([Na])

+ [urea] + [glucose]

- **Epidemiology:** In pts >55 y, hyponatremia found in 7.7%, hypernatremia in 3.4%
- **Pathophysiology:** Serum osmolality is tightly regulated at 275–290 mOsm/kg by osmostat in hypothalamus via thirst response & ADH (ADH = vasopressin)
  **Urine osm:** 50 mOsm/L (no ADH) to 1200 mOsm/L (max ADH) (*NEJM* 1960;262:1306)

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## HYPONATREMIA (*AFP* 2000;61:3623; 2004;69:2387)

### Evaluation (*NEJM* 2000;342:1581; *JASN* 2012;23:1140)

- **History:** Diarrhea, emesis, thirst, fatigue, nausea, fluid intake, urine volume, medications (e.g., diuretics), CHF, cirrhosis, renal disease, EtOH; cognitive slowing, gait disturbances/falls, osteoporosis (*QJM* 2008;101:583; *J Bone Miner Res* 2010;25:554)
  **Medications associated w/ hyponatremia:** Diuretics, SSRIs, carbamazepine, theophylline, amiodarone, ecstasy; ↓ Na w/ diuretics occurs in 1st 1–2 wks of Rx
- **Exam:** Volume status; ↑ JVP & edema seen in volume overload
- **Workup:** Chem-7 & other tests (below):
  **Plasma osmolality:** Confirms hypotonic "true" hyponatremia; excludes rare cases of isotonic (↑↑ TGs, paraproteinemia) & hypertonic (↑↑ glucose) hyponatremia
  **Urine osmolality:** Surrogate for ADH; $U_{osm}$ >100 mOsm/L in an euvolemic pt w/o other pathologies is suggestive of SIADH
  **Urine Na:** Good indicator of volume status in nonedematous pt & superior to physical exam (*Am J Med* 1987;803:905); $U_{Na}$ <20 → volume depletion; $U_{Na}$ >40 → suggests euvolemia; urine Na is unreliable if diuretic use, aldosterone deficiency, advanced CKD, metabolic alkalosis, polydipsia
  **TSH or ACTH stimulation test:** To exclude endocrinopathy
  **Pseudohyponatremia:** Seen in ↑↑ lipids, TG, or hyperproteinemia (MM)

## Hypovolemic Hyponatremia

- **Extrarenal loss (UNa <20):** Diarrhea, vomiting, poor solute intake
- **Renal losses (UNa >40):** Diuretics (esp thiazides), osmotic diuresis, aldo deficiency

## Euvolemic Hyponatremia

- **SIADH:** Inappropriate release of ADH w/ nl or mildly ↑ EAV → euvolemic hyponatremia; dx of exclusion; normal saline worsens ↓ Na due to SIADH

**Diagnosis of SIADH** (Adapted from *NEJM* 2007;356:2064)

| 1. ↓ Serum osmolality (<275 mOsm/kg), urine osmolality >100 mOsm/kg, $U_{Na}$ >30–40<br>2. Euvolemic, nl thyroid & adrenal function; no recent diuretic use | |
|---|---|
| **Common Outpatient Causes of SIADH** | |
| Meds | SSRIs, TCAs, antipsychotics, carbamazepine, bromocriptine, opiates, amiodarone, cyclophosphamide, chemotherapy, NSAIDs |
| CNS | Tumors, meningitis, SAH/subdural bleed, temporal arteritis, pain |
| Pulmonary | PNA, asthma/COPD flare, TB |
| Malignancy | Small cell lung (most common), pancreas, duodenal, lymphoma, leukemia |

- **Reset osmostat:** Variant of SIADH w/ nl osmostat response to $H_2O$ load/deprivation, but ↓ threshold for ADH release; suspect w/ chronic, mild (125–130) hyponatremia; causes include severe illness, malnutrition, pregnancy, idiopathic
- **Adrenal insufficiency:** ↓ cortisol → hyperkalemia (due to ↓ aldosterone) + hyponatremia due to cosecretion of ADH w/ CRH from hypothalamus
- **Primary polydipsia** ($U_{osm}$ <100; $U_{Na}$ often <20 b/c of dilution): $H_2O$ consumption >> kidney excretory capacity (12 L/d) in Ψ disease (schizophrenia) & hypothalamic disease
- **Poor solute intake (Uosm <100):** Solute intake insufficient to excrete daily water load; seen w/ "tea & toast" diet or "beer potomania"

## Thiazide-Induced Hyponatremia

- **Epidemiology:** Affects up to 30% of pts on long-term thiazide Rx (*Am J Med* 2011;124:1064)

- **Pathophysiology:** Manifests within first 1–2 wks of Rx (*Chest* 1993;103:601), w/ acute illness, & w/ Δ in dose → ✓ Na soon after starting & w/ Δ in clinical status
- **Risk factors:** Elderly & low BMI (*QJM* 2003;96:911); alcoholics; avoid in pts w/ hx ↓ Na

## Hypervolemic Hyponatremia

- **Pathophysiology:** CHF, cirrhosis, nephrotic syndrome ($U_{Na}$ <20; $U_{osm}$ >100): ↓ EAV → ↑ ADH → ↓ Na; in advanced CKD ($U_{Na}$ >40) there is a ↓ ability to excrete free water

## Treatment (*BMJ* 2007;334:473)

- **Hypovolemic:** ED for IVF if vomiting/diarrhea; stop diuretics & Rx underlying cause
- **SIADH:** Treat underlying cause & stop offending medications
  - **Fluid restriction:** Goal of <800 mL/d is mainstay of tx, but adherence difficult; If pt unable to comply, consider restricting free water
  - **Salt tabs:** Can help to liberalize fluid restriction (contraindicated in edematous states)
  - **Loop diuretics:** I.e., furosemide 20 mg/d impair medullary gradient →↑ free water loss
  - **Demeclocycline:** Abx → nephrogenic DI; should be prescribed by specialists
  - **Tolvaptan (V2 antagonist):** ↑ Na & improved cognition but ↑ thirst (*NEJM* 2006;355:2099; *JASN* 2010;21:705); Should only be prescribed by specialists; S/e include ↑ LFTs; Typically started inpt due to risk of overly rapid correction
- **Polydipsia:** Counsel on $H_2O$ restriction; avoid meds causing dry mouth (anticholinergics)
- **Hypervolemic:** Treat underlying disease (e.g., ACEI in CHF); loop diuretics impair medullary gradient →↑ free water loss; fluid restriction if symptomatic or severe

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## Background

- **Pathophysiology:** *Extrarenal $H_2O$ loss:* Hypotonic fluid loss from sweat, GI tract (diarrhea), & respiratory tract; *Renal $H_2O$ loss:* Osmotic diuresis (↑↑ glucose), loop diuretics
  **Drugs:** Lithium, demeclocycline, cidofovir, foscarnet, didanosine, Li → nephrogenic DI in 40% of pts (*Nat Rev Nephro* 2009;5:27), sometimes irreversible
  **Diabetes Insipidus:** (see *"Diabetes Insipidus"*)
  *Central diabetes insipidus* (↓ ADH): Hypothalamic/pituitary disease/surgery, anorexia, heat trauma, TB, syphilis
  *Nephrogenic diabetes insipidus:* ↓ response to ADH
  **Metabolic:** Hypercalcemia, persistent hypokalemia (<3 mEq/L)
  **Tubulointerstitial:** PKD, sickle cell dz/trait, Sjögren, sarcoidosis, amyloid, pregnancy

## Evaluation (*NEJM* 2000;342:1493)

- **History:** Lack of access to free $H_2O$ (dementia, nursing home resident, elderly) → ↓ thirst response to ↑ Na (*NEJM* 1984;311:753); lethargy, weakness, diarrhea, emesis, polyuria, polydipsia, diabetes (osmotic diuresis), hypothalamic lesions (hypodipsia); changes in UOP
- **Exam:** Volume status (JVP, mucous membranes), edema, orthostatics, axillary sweat
- **Urine osmolarity:** Should be >700 due to max ADH effect; **Uosm >700** → extrarenal $H_2O$ loss; **Uosm <700** → renal $H_2O$ loss
- **Endocrine referral:** $H_2O$ deprivation test if suspect DI (i.e., polyuria, polydipsia, mild ↑ serum Na) (*J Clin Endocrinol Metab* 2012;97:3426)

## Treatment

- **General principles:** Determine barrier to $H_2O$ access (i.e., AMS, hypodipsia, dependence on others); scheduled drinking totaling ≥ 1 L/d if impaired access to $H_2O$; Treat underlying cause & stop offending drugs
- **Central DI:** Refer to endocrine for desmopressin

- **Nephrogenic DI:** Thiazide → mild hypovolemia →↑ prox $H_2O$ reabsorption & ↓ $H_2O$ excretion; consider amiloride, esp if due to Li (blocks uptake of Li in principal cell) (*CJASN* 2008;3:1324); consider referral to nephrology

# ABNORMAL UTERINE BLEEDING

## Background (*AFP* 1999;60:1371; *Obstet Gynecol* 2012;120:197)

- **Normal menstrual cycle:** 21–35 d w/ avg duration of menses = 5 d, blood loss <80 mL
- Abnl bleeding accounts for 1/3 outpt gynecology visits overall & >70% gynecologic consults for peri- & postmenopausal pts
- **Definitions:** *Menorrhagia:* Heavy/prolonged menses; *Polymenorrhea:* Cycle length <21 d (↑ freq); *Oligomenorrhea:* Cycle length > 35 d (↓ freq); *Intermenstrual bleeding:* Bleeding at any time other than nl menses; includes metrorrhagia (irregular intermenstrual bleeding)
- **Dysfunctional uterine bleeding (DUB):** Dx of exclusion in pts w/abnl uterine bleeding not due to pregnancy, pelvic pathology, medications, or systemic disease

### Differential Diagnosis of Causes of Abnormal Bleeding

| | |
|---|---|
| **Genital tract lesions** | Malignancy, benign lesions (including polyps, leiomyomas, adenomyosis, endometriosis, ectropion), infection, pregnancy |
| **Trauma** | Foreign body, pelvic trauma, sexual intercourse, abuse |
| **Medications** | Contraception, HRT, steroids, antipsychotics, phenytoin, anticoagulants, supplements (ginseng, ginkgo, soy) |
| **Systemic disease** | Coagulopathy in up to 20% of women w/ heavy bleeding (von Willebrand, ↓ PLT, leukemia), ESLD, endocrine disease (thyroid, Cushing, adrenal hyperplasia, ↑ PRL), hypothalamic suppression (wt loss, excess exercise, stress), ESRD |

(*Am J Obstet Gynecol* 1996;175:766; *NEJM* 1991;324:1710; *AFP* 2004;69:1915)

## Evaluation (*AFP* 1999;60:1371; *Obstet Gynecol* 2012;120:197)

- **General approach:** Medical & menstrual hx to characterize menstrual pattern, menopausal status, & nature of bleeding; r/o nongenital sources (e.g., urinary/rectal)
- **Menstrual pattern:** *Ovulatory:* **regular** cycle length, ⊕ cervical mucus, ⊕ premenstrual sx → determine bleeding pattern (menorrhagia, polymenorrhea, oligomenorrhea, or intermenstrual bleeding); *Anovulatory* (more common in pts p/w AUB): **irregular** flow/duration of menses, premenstrual sx often absent
- **Menopausal status:** *Perimenopausal:* ⊕ onset of clinical/endocrinologic changes (hot flashes, vaginal dryness, irregular menses—see

*"Menses"*) but menses persistent; *Menopausal:* >12 mos amenorrhea (see *"Menopause"*)

- **Medical history:** Coagulopathy, ESLD, ESRD/HD, endocrine disease; sexual hx; *FHx:* Menstrual irregularity, fibroids/endometrial disease/CA; *Meds:* See above; if on HRT or OCPs, review adherence (irregular use may → spotting); *ROS:* Wt loss, stress, endocrine sx
- **Exam:** Pelvic exam to r/o genital tract lesion, eval uterus/adnexa, Pap ± Chlamydia test
- **Initial studies:** Must **r/o pregnancy** (β-hCG); ✔ CBC, TSH; if uterine enlargement or irregularities → TVUS; consider w/u for nongenital tract causes
- **Endometrial biopsy:** Indicated in perimenopausal women **>45 y w/ AUB**, women <45 y w/ persistent abnl bleeding, hx unopposed estrogen, or no response to Rx, & postmenopausal women who do not undergo TVUS for eval of endometrium

## Management

- **Premenopausal:** Based on ovulatory status (below)
- **Ovulatory:** Varies by bleeding pattern; *Menorrhagia:* r/o bleeding d/o, with transvaginal ultrasound (TVUS) for fibroids/uterine pathology → if ⊖, trial OCPs, levonorgestrel IUD or NSAIDs; *Polymenorrhea:* trial OCPs, consider eval for luteal phase defect; *Oligomenorrhea:* seen w/ prolonged follicular phase → trial OCPs or q3mos progesterone; *Intermenstrual:* r/o cervical pathology, consider IUD removal and/or trial OCPs
- **Anovulatory**
  1. Check TSH & PRL → Rx underlying condition
  2. Assess for hypothalamic dysfunction (stress, eating d/o, chronic disease) → trial OCP
  3. Consider PCOS and its Ddx (see *"PCOS"*), chronic anovulation (FSH −/↓); for either dx can consider tx w/ OCPs, levonorgestrel IUD, q3mos progesterone w/d
- **Perimenopausal:** If no genital tract lesion per hx/PE & ⊖ β-hCG, → **eval** to r/o endometrial hyperplasia/CA (see indications for TVUS vs bx) (*Obstet Gynecol* 2012;120:197)
  *Nl/atrophic* → observe vs. trial OCPs or levonorgestrel IUD

*Atypia/carcinoma* → refer to Gyn
*Hyperplasia* → refer to Gyn; tx w/ progesterone, D&C if persistent

- **Postmenopausal:** Bleeding usually 2/2 vaginal/endometrial atrophy, but CA must be excluded → **TVUS or endometrial bx** to r/o malignancy (cause of 5–10% of AUB)
  *Endometrial bx:* If abnl → refer as above; if nl but bleeding persists → TVUS, refer for hysteroscopy or sonohysterography; if nl & bleeding resolves can observe, o/w repeat bx
  *TVUS:* Endometrial stripe <4 mm c/w atrophic endometrium; ≥4 mm or irregular appearance → bx, refer per pathology, as above (*Obstet Gynecol* 2009;114:409)
- **Postmenopausal pts on HRT:** ↑↑ incidence of AUB (40–60%) (*Maturitas* 2009;63:45), particularly soon after initiation; assess HRT adherence (poor adherence can ↑ bleeding) & RFs for endometrial CA → use shared decision-making & clinical judgment re: observation vs. endometrial assessment; **if bleeding (1)** lasts ≥6 mos, **(2)** present prior to HRT initiation, **(3)** heavy/persistent despite ↑ progestin dose, or **(4)** develops after period of amenorrhea while on HRT → initiate w/u (*AFP* 1999;60:1371)

## When to Refer

- **Premenopausal:** For endometrial bx in pts <45 y w/ persistent abnl bleeding, hx unopposed estrogen exposure, or no response to Rx
- **Sev/heavy bleeding** which does not respond to initial tx, consideration of surgical tx
- **Persistent AUB** after initial Rx should undergo TVUS → if abnormal, refer for hysteroscopy ± bx or sonohysterography
- **If uterine enlargement/irregularities on examÆ** consider TVUS, referral for f/u sonohysterography/hysteroscopy

# AMENORRHEA

## Definitions (*AFP* 2006;73:1374)

- **Primary amenorrhea:** Absence of menarche in ♀ >16 y w/ secondary sex characteristics or ♀ >14 y w/o secondary sex characteristics

- **Secondary amenorrhea:** Absence of menses × 3 mos in ♀ w/ previously nl menstruation or 9 mos in ♀ w/ previous oligomenorrhea
- **Oligomenorrhea:** <9 menstrual cycles/year

## Background (*AFP* 2006;73:1374)

- **Normal physiology:** Pulsatile GnRH release by hypothalamus → LH, FSH release by anterior pituitary → ovulation, estrogen/progesterone production by ovaries; estrogen causes uterine lining proliferation, progesterone induces maturation → corpus luteum atresia → progesterone levels ↓ → shedding of uterine lining
- **Epidemiology:** Incidence of 1° amenorrhea = 0.3% general population, 2° amenorrhea = 1–3% general population; can be assoc w/ infertility, osteopenia, ↑ CV risk

## Etiologies

- **Primary amenorrhea:** Rare, initial w/u usually w/ pediatrician; etiologies include causes of 2° amenorrhea, anatomic & genetic defects (craniopharyngioma, primary ovarian insufficiency, Turner syndrome, Kallmann syndrome, Müllerian agenesis, androgen insensitivity); eval for 2° sex characteristics, presence of uterus/vagina; referral to pediatric endocrine or gyn
- **Secondary amenorrhea: Always consider pregnancy first;** PCOS, hypothalamic amenorrhea, hyperprolactinemia, & ovarian failure are most common medical causes

**Selected Etiologies of Secondary Amenorrhea**

| Cause | Examples |
|---|---|
| Thalamus | **Hypothalamic:** Frequently 2/2 eating d/o (esp anorexia nervosa), excess exercise/wt loss, ↑ stress; **female athlete triad** (restrictive eating + amenorrhea + osteoporosis)<br>Also: Hypothalamic destruction, CNS tumor, cranial XRT |
| Pituitary | **Hyperprolactinemia:** 2/2 pituitary adenoma, medications (antipsychotics), breastfeeding, idiopathic (see *"Hyperprolactinemia"*)<br>Hypopituitarism (↓ LH, FSH): Infiltrative, Sheehan's |
| Ovarian | **PCOS** (anovulation w/ hyperandrogenism): Obesity, hirsutism, acne, ♂-pattern baldness (see *"PCOS"*)<br>**Ovarian insufficiency** or failure: "Premature" = age < 40 y; (can be primary (POI) or 2/2 autoimmune disease, iatrogenic/chemo/XRT, genetic, 17-hydoxylase deficiency, mumps, pelvic XRT, idiopathic), mosaic Turner's |
| Uterine | Asherman syndrome (uterine scarring 2/2 D&C, infection)<br>Cervical stenosis (seen more w/ 1° amenorrhea) |
| Other | **Pregnancy, hypo/hyperthyroidism,** celiac disease, ↑ androgens (Cushing, nonclassical CAH, steroids) |

## Evaluation

- **General approach:** Majority of diagnoses can be made w/ careful history & basic labs
- **History:** *Gyn:* Age at menarche, pattern of missed periods, prior pregnancies, sexual hx, contraception hx, prior D&C/PID (Asherman's), current breastfeeding
  *Medical:* Obesity, DM (PCOS); thyroid disease, genetic d/o, prior pelvic or CNS chemo/XRT
  *Medications:* OCPs, antipsychotics, H2-blockers, opiates, cocaine, SSRIs, glucocorticoids
  *Lifestyle:* **Exercise** patterns + **wt changes** (eating d/o, ♀ athlete triad), **stress**
  *FHx:* Irregular menses, infertility, **premature menopause,** congenital abnormalities
- **ROS:** HA, visual disturbances, **galactorrhea** (pituitary tumor); **hot flashes** (ovarian failure); breast tenderness (pregnancy); s/sx of adrenal/thyroid disease, cyclic abdominal pain (Müllerian agenesis or outflow tract obstruction); anosmia (Kallmann syndrome)
- **Exam:** Ht, wt, BMI, 2° sex characteristics, *pelvic exam* (imperforate hymen, transverse vaginal septum); signs of *androgen excess* (hirsutism, acne, clitoromegaly), *insulin resistance* (acanthosis nigricans), *estrogen deficiency* (vaginal mucosal atrophy), *Cushing disease* (striae, buffalo hump, central obesity, ecchymoses, HTN, proximal muscle weakness), *thyroid disease* (nodules, goiter, skin

changes, abnl reflexes), *pituitary adenoma* (galactorrhea, visual field defects)

- **Initial labs: b-hCG, TSH, PRL, & FSH**

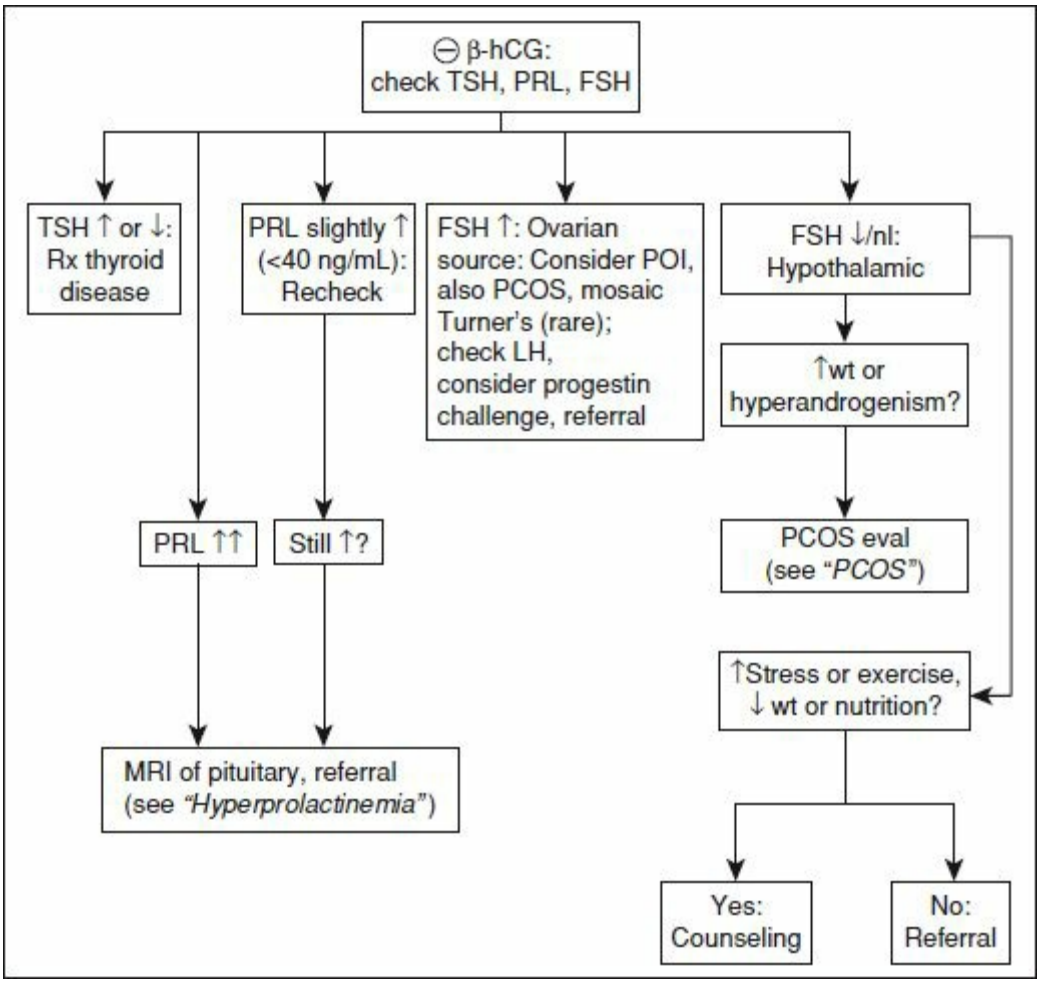


Figure **14-1** Diagnostic w/u of amenorrhea

(Adapted from *Fertil Steril* 2008;90:S219)

- **Additional testing:** May be useful in specific circumstances

  *Progesterone challenge test:* Administer progesterone (e.g., Provera 10 mg po QD × 7–10 d); presence of progesterone should → mature uterine lining, and w/d should → menses, lack of response indicates low-estrogen state; however, poor Se/Sp (e.g., 50% of POI pts have some w/d bleeding) (*Fertil Steril* 2008;90:S219)

  *Progesterone/estrogen challenge test:* Evaluates uterine response to nl hormone levels; w/d should → menses; abnl test suggestive of uterine abnormality

  *Free T, DHEAS:* To detect hyperandrogenism when PCOS suspected; if

c/w PCOS, check fasting glucose or 2 h GTT, r/o other causes of androgen excess

*Serum estrogen:* Variable in physiologic + pathologic states; may help interpret FSH levels

*Pelvic U/S:* Consider if uterine pathology suspected (e.g., Asherman's)

### Treatment (*NEJM* 2010;363:365)

- Based on causative factor & desire for fertility; general goals = prevention of complications (osteoporosis, endometrial hyperplasia, CVD, preservation of fertility)
- **Thyroid** (*see "Thyroid Disease"*): Return of nl menses may take several mos after tx
- **PCOS:** Wt loss via diet, exercise; OCPs or cyclic progestational agents to maintain nl endometrium; metformin (see *"PCOS"*)
- **Female athlete triad:** Counsel re: need for ↑ caloric intake or ↓ energy expenditure; consider DEXA scan, encourage adequate Ca/vit D, consider estrogen tx in conjunction w/ specialist; CBT to ↓ stress may restore ovulation (*Fertil Steril* 2003;80:976)

### When to Refer

- Suspected ovarian insufficiency, unclear dx, lack of response to tx, or desired pregnancy in setting of persistent amenorrhea → Reproductive Endocrinology (gynecology)
- Prolactinoma (see *"Hyperprolactinemia"*); hyperthyroidism or other endocrinopathies → medical endocrinology
- Consideration of estrogen tx → Gynecology or Endocrinology
- Uterine pathology or outflow obstruction → Gynecology

# BREAST DISEASE

## Breast Pain (Mastalgia)

### Background (*AFP* 2000;61:2371)

- Most common breast sx prompting consultation to PCP, premenopausal > postmenopausal women; most commonly benign etiology: 0–3%

pts w/ isolated pain will be found to have CA; localized pain = only presenting sx in <15% breast CA pts (*JGIM* 2012;27:817; *Mayo Clin Proc* 2004;79:353)

- No histologic correlations; 50–90% asx women have fibrocystic changes

## Patterns (*AFP* 2000;61:2371)

- **Cyclic mastalgia:** Assoc w/ menstrual cycle, most severe before menses or relieved by menses onset; typically b/l, poorly localized, radiating to axilla/arm, common in younger pts; likely due to hormonal stimulation of breast lobules
- **Noncyclic mastalgia:** *Unrelated* to menstrual cycle or in postmenopausal pts; typically unilateral, sharp/burning, localized, most common in pts 40 y–50 y; *Ddx:* stretch of Cooper ligaments, fat necrosis, pressure from brassiere, focal/periductal mastitis, hidradenitis suppurativa, cyst, thrombophlebitis (Mondor disease), costochondritis, cervical arthritis w/ radiculopathy (*NEJM* 2005;353:275)

## Evaluation (*AFP* 2000;61:2371)

- **History:** Pain (type, location, relationship to menses, bi- vs. unilateral, radiation, duration, resolution), exacerbating factors (irregular menses; stress; medications, esp OCPs, spironolactone); note that limited, burning or stabbing pain may localize to chest wall rather than breast
- **Exam:** Thorough breast exam to exclude mass; costochondral/chest wall palpation
- **Red flags:** Hx rapid onset breast erythema, edema, crusting/retraction/flattening of nipple, ± palpable mass or regional LAD strongly suggestive of inflammatory breast CA → prompt diagnostic U/S & mammography (*Ann Oncol* 2011;22:515)
- **Imaging** (*AFP* 2012;86:343)
  **Diffuse pain:** Pts > 40 y → mammogram if none in past 12 mos, consider for pts >30 y if ⊕ RFs for breast CA (limited data to support; see *"Disease Screening"*)
  **Focal pain:** Pts ≥ 30 y → mammogram + targeted U/S, pts < 30 y → targeted U/S

Note that some studies have shown benefit of ⊖ initial imaging for pt reassurance though may → add'l imaging, bx, & f/u visits (*JGIM* 2012;27:817)

## Treatment (*AFP* 2000;61:2371)

- **General approach: Reassurance** for the majority of pts w/ no abnormality on exam ± imaging; review nl breast physiology; **spontaneous remission rate** = 60–80%; Rx indicated only if pain interferes w/ activity or lasts several days/month (can ask pt to document daily pain freq/severity × 1 menstrual cycle prior to Rx)
- **CAM:** Conflicting evidence for efficacy of caffeine restriction, Vit E supplementation, evening primrose oil (*J R Soc Med* 1992;85:12; *NEJM* 2005;353:275)
- **Initial treatment: NSAIDs** (including topical), APAP, or ASA are 1st-line (*NEJM* 2005;353:275)
- **Alternatives:** Danazol (100–400 mg/d): Only FDA-approved Rx, reserve for severe sx not controlled w/ NSAIDs, r/o pregnancy before Rx, counsel about s/e (irregular menses, acne, wt gain, hirsutism); tamoxifen, bromocriptine have shown efficacy; should be considered in consultation w/ specialist (*J Reprod Med* 2005;50:933)

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# Nipple Discharge

## Background (*AFP* 2000;61:2371; *AFP* 2012;86:343; *NEJM* 2005;353:275)

- Second most common breast complaint (after breast pain); usually benign, but pathologic d/c can be assoc w/ malignancy (~5–15% of pts, ↑ risk in pts >40 y) (*Ann R Coll Surg Engl* 2007;89:124; *Am J Surg* 2010;200:73)
- **Definitions:** *Lactation:* Physiologic response (milk production) to pregnancy or breastfeeding; some d/c is nl up to 1 y after weaning; *Galactorrhea:* Milk production in response to inappropriate stimulus, e.g., prolactinoma; *Physiologic:* Nl variant; up to 80% of reproductive-age ♀ able to express small amount of d/c w/ compression; *Pathologic:* Nonmilk discharge w/ concerning features (see *"History"*); most common: Papilloma > duct ectasia > breast CA

## Evaluation (*AFP* 2000;61:2371)

- **General approach:** Exclude lactation, then differentiate btw physiologic vs. pathologic d/c, based on hx/PE
- **History:** *Discharge:* Unilateral or b/l, spontaneous or only w/ compression, color (may be clear, yellow, white, or dark green w/ either physiologic or pathologic), ± bloody, assoc w/ mass
  *Gyn hx:* Menstrual hx, pregnancy, fibrocystic or other prior breast disease
  *Medical hx:* chest wall trauma, hypothyroidism, pituitary disease
  *Meds:* OCPs; spironolactone, antipsychotics, esp phenothiazines & risperidone
  *ROS:* Endocrine ROS for thyroid disease, pituitary tumor (visual field defect, HA, amenorrhea)

### Clinical Features of Discharge

| Cause | Features |
|---|---|
| Lactation | Bilateral milk d/c up to 1 y after weaning of infant |
| Physiologic | **Bilateral,** involving multiple ducts, w/ d/c only on compression |
| Pathologic | Often **unilateral,** confined to 1 duct, spontaneous (i.e., w/o manipulation), **bloody,** or **a/w mass** (greatly ↑ risk of CA); itching/burning sensation |

- **Exam:** Thorough breast exam: Inspect discharge, differentiate single vs. multiple duct involvement; inspect/**palpate for associated mass**
- **Red flags** (in addition to pathologic features above):
  Erythema/dermatitis of nipple suggestive of Paget disease of the breast → refer for bx & mammography
- **Initial studies:**
  *Physiologic:* Mammogram in pts >35 y, in women <35 y → no further initial w/u
  *Pathologic:* Examine d/c for occult blood, obtain **dx mammogram** (retroareolar magnification views may be helpful); **surgical referral for all pts** w/ spontaneous or unilateral d/c for terminal duct excision; cytology not recommended (poor Se/Sp & ↓ cost-effectiveness)
  *Galactorrhea:* Check β-hCG, TSH, & PRL

## Treatment (*AFP* 2000;61:2371)

- **Physiologic:** If exam ± mammogram nl → reassure, counsel to avoid nipple stimulation & report any spontaneous discharge
- **Pathologic:** Surgical referral for duct excision
- **Galactorrhea: Stop potentially offending medications;** if TSH or PRL abnl, treat as indicated (see *Section Endocrine*); if both nl, consider dopaminergic agonist to ↓ sx

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## Breast Mass

### Background (*AFP* 2000;61:2371; *NEJM* 2005;353:275; *AFP* 2005;71:1731)

- **Nodularity** (esp in upper outer quadrant) very common, as normal glandular breast tissue is nodular; **fibroadenomas** very common, including younger pts
- **Cysts:** Common masses in premenopausal women >40 y; infrequent in younger pts & postmenopausal pts not on HRT; *Risk factors:* Late menopause, HRT, low BMI (*NEJM* 2005;353:275)
- **Dominant mass:** Single mass differing from surrounding tissue & from corresponding area in contralateral breast, persisting throughout menstrual cycle; may be discrete or poorly defined
- **Differential diagnosis:** Fibrocystic changes, usual ductal hyperplasia, atypical ductal hyperplasia, atypical lobular hyperplasia, ductal carcinoma in situ, invasive CA
- Although many palpable masses are benign, **breast CA** must always be considered

### Evaluation (*AFP* 2000;61:2371; *NEJM* 2005;353:275)

- **History:** *Mass:* Timing of appearance, changes in size/character, assoc pain, fluctuations w/ menstrual cycle (suggests cyst); hx prior cyst at site; review RFs for breast cancer (see *"Disease Screening"*)
- **Exam:** Thorough breast exam, including visual inspection (asymmetry, d/c, masses, skin changes, nipple retraction) & palpation of entire breast, axillae, & supraclavicular areas b/l; document mass location, size, texture, mobility

### Management (*AFP* 2000;61:2371; *NEJM* 2005;353:275; *AFP* 2005;71:1731)

- **Communication:** Breast masses are source of anxiety for clinicians & pts; be open about potential for false ⊕ & false ⊖ results; encourage pts to f/u promptly w/ persistent concerns; establish a plan for f/u & discussion of test results
- If *no mass palpable* → reassure, review self-breast exam (SBE); confirm screening up-to-date, encourage f/u
- If *irregularity* (i.e., vague nodularity/asymmetry) noted but *no clear dominant mass*

  **Women < 35 y:** May observe 1–2 menstrual cycles, consider directed U/S

  **Women > 35 y:** Mammogram w/ f/u midcycle PE in 1–2 mos; refer for bx if persistent (even if imaging ⊖)
- MRI usually not recommended, given poor Sp compared with mammogram; consider in pts w/ breast implants, s/p breast surgery, or extremely dense tissue
- Note that pts w/benign breast lesions may still be at ↑ risk of breast CA → discuss tamoxifen as preventive Rx if predicted Gail 5 y risk >1.67%

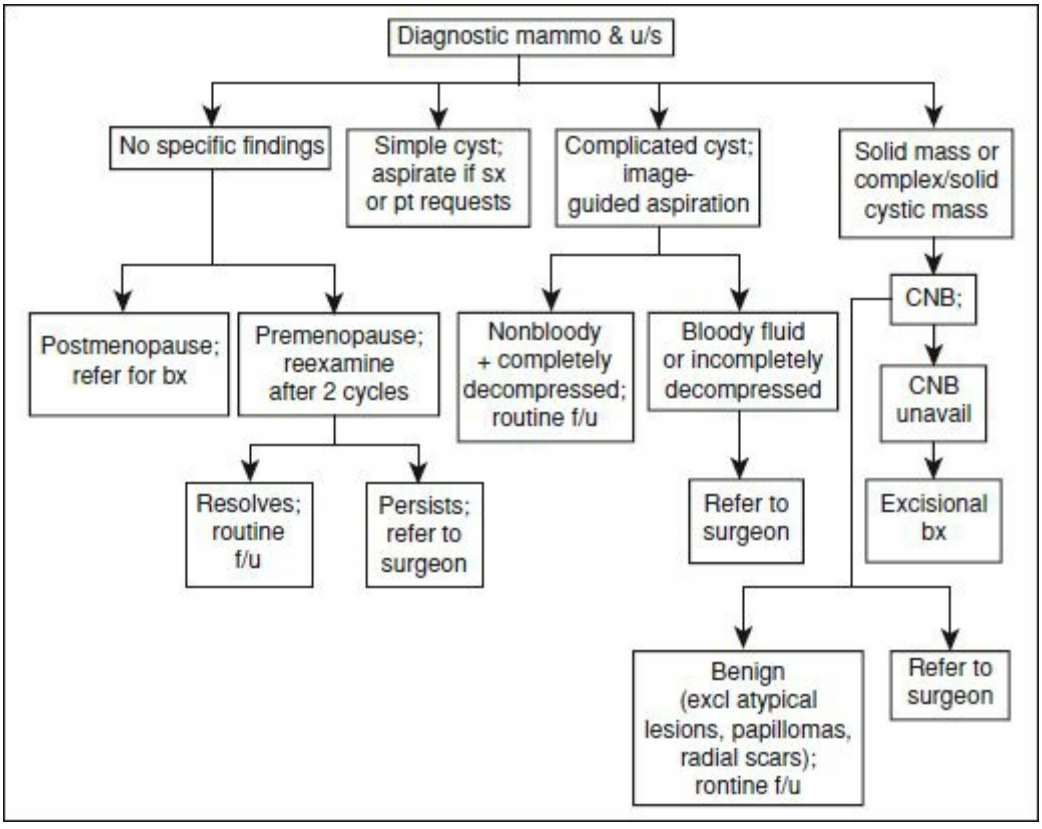


Figure 14-2 Breast care management algorithm

(Adapted from http://www.rmf.harvard.edu/~/media/Files/_Global/KC/PDFs/cricormf_

# CERVICAL CANCER SCREENING

## Background

- Cervical CA: malignancy of squamous (most common) or glandular cervical cells; progressive, predictable disease involving clearly defined precursor lesions → well-suited for screening; incidence in US ↓ >50% since screening began (www.seer.gov)
- **Epidemiology:** >12,000 new diagnoses of invasive cervical CA & >4200 cervical CA deaths annually in US (*CA Cancer J Clin* 2011;61:212); incidence/mortality rates ↑ in ethnic minorities (Hispanics/Latinos > African-Americans > Native Americans > whites), women living in rural areas or poverty; disparities primarily mediated by ↓ screening & ↓ f/u care (*Canc Epi Biomarkers Prev* 2012;21:1402)
- **Pathophysiology:** Essentially all cervical CA thought to be assoc w/ HPV infection, acquired through sexual contact; >90% infections clear spontaneously w/in 2–5 y, but persistent HPV can → dysplasia → malignancy (*Lancet* 2001;357:1831)

## Human Papilloma Virus (HPV) (*NEJM* 2009;361:271)

- **Classification:** dsDNA infecting mucocutaneous tissues; ~30 strains trophic for genital area; of these, "low-risk" strains (6, 11) generally assoc w/ anogenital warts; "high-risk" strains (16, 18) account for ~70% cervical CA cases, included in HPV vaccine (see *"Immunizations"*)
- **Epidemiology:** HPV prevalence = 39% in women 18–40 (*J Inf Dis* 2001;183:1554), ↓ w/ age; prior to HPV vaccine, lifetime incidence in US population = ~80% (*Am J Med* 1997;102(5A):3)
- **Risk factors** assoc w/ HPV acquisition/persistence: Multiple sexual partners, early onset sexual activity, high-risk sexual partners, hx STIs, immunosuppression (incl HIV)

## Cytologic Classification of Intraepithelial Cell Abnormalities (*JAMA* 2002;287:2114)

- **Squamous cell: (1)** Atypical squamous cells (ASC) of undetermined

significance (ASC-US) or high grade (ASC-H) **(2)** Low-grade squamous intraepithelial lesion (LSIL): Usually assoc w/ active HPV infection, mild dysplasia, corresponds to cervical intraepithelial neoplasia (CIN)-1 on histology **(3)** High-grade squamous intraepithelial lesion (HSIL): Mod/severe dysplasia, CIN2—3 or carcinoma *in situ* on histology **(4)** Squamous cell carcinoma

- **Glandular cell: (1)** Atypical glandular cells (AGC): Endocervical, endometrial, NOS or "favor neoplastic" **(2)** Endocervical adenocarcinoma in situ **(3)** Adenocarcinoma

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## SCREENING

### Modalities

- **Cytology** (Papanicolaou smear): Sampling of endocervical/ectocervical cells; does not give histology □ colposcopy + bx required to dx/stage dysplasia/CA
- **HPV testing:** Indicated in some instances (below) as component of 1° screening & to aid in risk stratification and f/u strategy
- **Visual inspection:** If concern for cervical malignancy on exam, **refer for colposcopy** regardless of cytology or HPV findings

### Guidelines (*Ann Int Med* 2012;156:880, *CA Cancer J Clin* 2013;63:87)

- Recommendations have evolved over time; 2012 USPSTF, ACOG, & ACS updates suggest ↓ screening freq to prevent overdiagnosis & overtreatment of HPV-related abnormalities that would clear spontaneously

**Screening Recommendations (for pts w/o prior abnl screenings)**

| Patient Group | Recommendation |
|---|---|
| ≤21 y | No screening |
| 21–29 y | Pap q3y (do **not** check HPV unless for f/u of abnl Pap) |
| 30–65 y | Pap + HPV q5y (cotesting; preferred by ACS/ACOG) **or** Pap q3y (cytology alone) |
| Over 65 y | Stop screening **if** pt has had adequate screening (below) & ≥20 y elapsed since resolution of CIN2–3 (if ⊕ hx); |
| S/p complete hysterectomy for benign reasons | No screening if no other RFs |
| Immunocompromised, HIV, hx cervical CA, hx *in utero* DES exposure | Annual screening indefinitely |

- **Adequate screening:** Defined as 3 consecutive ⊖ Pap tests or 2 consecutive ⊖ Pap + HPV tests w/in 10 y, w/ most recent tests w/in 5 y → return to guidelines above

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## CYTOLOGY INTERPRETATION AND MANAGEMENT

- Given myriad potential results & clinical scenarios, only selected guidelines included here; full American Society for Colposcopy & Cervical Pathology (ASCCP) 2012 updated consensus guidelines include 19 algorithms → see *Obstet Gynecol* 2013;121:829

### Selected Cytology Results and Follow-up

| Result | Management |
|---|---|
| Unsatisfactory (inadequate sample) | Repeat |
| Negative but lacking endocervical cells | Continue routine screening w/o early repeat |
| Negative for intraepithelial malignancy ("normal") | Routine screening, Pap q3y **or** Pap + HPV q5y if 30–65 y |
| Atypical squamous cells of undetermined significance (ASC-US) in women 21–24 y | Repeat cytology at 12 mos **(preferred)** or reflex HPV<br>**Reflex HPV Testing:**<br>If HPV ⊖ → routine screening<br>If HPV ⊕ → repeat cytology at 12 mos<br>**12 mos cytology:**<br>Negative, ASCUS, or LSIL → repeat in12 mos<br>ASC-H, AGC, HSIL → colposcopy<br>**24 mos cytology:**<br>Negative × 2 → routine screening<br>≥ASC-US → colposcopy |
| ASC-US in women >24 | Reflex HPV **(preferred)** or repeat cytology at 12 mos<br>**Reflex HPV testing:**<br>If HPV ⊖ → cotest at 3 y<br>If HPV ⊕ → refer for colposcopy<br>If reflex HPV unavailable → repeat cytology at 12 mos<br>**12 mos cytology:**<br>Negative → resume routine screening<br>≥ASC-US → colposcopy |
| Atypical squamous cells-high grade (ASC-H) | Refer for colposcopy |
| Low-grade squamous intraepithelial lesion (LSIL) in premenopausal pt | For pts **21–24 y,** repeat cytology at 12 mos<br>**12 mos cytology:**<br>Negative, ASC-US, LSIL → repeat in12 mos<br>ASC-H, AGC, HSIL → colposcopy<br>**24 mos cytology:**<br>Negative × 2 → routine screening<br>≥ASC-US → colposcopy<br>For pts >**24 y:**<br>If no HPV test or HPV ⊕ → colposcopy<br>If HPV ⊖, repeat cotesting at 12 mos preferred, but colposcopy acceptable<br>**12 mos cytology:**<br>Negative **&** HPV ⊖ → resume routine screening, HPV ⊕ and/or ≥ASC-US → colposcopy |
| LSIL in postmenopausal pt | Refer for colposcopy **or**<br>Repeat cytology at 6 mos & 12 mos **or**<br>HPV test: If ⊕, refer to colposcopy; if ⊖, repeat cytology in 12 mos |
| LSIL in pregnant pt | Refer for colposcopy |
| High-grade intraepithelial lesion (HSIL) | Refer for colposcopy |
| Atypical glandular cells (AGC) | Refer for colposcopy, HPV test, ± endometrial bx |
| AGC-endometrial | Refer for endometrial bx/endocervical sampling |

(*Am J Obstet Gynecol* 2007;197:346; *J Low Genit Tract Dis* 2013;17:S1; *Obstet Gynecol* 2013;121:829)

- **Cotesting:** Using HPV w/ cytology for 1° screening; preferred

screening strategy of ASCCP & ACOG **for women >30 y** (not appropriate strategy for women <30 y)

**Selected Cotesting Results and Follow-up**

| Result | Management |
|---|---|
| Negative for intraepithelial malignancy & HPV ⊖ | Continue routine screening; repeat combined screening in 5 y |
| Negative for intraepithelial malignancy **&** HPV ⊕ | Immediate **HPV genotyping** for 16 or 16/18:<br>If ⊕ → colposcopy<br>If ⊖ → repeat cotesting at 12 mos<br>**Or:** Repeat cotesting at 12 mos:<br>If both ⊖ → rpt cotesting at 3 y<br>If either ≥ASC-US or HPV⊕ → colposcopy |
| ASC-US & HPV ⊖ | Repeat cotesting at 3 y |
| ASC-US & HPV ⊕ | Refer for colposcopy |
| LSIL & HPV ⊖ | Repeat cotesting in 12 mos (preferred) or colposcopy |
| LSIL & HPV ⊕ | Refer for colposcopy |
| ASC-H or HSIL w/ any HPV result | Refer for colposcopy |
| AGC w/ any HPV result | Refer for colposcopy + endometrial ± endocervical sampling |

## Further Evaluation

- **Colposcopy** identifies macroscopic changes in cervical epithelium contour, color & vasculature assoc w/ malignancy/premalignancy; accuracy varies w/ experience of colposcopist
- **Dysplasia requires specialist management;** provide general education for pts re: "what to expect": *CIN1:* Managed expectantly **if** preceded by low-grade lesion **or** if present for <24 mos; *CIN2–3:* Managed w/ ablative (e.g., cryotherapy/laser) or excisional (e.g., loop electrosurgical excision) tx; *Cervical CA:* Mgmt depends on staging, comorbidities, desire to preserve fertility

# CONTRACEPTION

## Background

- Almost **half** of all US pregnancies are unintended (pregnancy not desired at time of conception); 33% of women using contraception inconsistently, incorrectly, or not at all → 95% of these pregnancies

(*Perspect Sex Repro Health* 2006;38:90; Facts on Unintended Pregnancies, 2012 *guttmacher.org*)

- Half of all US women at risk of unintended pregnancy (sexually active, fertile, not currently pregnant); appropriate to **discuss contraception w/ all pts of reproductive age**
- **Risk factors:** ↑ rates of unintended pregnancy in women 18–24 y, women living in poverty, nonwhite ethnicity, & ↓ education (*Contraception* 2011;84:478)
- Conditions assoc w/ ↑ health risk from unintended pregnancy: Estrogen-sensitive cancer, cyanotic CHD, recent bariatric surgery or transplant, epilepsy, HTN, SLE, APS

## Choosing a Method

- Counsel pt to choose most effective method she (& partner) able to *use successfully*
- **Women w/ medical issues:** Refer to CDC US Medical Eligibility Criteria for Contraceptive Use, 2010: www.cdc.gov/mmwr/preview/mmwrhtml/rr59e0528a1.htm

**First-year Contraceptive Failure Rates (Selected)**

| Method | Annual # of pregnancies/100 using method | |
|---|---|---|
| | Perfect Use | Typical Use |
| Implant (*Implanon*) | <1 | <1 |
| Sterilization (tubal or vasectomy) | <1 | <1 |
| IUD (Copper-T or *Mirena*) | <1 | <1 |
| Depo Provera | <1 | 6 |
| Pill (combined or progestin only) | <1 | 9 |
| Patch/Ring | <1 | 9 |
| Male condom | 2 | 18 |
| Diaphragm | 6 | 12 |
| Withdrawal | 4 | 22 |
| Periodic abstinence | — | 24 |
| Calendar | 5 | — |
| Ovulation method | 4 | — |
| Symptothermal | <1 | — |
| No method | 85 | 85 |

(Adapted from Guttmacher Institute; http://www.guttmacher.org/pubs/fb_contr_use.html)

## Combined Hormonal Methods (*NEJM* 2003;349:1443)

- Combo of synthetic **estrogen** (usually ethinyl estradiol [EE]) & **progestin** (multiple types)
- **Estrogen** suppresses gonadotropin surge → prevents ovulation
- **Progestin** affects cervical mucus, tubal peristalsis, & endometrial lining → ↓ sperm motility, prevents egg fertilization/implantation
- *Benefits:* Include improvement in menorrhagia, dysmenorrhea, anemia, PMS, acne, hirsutism; ↓ risk ovarian/endometrial CA
- *Risks:* Include HTN, venous thromboembolic disease (up to 3–4× ↑ risk if no underlying RFs; up to 1.8× further ↑ w/ 3rd & 4th gen progestins; absolute risk still low & much < VTE risk w/ pregnancy), MI, stroke; risks ↑ w/ older preparations (estrogen >50 μg)
- **Absolute contraindications:** Include hx DVT/PE or stroke, AMI, known thrombogenic mutations, migraine w/ aura or neuro s/sx, smokers ≥35 y, active liver disease, known/suspected estrogen-dependent tumor (*CDC MMWR* 2010;59:11)
- **Vaginal ring:** NuvaRing (15 μg EE, 150 μg etonogestrel); flexible plastic ring inserted by pt; intravaginal × 3 wk, removed × 1 wk; high pt satisfaction rates
- **Transdermal patch:** Ortho Evra (20 μg EE, 150 μg norelgestromin); apply q1wk; ↓ efficacy in pts >90 kg (*Fertil Steril* 2002;77:S13); **FDA warning:** ↑ systemic estrogen exposure w/ patch than from OCP (w/ 35 μg EE); may cause ↑ risk VTE

## Combination Oral Contraceptive Pills (OCPs)

- **General Approach** to prescribing OCPs: After review of medical hx & contraindications (above):
  1. Select estrogen & progesterone formulations
  2. Set initiation plan w/ pt (quick vs. 1st day vs. Sunday start)
  3. Decide on planned pattern of use (cyclic vs. extended vs. continuous)
  4. Discuss indications for backup methods
  5. Counsel re: side effects
- **Estrogen formulations:** Low-dose (10–20 μg) to high-dose (50 μg) formulations; standard 20–35 μg; breakthrough bleeding may ↑ w/ ≤20 μg dose
- **Progestin formulations:** Multiple options, vary in androgenic activity

*2nd gen:* E.g., levonorgestrel (↑ androgenic), norethindrone (↓ androgenic)
*3rd gen:* E.g., norgestimate, desogestrel (least androgenic)
*4th gen:* Drospirenone (*anti*androgenic + antimineralocorticoid activity)

- **Initiation***:* Can be safely provided after careful medical hx & BP
  *Quick start* (preferred): Take 1st pill as soon as prescription filled; ↑ compliance w/o ↑ s/e; need backup contraception × 7 d (*Obstet Gynecol* 2007;109:1270)
  *1st day start:* Take 1st pill on 1st day of period; backup contraception not needed
  *Sunday start:* Take 1st pill on Sunday after period begins; need backup × 7 d
- **Pattern of use***:* Can be given cyclically (21 active pills → 7 hormone-free pills), on extended cycle regimen (e.g., 84 active pills → 7 hormone-free pills), or continuously; extended/continuous options may be preferred in women w/ premenstrual sx or for lifestyle; efficacy & safety equivalent to cyclic use
- **Backup method indications:**
  *Missed pills:* Use backup contraception × 7 d after ≥2 missed pills
  *Medication interactions:* Efficacy ↓ by meds that ↑ liver microsomal enzyme activity (e.g., anticonvulsants, griseofulvin, rifampin, St. John's wort); no clinical evidence re: other abx, although some case reports w/ PCN, tetracyclines (*Obstet Gynecol* 2001;98:853)
- **Side effects/monitoring:**
  *S/e:* Counsel pts in advance re: anticipated s/e (see below) these typically self-resolve w/in 2–3 mos; also discuss risk/benefits of combined hormonal tx (above)
  *F/u:* Consider f/u 3 mos to check BP, evaluate for tolerance & s/e; can switch pill to adjust amount of EE or type of progestin per s/e
  *Pregnancy:* If pregnancy occurs while on OCPs, d/c upon dx, but reassure pt no adverse outcome a/w using OCPs at time of conception

**Adjusting Ocp Formulation for Side Effects**

| Side Effects | Cause | Adjustment |
|---|---|---|
| HA, nausea, mastalgia | Estrogen excess | Try dosing QHS vs. low estrogen pill (↑ risk breakthrough bleeding) |
| Hirsutism, acne, wt gain | Progestin and/or androgen excess | → 3rd generation progestin |
| Mood changes, ↓ libido | Progestin excess | → 3rd generation progestin |
| Breakthrough bleeding | Often multifactorial | Consider alt etiology (polyp/infection), missed dose<br>Early cycle/continuous: → ↑ EE<br>Late cycle bleeding: → ↑ progestin (desogestrel > norgestimate) **or** change to triphasic preparation |
| Amenorrhea | Pregnancy; nonpathologic suppression of endometrial shedding | Pregnancy test: If ⊕, d/c OCP; if ⊖, reassurance; if pt desires menses: → ↑ EE **or** choose progestin w/ ↑ endometrial activity (e.g., 1 mg norethindrone → 5 mg); triphasic pill may be effective |

## Progestin-only Methods

- **Progestin-only ("mini-") pills:** Option for pts w/ contraindication to estrogen (including lactation); ↑ risk breakthrough bleeding; must take at same time every d
- **Injectable:** Depot medroxyprogesterone acetate (DMPA); IM/SC injection q3mos
  *Benefits:* No need for daily pt adherence, amenorrhea w/ ongoing use, ↓ endometrial CA; *S/e:* Irregular bleeding (frequent cause for d/c), ↑ wt, HA,
  ***FDA Black Box Warning:*** can ↓ *BMD* (esp in adolescents)
- **Subdermal contraceptive implant:** *Implanon* (etonogestrel); very effective up to 3 y; fertility returns soon after removal; risk of irregular bleeding (1° reason for d/c)

## Barrier Methods

- **Condoms:** Consistent, correct use protects from STI acquisition/transmission; latex condoms ↓ HIV risk by 80–95% (*Cochrane Data* 2001:CD003255; *Soc Sci Med* 1997;44:1303)
  *Latex allergy:* 1–6% US pop; synthetic & natural membrane condoms exist (↓ efficacy)
  ♀ *condoms:* Polyurethane sheath; option if cannot use ♂ condom
  *Spermicides:* Do not protect against STIs; irritation may ↑ risk infection
- **Diaphragm, cervical cap:** Require fitting by trained clinician; only

effective when used w/ spermicide; do *not* prevent transmission of STIs

## Intrauterine Contraception (*Am J Obstet Gynecol* 2008;198:248; *CDC MMWR* 2010;59:52)

- *Benefits:* **Very effective, no maintenance;** good option for women who desire to avoid pregnancy for >3 y; avoids estrogen exposure
- *Risk of ectopic pregnancy:* ↓ overall risk c/w pts who do not use contraceptives, but ↑ risk *if* pregnancy occurs (*Am J Obstet Gynecol* 2004;190:50)
- *Contraindications:* Uterine distortion, active pelvic infection (wait 3 mos before insertion), women w/ ↑↑ risk for STIs, pregnancy, unexplained uterine bleeding, active cervical/endometrial CA; ***not* contraindicated in adolescents/young adults or nulliparous women**
- **Levonorgestrel-releasing IUD** (*Mirena, Skyla*): Inhibits sperm transport & ova fertilization; partially inhibits ovulation; ↓ blood loss, ↓ dysmenorrhea; effective for 5 y (Mirena) or 3 y (Skyla)
- **Copper IUD:** Releases copper continuously into uterine cavity; interferes w/ sperm transport, prevents fertilization; effective for at least 10 y

## Sterilization

- **Tubal obstruction:** Prevents pregnancy by occluding or disrupting tubal patency; laparoscopic (general anesthesia) vs. hysteroscopic (often local anesthesia)
- **Vasectomy:** Interruption or occlusion of the vas deferens; can be performed in outpt setting w/ local anesthesia; *safest, least costly method of surgical sterilization*

## Emergency Contraception (EC) (*NEJM* 2003;349:1830)

- **Indications:** Pts who have had unprotected intercourse, including failure of another method w/in previous 120 h; improved access does not ↑ sexual risk taking or STI acquisition (*Obstet Gynecol* 2006;108:1098)
- **Access: Plan B One-Step available w/o prescription regardless of**

**age;** other options available to women aged 17 and over w/o Rx, and to younger women w/ Rx
*Contraindications* (*VTE, migraines, liver disease*) *to daily OCPs do NOT apply to EC*

- **Efficacy:** ↓ pregnancy risk up to 88% (levonorgestrel EC); does *not* interrupt established pregnancy
- **Options:** May refer pts to **www.not-2-late.com**
  ***Levonorgestrel EC:*** 1 (1.5 mg) dose **(Plan B One-Step)** or 2 × 0.75 mg taken 12 h apart *Single dose as effective;* safer & more effective than Yuzpe regimen w/ ↓ rates of N/V, however **minimally** effective for women > 154 lb (70 kg) (*Contraception* 2011;84:363)
  ***Yuzpe regimen* (EE + progestin):** 2 × [100 μg EE + 0.5 mg levonorgestrel]
  Many OCPs can be used; less effective than progestin-only, ↑ N/V
  ***Ulipristal acetate*** (*ella*): Rx only; *most effective oral option:* Pregnancy rate = 1.3% ulipristal acetate vs. 2.2% for levonorgestrel (use 0–120 h after intercourse) (*Lancet* 2010;375:555), preferable for obese women (*Contraception* 2011;84:363)
  ***Copper IUD:*** Most effective form of EC (>10× efficacy of pills); insert w/in 5 d of intercourse; provides continuing contraception; avoid w/ active gonorrhea/chlamydial infection (*CDC MMWR* 2010;59:64; *Hum Reprod* 2012;27:1994)
- **Counseling:** Emphasize regular contraception use (can start OCPs d after EC)
  Consider screening for STIs; ✔ pregnancy test if no menses in 3–4 wks

# DYSMENORRHEA

## Background

- **Definitions:** *Primary dysmenorrhea:* Painful menses w/ nl pelvic anatomy; clinical dx based on hx recurrent, midline pelvic pain at/near onset of menses × 1–3 d w/o other explanation; *Secondary dysmenorrhea:* Painful menses due to pelvic d/o (e.g., endometriosis, fibroids)
- **Pathogenesis:** Prostaglandin release w/ endometrial sloughing →

frequent, uncoordinated contractions → ↑ intrauterine pressure > arterial pressure → uterine ischemia, ↑ anaerobic metabolites → stimulates type C pain neurons (*Obstet Gynecol* 2006;108:428)

- **Epidemiology and risk factors:** Affects 50–90% of reproductive-age ♀; prevalence highest in adolescents, ↓ w/ age; most have 1° dysmenorrhea; *Risk Factors:* Nulliparity, heavy menstrual flow, smoking, depression; unclear assoc w/ endometriosis (which can be asx or cause pelvic pain outside of menses) (*AFP* 2005;71:285)

## Evaluation

- **General approach:** (1) Exclude 2° causes (GI, GU, ID), (2) assess severity, (3) assess prior tx used
- **History:** Crampy pelvic pain assoc w/ menstruation; lasts 1–3 d; onset usually in adolescence
- **Red flags:** Suspect 2° cause if onset > age 25 y, pain not related to menses, AUB, nonmidline pelvic pain, ⊕ dyspareunia, ↑ sx severity → referral to OB/GYN
- **Exam:** Unremarkable in 1°; evaluate for abdominal masses, point tenderness; pelvic exam important to r/o STI (e.g., GC/CT)
- **Diagnostics:** Not indicated if hx/PE c/w 1° dysmenorrhea; may test for STI as appropriate; r/o ectopic or miscarriage w/ b-hCG if recent onset of sx & irregular menses; **Pelvic U/S** if suspect pelvic pathology (mass, ovarian cysts, endometriosis) or severe dysmenorrhea refractory to initial Rx

**Dysmenorrhea Grading System**

| Grade | Characteristic | Analgesics |
|---|---|---|
| 0 | Menstruation not painful; daily activity unaffected | None needed |
| 1 | Menstruation mildly painful; daily activity seldom affected | Rarely needed |
| 2 | Menstruation moderately painful; inhibits daily activity (work/school attendance); relieved w/ analgesics | Routine use |
| 3 | Menstruation severely painful; inhibits daily activity; poorly responsive to analgesics; a/w vegetative sx (HA, fatigue, vomiting, diarrhea) | Poor effect |

(Adapted from *Am J Obstet Gynecol* 1982;144:655)

## Management

- Management below for 1° dysmenorrhea, for severe or suspected 2° causes → refer
- **Goals of treatment:** Adequate pain relief to resume daily activities; complete resolution of sx is often unrealistic
- **Nonpharmacologic:** *Heat:* Equal efficacy to ibuprofen, better than APAP (*Obstet Gynecol* 2001;97:343; *J Reprod Med* 2004;49:739); pt may find cumbersome; *Exercise, low-fat vegetarian diet, dairy, fish oil, Vit B,D,E:* Varied results in limited, small studies
- **Pharmacologic:** NSAIDs, hormonal contraception are mainstay (*JAMA* 2001;285:2347)

  No RCT comparing NSAIDs & hormonal contraception; can initiate either

  **NSAID approach:** Depending on cost, pt preference, convenience, can start w/ cheaper options (e.g., ibuprofen, naproxen) then → prescription/costly ones (e.g., mefenamic acid); start w/ onset of sx or menses, continue for 2–3 d based on pt's usual sx pattern

  **Hormonal approach:** Initiate depending on pt preference as mostly = efficacy; can initiate cyclic OCP & → continuous if no response
- Can change to other modality if no response after 3 mos; can also do in combination
- If refractory to combination NSAID + hormonal contraception × 3 mos, consider 2° cause & gynecology referral for laparoscopy

**First-line Pharmacologic Therapy**

| Class | Sample Rx w/ Usual Dosing | Notes |
|---|---|---|
| NSAID | Ibuprofen 800 mg q8h × 3 d<br>Mefenamic acid 500 mg × 1, then 250 mg q6h × 3 d<br>Naproxen 500–550 mg BID | Efficacy > placebo/acetaminophen in RCTs (*Cochrane Database Syst Rev* 2010:CD001751); unclear if specific NSAIDs better than others |
| OCP | Any preparation (low or high dose estrogen) 1 tablet QD<br>Extended or continuous cycle > relief than cyclic (*Contraception* 2010;81:215) | Efficacy > placebo; no evidence 1 preparation better than another (*Cochrane Database Syst Rev* 2009:CD002120) |
| Other Hormone | Vaginal ring<br>Depot medroxyprogesterone acetate | Efficacy: Ring = OCP<br>50% pts amenorrheic in 1st y of depot; no studies w/ relief of dysmenorrheal as 1° outcome (*Contraception* 2009;80:113); avoid if planning to conceive w/in 1–2 y |
| IUD | Levonorgestrel-IUD | Nulliparity not contraindication; copper IUDs may dysmenorrhea |

- **Complementary/alternative medicine:** Insufficient data on effectiveness of CAM (e.g., herbs, acupuncture, acupressure, spinal manipulation)
- **Patient Information:** http://www.acog.org/Resources_And_Publications/Patient_Education_ (see *"Dysmenorrhea (FAQ046)"* under Gynecological Problems)

# MENOPAUSE

## Background

- **Menopause:** Permanent cessation of menstruation due to loss of ovarian follicular activity, defined retrospectively after 12 consecutive mos of amenorrhea w/o other cause
- **Perimenopause:** Period from onset of clinical/endocrinologic changes immediately prior to menopause until 1 y after final menstrual period (FMP)
- **Menopausal transition:** Period of menstrual variability preceding FMP (mean = 4 y)
- **Epidemiology:** Median age 51 y (studies in white women in industrialized countries); cigarette smokers undergo menopause avg 2 y earlier
- **Early menopause:** FMP ≤ 40 y: assoc w/ ↑ CVD risk, earlier cognitive decline; inconclusive evidence that early menopause may be assoc w/

↓ SES, residence in rural/developing areas, African-American/Latina heritage, parity, lack of OCP use (*Obstet Gynecol Clin North Am* 2011;38:425)

## Evaluation

- **General Approach:** Dx is primarily clinical, based on hx & PE
- **History:** Assess for menopause vs. any features suggestive of alt cause for AUB or amenorrhea (e.g., pregnancy, ↑ PRL, PCOS, meds; see *"AUB"* & *"Amenorrhea"*)
  *Menstrual hx:* Age; menstrual timing, freq, duration, quantity, and/or cessation
  *ROS:* Presence/severity of hot flashes, night sweats, disturbed sleep, mood swings, depressed/anxious mood, difficulty concentrating, memory loss, HA, fatigue, dyspareunia, vaginal dryness/itching, ↓ libido, urethral irritation/other UTI sx
  *PMHx:* Consider hx disease that may impact Rx choice (CAD, breast/uterine cancer, DVT, acute liver disease)
  *FHx:* Age of menopause in mother/sisters, any hx early menopause
  *Consider other causes of vasomotor instability:* EtOH consumption; panic attacks; carcinoid; dumping syndrome; thyroid dysfunction; pheo; narcotic w/d; use of nitrates, niacin, CCBs, GnRH agonists, or antiestrogens
- **Exam:** Pelvic exam (vaginal pallor, dryness, ↓ mucosal rugosity = atrophy; r/o trauma, infection); consider HEENT, neck, abdominal, & skin exams if hx suggests alt etiology for vasomotor instability
- **Diagnostics:** In women late 40s–mid-50s w/ classic sx, no role for labs; LH & FSH **not** routine as both may be nl during menopausal transition (*NEJM* 2006;355:2338); check FSH in younger ♀ w/ vasomotor sx s/p hysterectomy; check β-hCG if concern for early menopause

**Menopausal Transition Stages** (*NEJM* 2006;355:2338)

| | Premenopause | Menopausal Transition | Postmenopause |
|---|---|---|---|
| **Menstrual cycle** | Regular vs. variable (early) | Variable; 1–2 missed cycles/y (early) vs. ≥3 missed cycles/y | None |
| **Estradiol** (pg/mL) | 50–200 | 50–200+ | 40 (early)<br>0–15 (late) |
| **Testosterone** (pg/mL) | 400 | 400 | 400 |
| **FSH** (mU/mL) | 10 on d 2–4 | ≥10 on d 2–4 | >100 |
| **LH** (mU/mL) | 10 on d 2–4 | ≥10 on d 2–4 | >100 |
| **Hot flash prevalence** (%) | 10 (late) | 40 (early); 65 (late) | 50 (early)<br>10–15 (late) |

## Manifestations

- **General:** In longitudinal studies adjusted for confounders, only vasomotor sx, vaginal sx, & sleep disturbances consistently assoc w/ menopausal transition (*NEJM* 2006;355:2338)
- **Vasomotor instability:** Exact hormonal mechanism(s) unclear, likely involve estrogen w/d, ↑ FSH; sx prevalence/severity vary markedly (e.g., by ethnicity, smoking, stress) but peak in late menopausal transition, affect up to 65% women; **most are transient, w/ spontaneous improvement** w/in 2–3 mos in 30–50% pts & w/in 4–5 y in 85–90% pts; hot flashes (flushes) continue for y in only 10–15% pts (*Ann NY Acad Sci* 1990;592:52)
- **Vaginal symptoms:** ↓ estrogen → vaginal atrophy & ↓ secretions; incidence from 30% (early postmenopausal) to 47% (late), as sx tend to ↑ w/ aging (*Obstet Gynecol* 2000;96:351)
- **Urinary symptoms:** Vaginal fluid pH ↑ after menopause → ↑ UTI-related enteric organisms, ↓ estrogen → vaginal shortening; however, no clear correlation w/ menopausal transition (*Obstet Gynecol* 2000;96:351)
- **Sexual symptoms:** Very common but underreported; may have multiple manifestations, including dyspareunia, ↓ desire, ↓ arousal, and/or difficulty w/ orgasm; a/w ↓ satisfaction w/ relationships & premenopausal sexual function; emphasize ↓ desire is expected, nl & that contributing factors can be individually addressed (see "Treatment", below)

## Treatment (*NEJM* 2006;355:2338; *AFP* 2000;61:1391)

- **General:** Not all women seek treament for menopausal symptoms;

those who do often seek Rx for vasomotor/vaginal sx; counseling/education important part of tx

- **Vasomotor instability:** Self-reported freq/severity of hot flashes ↓ w/ placebo alone
  *Behavioral*: All pts should be counseled re: behavior changes (dressing in layers, ↓ ambient temperature, ↓ /avoid EtOH)
  *CAM*: No RCT evidence for efficacy of acupuncture, yoga, Chinese herbs, evening primrose oil, ginseng, kava, red clover; modest benefit from Vit E; mixed evidence for dietary soy/phytoestrogens & black cohosh (*Menopause Int* 2012;18:20; *Cochrane Database Syst Rev* 2007;4:CD001395)
  *Estrogen:* For mod–severe disease; ↓ freq of flashes by 80–95%, regardless of type/route, w/ dose-related response (see *"Estrogen Therapy,"* below)
  *Alt Rx:* SSRIs/SNRIs (best evidence for paroxetine in breast CA survivors), gabapentin (consider s/e); no clear benefit from clonidine
- **Vaginal symptoms:**
  *Vaginal estrogens:* (crm, PV tablet, estradiol-releasing ring): **1st-line;** sx improve in 80–100% pts, minimally ↑ serum estrogen → no need to add progestin if using std dosing; PO estrogen generally **not** indicated for relief of isolated vaginal sx
  *Polycarbophil vaginal moisturizer* (*Replens*): Provides sx relief equal to vaginal estrogens (*Fertil Steril* 1994;61:178)
  Ospemifene (*Osphena*): New FDA-approved SERM can be used for dyspareunia 2/2 to vulvovaginal atrophy; *Contraindications:* Estrogen-dependent neoplasia or hx VTE, stroke, MI, or breast CA; *Common s/e:* Hot flashes, vaginal d/c, muscle spasms
- **Sexual symptoms:**
  ↓ *arousal/dyspareunia:* Trial vaginal estrogens & lubricants; consider ospemifene
  ↓ *libido:* Evidence for bupropion in premenopausal pts but no studies in perimenopausal pts (*BJU Int* 2010;106:832)
- **Urinary symptoms:** Estrogen Rx (PO or PV) may improve subjective urinary incontinence sx, but not known to improve objective measures (e.g., urodynamic testing) (*Obstet Gynecol* 1996;88:745); PV estrogen may ↓ UTI recurrence (*NEJM* 1993;329:753)

- **Psychological symptoms:** Estrogen Rx may improve mood/dysphoria (possibly via CNS serotonin metabolism) but ineffective for 1° depression (*Obstet Gynecol* 1996;87:20S); fatigue/difficulty concentrating/poor memory likely due to sleep disturbances, may improve w/ Rx for vasomotor instability; SSRIs may be helpful, but caution re: ↓ libido

## Estrogen Therapy

- **Efficacy:** Excellent for mod–severe vasomotor or vaginal sx; ± for urinary, psychological sx
- **Low-dose progestin:** Recommended as addition to PO estrogen (combination tx) if uterus intact to avoid uterine hyperplasia/CA (see *Side effects*)
- **Dosing:** *Prescribe lowest effective dose for shortest possible time;* peak effect reached w/in 4 wks (standard dosing) vs. 8–12 wks (lower dose); attempt d/c q6–12mos w/ gradual taper
- **Side effects:** Both estrogen alone & w/ progestin ↑ stroke risk 40%; estrogen + progestin assoc w/ ↑ risk MI, PE, breast CA (*JAMA* 2002;288:321; *JAMA* 2004;291:1701); common s/e include uterine bleeding, breast tenderness
- **Contraindications:** If hx or high risk for CVD, breast/uterine cancer, DVT, active liver disease, inability to obtain annual mammogram

**Sample Estrogen and Progestin Rx for Vasomotor Sx** (*NEJM* 2006;355:2338)

| Preparation | Generic Name | Brand Name | Dosing (mg) |
|---|---|---|---|
| **Estrogen** | | | |
| Oral | Conjugated estrogens | Premarin | 0.3, 0.45, 0.625, 0.9, 1.25 (daily) |
| Transdermal | 17β-estradiol | Climara | 0.025, 0.0375, 0.05, 0.075, 0.1 (weekly) |
| Vaginal | Estradiol acetate | Femring | 0.05, 0.1 (every 90 d) |
| **Progesterone/Progestin** | | | |
| Oral | MPA | Provera | 2.5, 5, 10 (daily) |
| Vaginal | Progesterone | Prochieve 4% | 45 (daily) |
| **Combination** | | | |
| Oral | Conjugated estrogens + MPA | Prempro | 0.625/2.5; 0.625/5; 0.45/2.5; 0.3/1.5; 0.45/1.5 (daily) |
| Transdermal | 17β-estradiol-norethindrone acetate | CombiPatch | 0.05/0.14 or 0.05/0.25 (twice weekly) |

# PELVIC PAIN

## Background (*AFP* 2010;82:148)

- **Definition:** Pain localized to the pelvis, anterior abdominal wall at/below the umbilicus, lower back, or buttocks, severe enough to cause functional disability or require Rx
- **Epidemiology:** 30–40% women of reproductive age in primary care have pelvic pain outside of menstruation at some point
- **General approach:** Distinguish **acute** (≤3 mos) vs. **chronic** (≥6 mos); in determining cause, consider age & pregnancy status, then Ddx by organ system: GI, GYN, MSK, psych/neuro, urologic, other

### Differential Diagnosis of Pelvic Pain

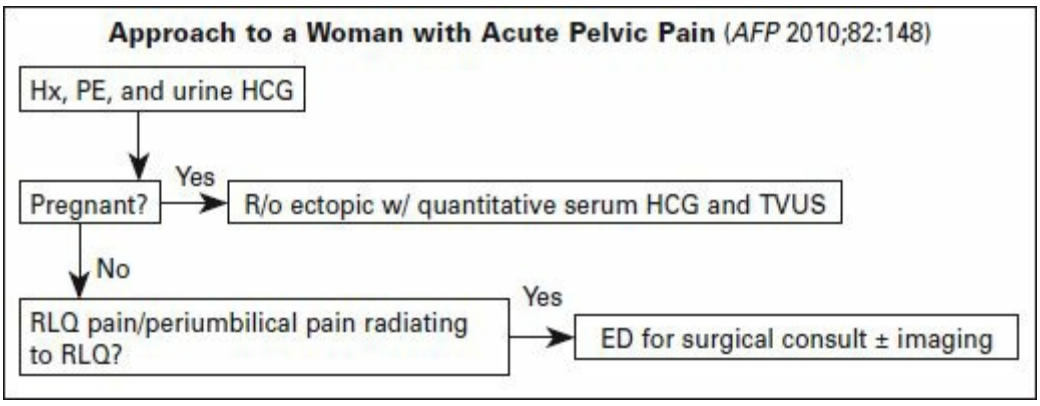
| | Acute | Chronic |
|---|---|---|
| **General approach** | First r/o most common emergent causes: PID, appendicitis, ovarian torsion, ectopic pregnancy, cyst rupture; no dx found 8–37% cases | Up to 40% have >1 dx; dysmenorrhea, dyspareunia & IBS most frequently reported comorbidities |
| **GYN** | PID/TOA (19–50%), ruptured ovarian cyst (12–27%), ectopic pregnancy (9–17%), ovarian torsion (1–10%), miscarriage, torsion/degeneration of uterine fibroid, endometriosis (2–16%), mittelschmerz | Endometriosis, dysmenorrhea, chronic PID/endometritis, adhesions, adenomyosis, uterine fibroid, pelvic congestion syndrome, ovarian cysts, malignancy |
| **Non-GYN** | *GI:* Appendicitis (2–18%), diverticulitis, bowel obstruction, mesenteric venous thrombosis, IBD flare, perirectal abscess<br>*GU:* Cystitis, pyelonephritis, nephrolithiasis<br>*Ψ/neuro:* Somatization d/o (anxiety, depression, physical or sexual abuse: see *"Somatic Disorders"*)<br>*Other:* Sickle cell, trauma, porphyria, lead poisoning | *GU:* Interstitial cystitis, radiation cystitis, recurrent UTI, bladder neoplasm, detrusor dyssynergia<br>*GI:* IBS, IBD, constipation, inguinal hernia, celiac disease, diverticulitis, colitis, colon CA<br>*MSK:* Fibromyalgia, coccydynia, piriformis syndrome, levator ani syndrome, hip arthritis, DJD, stress fx of hip/pelvis/spine<br>*Neuro:* Abdominal cutaneous nerve entrapment syndrome, abdominal epilepsy/migraine<br>*Ψ:* Depression, sleep d/o somatization,<br>*Other:* Porphyria, shingles, FMF |

## Evaluation (*AFP* 2010;82:148; *AFP* 2008;77:1535)

- **History:** *Onset* (acute vs. chronic); age, *location* (radiating: appendicitis, kidney stone, ovarian torsion, discitis); quality, exacerbating & alleviating factors, *assoc sx* (menses, constipation, diarrhea, hematochezia, dysuria, vaginal d/c); PMHx, PSHx, *FHx* (sickle cell, coagulation d/o); *social hx* (trauma, hx physical, sexual, or domestic abuse, SUD); thorough *reproductive/sexual hx:* Infertility (endometriosis), STI hx (PID), menorrhagia (fibroids)
- **Exam:** VS, general level of comfort/distress, bowel sounds, palpate for abdominal/pelvic masses; *Carnett sign:* have pt raise legs off table while supine w/ finger on painful area → ↑ pain consistent with myofascial rather than visceral pain; *CVA tenderness:* pyelonephritis/nephrolithiasis; *Pelvic exam*: Erosive/vesicular lesions (HSV), vaginal d/c, cervical d/c, cervical motion tenderness (PID), nodules/tenderness in posterior cul-de-sac (endometriosis), rectal exam
- **Diagnostics:** As dictated by history

  *Acute:* Urine hCG in any woman of reproductive age; GC/CT; U/A ± UCx; CBC w/ diff; vaginal wet prep/Cx; TVUS = 1st-line imaging study; CT occasionally helpful, particularly for RLQ pain (appendicitis, abscess)

  *Chronic:* If initial H&P nondiagnostic, w/u as above + TVUS & ESR; attempt Rx (below)




## Treatment (*Obstet Gynecol* 2003;101:594)

**Treatment of Pelvic Pain, by Etiology**

| Treatment | Therapy |
|---|---|
| PID, TOA | See *"Pelvic Inflammatory Disease"*; early surgical c/s & intpt mgmt for TOA |
| Genital HSV | See *"Herpes Simplex Virus"* |
| Dysmenorrhea | See *"Dysmenorrhea"*; OCPs + NSAIDs or acetaminophen |
| Endometriosis | OCP (monthly or, if fails, trial of continuous); may try medroxyprogesterone acetate (continuous progestin), Gyn referral for consideration of GnRH agonist (leuprolide), Danazol (progestin-like effects), or laparoscopy for dx & tx |
| Adhesions | Evidence inconsistent re: laparoscopy for adhesiolysis |
| Chronic Pelvic Pain | *Surgical:* No shown benefit over non-surg (except adenomyosis)<br>*Nonsurgical:* Trial empiric tx for endometriosis (above)<br>*Other modalities:* NSAIDs, consider SSRI for concomitant depression, amitriptyline or neurontin for neuropathic pain<br>*Multidisciplinary:* Pelvic floor PT, trigger point injections, topical analgesics, heat, acupuncture, CBT, biofeedback, TENS |

## When to Refer

- **Pregnant or postpartum:** Pts w/ pelvic pain should be managed by OB-GYN
- **Acute pelvic pain:** ⊕ peritoneal signs, systemically ill, or concern for severe PID → ED
- **Chronic pelvic pain:** Dx uncertain and/or not responsive to initial Rx → Gyn; pts w/ unresponsive chronic pelvic pain may benefit from multidisciplinary pain center referral
- **Patient Information:** Familydoctor.org/familydoctor/en/diseases-conditions/chronic-pelvic-pain.html (Chronic Pelvic Pain)

# PELVIC INFLAMMATORY DISEASE

## Background (*CDC MMWR* 2006;55:11)

- **Definition:** Acute infection of the upper genital tract in women; includes endometritis, salpingitis, TOA, pelvic peritonitis; can be acute, subacute, or subclinical
- **Etiology:** Upward migration of organisms (STIs & vaginal flora) through cervix & into uterus, fallopian tubes, and/or peritoneal cavity

  *Pathogens:* Often polymicrobial & never identified, **most common** = *N. gonorrhoeae* & *C. trachomatis;* others: Aerobic & anaerobic vaginal flora (e.g., *G. vaginalis*, *H. influenzae*, *Mycoplasma genitalium*, enteric GNRs, & *S. agalactiae, Prevotella, Bacteroides,*

*Peptostreptococcus);* high prevalence of coexisting BV

- **Incidence:** Declining in US, but remains most frequent Gyn cause for ED visits; ~1 million women in the United States diagnosed w/ PID each y, >50% = adolescents, young adults (*Clin Infect Dis* 2007;44:S111); subclinical PID (endometritis) as common as clinically diagnosed PID & can → same rate of complications (*Infect Dis Obstet Gyn* 2011;2011:561909)
- **Complications/sequelae: TOA, chronic pelvic pain** (up to 30%) (*Am J Obstet Gynecol* 2002;186:929), **infertility, ectopic pregnancy;** risk ↑ w/ number of episodes/severity (>3 d sx), delays in care, & w/ chlamydia as causative organism

## Evaluation (*AFP* 2006;73:859; *Lancet* 1992;339:785)

- **History:** Sx include **lower abdominal pain** (usually b/l, ↑ w/ intercourse/palpation/valsava), dyspareunia, recent menses, fever, chills, back pain, vomiting, & sx of lower genital tract infection (abnl vaginal d/c or bleeding, itching, odor); sx can be mild or absent
- **Risk factors:** Age <25 y; multiple, new, or sx partners; hx PID or STIs; lack of barrier contraception, IUD (↑ risk *only* w/in 3 wks of insertion), douching
- **Physical exam:** Tenderness typically in lower quadrants; RUQ pain → perihepatitis/Fitz-Hugh–Curtis syndrome; only 50% p/w fever
  *Pelvic exam:* Purulent endocervical d/c and/or acute cervical motion/adnexal tenderness w/ bimanual exam; adnexal tenderness = 95.5% Se for histologic endometritis (*Am J Obstet Gynecol* 2001;184:856)
- **Labs:** Urine hCG, U/A, vaginal wet prep (87–91% Se for PID if 3+ WBCs/hpf seen; 95% NPV if no WBCs seen), CBC, chlamydia & gonorrhea, CRP/ESR (Se = 74–93%); also test for HIV, Hep B S Ag/Ab, syphilis
- **Imaging:** TVUS indicated in clinically ill, severe pain, or adnexal mass to dx TOA; thickened, fluid-filled tubes on TVUS definitive for PID; do not delay tx for imaging
- **Differential diagnosis:** Consider other "neighboring structures" (appendix, colon, bladder, urinary tract) as well as other gynecologic phenomena (miscarriage, ectopic, ovarian pathology); see *"Pelvic*

*Pain"*

## Treatment (*CDC MMWR* 2006;55:11; *MMWR* 2007;56:332; *MMWR* 2012;61:590)

- **Treatment criteria:** For all sexually active pts, initiate **empiric tx if pt has any adnexal, uterine, or cervical motion tenderness w/o other apparent cause;** pts w/ even min. findings have high likelihood of subclinical PID (*cdc.gov/std/pid*)
- **Follow up:** All pts should be clinically reassessed at 72 h for improvement
- All Rx regimens should be effective against *N. gonorrhoeae* & *C. trachomatis;* FQs & PO ceph **not** recommended due to ↑↑ gonorrhea resistance

**CDC 2010 Recommendations for PID Treatment**

| | |
|---|---|
| **Oral/IM** (Reevaluate at 72 h; if not responding → IV abx, inpt or outpt) | Ceftriaxone 250 mg IM × 1 **&** doxycycline 100 mg PO BID × 14 d **OR** Cefoxitin 2 g IM × 1 **&** Probenecid 1 g PO **&** doxycycline 100 mg PO BID (± MNZ 500 mg PO BID) × 14 d |
| **Parenteral** | Cefotetan 2 g IV q12h OR Cefoxitin 2 g IV q6h **PLUS** doxycycline 100 mg PO or IV q12h, (cf. *cdc.gov* for alt regimens) |

(www.cdc.gov/std/PID/treatment.htm)

- **Sex partners:** Examine/treat ♂ partners from previous 60 d (ceftriaxone 250 mg IM × 1 **plus** either azithromycin 1 g PO × 1 **or** doxycycline 100 mg PO BID × 7 d)
- **IUDs in women with PID:** Insufficient evidence to recommend removal, but close clinical f/u mandatory to confirm resolution
- **Prevention/Counseling:** All pts evaluated for PID should be tested for HIV, HBV, syphilis; also discuss safe sex practices, offer HPV immunization for pts aged 9–26 y; regular screening for GC/CT in pts <26 y

## When to Refer

- If cannot exclude surgical emergencies (e.g., appendicitis), ⊕ hCG, inability to adhere to/tolerate PO meds, severe clinical illness (high fever, N/V, severe abdominal pain), TOA or pelvic abscess → ED

# VAGINITIS

## Background (*JAMA* 2004;291:1368; *AFP* 2011;83:816; *AFP* 2004;70:2125)

- **Definition:** Inflammation of the vagina, due to infectious or noninfectious cause; may or may not be assoc w/ discharge, pruritis, pain
- **Epidemiology:** Vaginal complaints account for 10 million visits/y; most common gynecologic complaint; despite ↑ awareness/Rx, only 50% of cases adequately addressed (*JAMA* 2010;303:2043; NHANES, CDC 2010)
- **Etiologies:** In US pts w/ vaginal sx, bacterial vaginosis (BV) 40–50% > vaginal candidiasis (VC) 20–25% > trichomoniasis 15–20%

### Vaginitis Etiologies

| | Causative Factor/Pathogen | Notes |
|---|---|---|
| Bacterial vaginosis | *Gardnerella vaginalis*>*Lactobacillus*; Others: *Mobiluncus*, *M. hominis*, anaerobic GNRs | Often chronic; most prevalent cause of vaginal d/c or malodor<br>>50% ♀ w/ BV are asx<br>A/w posthysterectomy cuff cellulitis |
| Vaginal candidiasis | *Candida albicans*><br>*C. glabrata*/*C. tropicalis* | Highest incidence (75% of women have ≥1 episode) |
| Trichomoniasis | *Trichomonas vaginalis* | Highly transmissible, frequent coinfection w/ other STIs; assoc w/ posthysterectomy cuff cellulitis |
| Gonorrhea/ chlamydia | *N. gonorrhoeae*<br>*Chlamydia trachomatis* | Often asx; test all pts <25 y w/ vaginal sx; test/treat all pts w/ sx & multiple partners or PID sx (see *"Pelvic Inflammatory Disease"* & *"Sexually Transmitted Infections"*) |
| Irritant/allergic contact dermatitis | *Irritants;* excessive washing, cleansers/deodorizers, condoms, topical antibacterial/antifungals, *Allergens:* Latex, antifungals | Diseased vulvar skin more prone to irritation; irritation dermatitis more common than allergic (*Dermatol Clin* 2010;28:639) |
| Atrophic vaginitis | ↓ estrogen → vaginal atrophy & ↓ secretions | 10–40% of postmenopausal ♀ (See *"Menopause"*) |
| Other | Lichen planus, pemphigus vulgaris, cicatricial pemphigoid, desquamative inflammatory vaginitis, Behcet syndrome | Consider gynecology, dermatology, or rheumatology referral, as appropriate |

(*AFP* 2011;83:816; *AFP* 2004;70:2125; *Infect Dis Clin North Am* 2008;22:637; *NEJM* 1997;337:1896)

## Evaluation (*AFP* 2011;83:816)

- **General approach:** S/sx often nonspecific, & diagnostic studies & demographics key
- **History:**
  *HPI:* Sx: onset, nature of discharge (see *Exam*, below), pruritus (VC, noninfectious), pain/dyspareunia (PID, trichomoniasis, noninfectious, esp desquamative inflammatory vaginitis), systemic sx (PID)
  *Potential triggers:* Contact w/ feminine hygiene products, detergents, soaps, contraceptive materials, pessaries, sex toys, medication, clothing (irritant/contact dermatitis), tight-fitting/nonbreathable clothing (VC)
  *PMHx:* DM, immunosuppression, recent abx use (VC); hx atopy (irritant/contact dermatitis); menopausal (atrophic vaginitis)
  *Social hx:* Smoking (BV, trichomoniasis); diet high in refined sugars (VC)
  *Sexual hx:* New/multiple partners (BV, trichomoniasis, GC/CT, PID), sex w/ women (BV), (*CID* 2008;47:1426), vaginal douching (BV), barrier contraception (contact dermatitis, latex allergy), IUD/diaphragm/spermicide (BV, VC), unprotected intercourse (BV, trichomoniasis), orogenital sex (VC), hx STIs (trichomoniasis, GC/CT, PID)
- **Exam:** Pelvic exam, w/ attention to appearance of vaginal introitus & d/c
  *BV:* Malodorous (fishy) clear/white/gray d/c; no vulvar/vaginal inflammation
  *VC:* White/thick/odorless d/c; ⊕ vulvar excoriations, vaginal inflammation
  *Trichomoniasis:* Green/yellow/frothy d/c; ± vestibular and/or cervical inflammation
  ("strawberry cervix")
  *Noninfectious causes:* Presence of d/c, vulvovaginal inflammation is variable
- **Point-of-care testing:** Critical part of diagnosis: For **"Whiff test,"** mix 10% KOH w/ vaginal d/c, evaluate for amine ("fishy") odor

**Point-of-care Testing and Follow-up** (*AFP* 2011;83:810)

| | pH | Whiff Test | Microscopy | Other Tests |
|---|---|---|---|---|
| **Bacterial Vaginosis** | >4.5 | ⊕ | >20% clue cells (vaginal epithelial cells w/ borders obscured by adherent coccobacilli) | No role for vaginal cx or cervical cytology; consider PCR if unable to perform microscopy |
| **Vaginal Candidiasis** | 4–4.5 | ⊖ | Hyphae/pseudohyphae visible w/ addition of 10% KOH | Pap smear ↑ Sp but ↓ Se<br>OTC rapid yeast detection kit convenient/inexpensive<br>PCR ↑ Se but expensive<br>Cx if recurrent sx w/ ⊖ microscopy |
| **Trichomoniasis** | >5.4 | ⊕ | Trichomonads present<br>Leukocytes > epithelial cells | Cx, rapid Ag testing more Se (microscopy dependent on operator experience)<br>PCR most Se/expensive |

- **Additional labs:** Rarely needed (except for GC/CT), as hx/PE + point-of-care testing (above) combined have good Se/Sp compared with DNA probe standard (81/70% BV; 84/85% VC; 85/100% trichomoniasis) (*AFP* 2011;83:807)

## Treatment (*AFP* 2011;83:816; *AFP* 2004;70:2125)

- **General Approach:** Most etiologies have multiple Rx options; consider effectiveness/preference of PO vs. topical preparations, pregnancy status, need to Rx sexual partner(s)
- **BV:** Metronidazole (MNZ) is standard; recurrence risk highest w/in 1 y,
  *Standard tx:* MNZ 500 mg BID × 7 d; remember to counsel against EtOH use; intravaginal MNZ (0.75 gel, QD × 5 d) & clindamycin crm (2%, QD × 7 d) ~equivalent efficacy but ↑ recurrence rates
  *Alt:* PO clindamycin/intravaginal clindamycin ovules (↓ effective); single-dose PO MNZ (2 g) **not** recommended, as ↓ effective
  *Sex partners:* Tx **not** recommended
- **VC:** Tx course determined by uncomplicated vs. complicated status
  *Uncomplicated* (healthy, nonpregnant, mild–mod disease, <4 episodes/y, hyphae visible on microscopy): Short antifungal course; PO (fluconazole 150 mg × 1) or topical preparations (multiple azole agents, most 1-, 3-, & 7-d course) similarly effective
  *Complicated* (mod to severe disease, >4 episodes/y, only

pseudohyphae visible on microscopy, pregnancy, DM, immunocompromise): Topical Rx (10–14 d) more effective than single-dose PO Rx; if PO preferred → fluconazole 150 mg × 2 doses, 3 d apart

*Sex partners:* Tx **not** recommended

- **Trichomoniasis:** Cure rate 90% w/ almost any nitroimidazole drug

  *Standard:* MNZ 2 g PO × 1 adequate but can → dyspepsia & metallic taste; 500 mg BID × 7 d better tolerated; intravaginal nitroimidazole crm not recommended (cure rate ~50%)

  *Resistant:* MNZ 2–4 g/d × 7–14 d recommended in resistant strains; Oral + intravaginal Rx more effective than PO alone

  *Sex partners:* **Should** be treated simultaneously; counsel to avoid resuming intercourse until both pt & partner have completed Rx & are asx

## When to Refer

- If sx persist despite Rx, dx unclear, or "other" causes (see *Etiologies* table) → consider dermatology or gynecology referral

# BPH & LOWER URINARY TRACT SYMPTOMS

## Background ( *J Urol* 2009;181:1779; *NEJM* 2012;367:248)

- **Lower urinary tract symptoms:** *Storage:* Frequency, nocturia, urgency, incontinence; *Voiding:* Incomplete emptying, intermittency, straining, dysuria, weak stream, hesitancy; *Polyuria:* ≥3 L UOP/24 h; nocturnal polyuria of ≥33% UOP at night
- **Benign prostatic hyperplasia (BPH):** Prostatic enlargement due to ↑ smooth muscle & epithelial cells within the prostatic transition zone, which can lead to LUTS; complications include CKD, urinary retention, recurrent UTI, insomnia, depression, bladder stones, gross hematuria, acute/chronic urinary retention
- **Benign prostatic obstruction (BPO):** Bladder outlet obstruction due to BPH
- **Acute urinary retention:** Painful, palpable/percussible bladder in pt unable to void; may be caused by BPH, constipation, strictures, UTI, neuro d/o, overdistended bladder, medications (nasal decongestants, opiates, antipsychotics, antihistamines); Urgent catheterization for bladder decompression ± nontitratable αB, laxatives, medication mgmt; ✔ renal function & monitor UOP for postobstruction diuresis
- **Chronic urinary retention:** Nonpainful bladder palpable/percussable after voiding, usually persistent PVR > 300 mL
- **Overactive bladder:** Urinary urgency & frequency ± incontinence; may be 2/2 neurologic disorder (stroke, PD) or non-neurologic (BPH, bladder stones) causes, ± overlap w/ BPO
- **Epidemiology:** ↑ w/ age; 25% in 40–49 y; >50% in 60–69 y; >80% in 70–79 y ( *J Urol* 1984;132:474); accounts for 1.9 million PCP visits/y
- **Differential diagnosis:** Prostate/bladder cancer, bladder stone, UTI, prostatitis, neurogenic bladder, ureteral or bladder neck stricture

## Evaluation and Prognosis ( *J Urol* 2009;181:1779; *NEJM* 2012;367:248)

- **History:** LUTS sx (see above), pain (prostatitis), dysuria (UTI), hematuria (cancer, stone, UTI), sexual function; ask which sx

interfere most w/ QoL; fluid intake, caffeine *PMHx/PSHx:* Including neuro (stroke, PD, dementia), DM (polyuria, polydipsia)
*Medications:* Diuretics, antidepressants, bronchodilators, antihistamines, anticholinergics, (↓ bladder function/ ↑ urinary sphincter tone), α-agonists (↑ prostatic smooth muscle tone)
**Frequency-volume chart:** For pts w/ nocturia, record time/volume of every void for 72 h
**IPSS score:** Quantitates LUTS sx after dx & in response to tx

**International Prostate Symptom Score (IPSS)** (Adapted from J Urol 1992;148:1549)

| Over the past month how often... |
|---|
| (1) Have you had a sensation of incomplete bladder emptying after urination? |
| (2) Have you had to urinate <2 h after you finished urinating? |
| (3) Have you stopped/started again several times when urinating? |
| (4) Have you found it difficult to postpone urination? |
| (5) Have you had a weak urinary stream? |
| (6) Have you had to push/strain to begin urination? |
| (7) Did you get up to urinate from the time you went to bed at night until waking in the morning (scored differently: 0 [0 pts], 1× [1 pt], 2× [2 pts], 3× [3 pts], 4× [4 pts], ≥5× [5 pts]) |
| **Scoring (based on answers):** Not at all (0 pts), <1 time in 5 (1 pt), <half the time (2 pts), about half the time (3 pts), >half the time (4 pts), almost always (5 pts); **Mild sx:** 0–7, **Mod:** 8–19, **Severe:** 20–35 |

- **Exam:** Suprapubic palpation (r/o bladder distention), overall motor/sensory function (r/o neuro disease, esp perineum/lower limbs), DRE (tone, prostate gland size, consistency, pain, shape abnormalities, nodules)
- **Workup:** Serum glucose, Cr, U/A; consider UCx (UTI sx), cytology (r/o cancer); check serum PSA as a surrogate marker for prostate size & response to medical Rx (different than PSA screening for an asx pt)
  **Postvoid residual:** To r/o silent urinary retention (nl < 100 mL)
  **Uroflowmetry:** Measures urine volume/time to assess for bladder outlet obstruction
  **Urodynamics:** Measures bladder/abdominal pressure during urination (for pts w/ discrepancy between storage & voiding sx)

## Treatment (*AFP* 2008;77:1403; *BJU Int* 2004;94:738; *NEJM* 2012;367:248)

- **Conservative management:** Appropriate if mild sx (sx may stabilize/improve w/ time); *adjust meds* (avoid α-agonists, anticholinergics, diuretics), *adjust fluid intake* (UOP goal 1L/24 h, ↓ intake in evening), *lifestyle changes* (wt loss, exercise), *dietary advice* (avoid caffeine, spicy/acidic foods, EtOH); Pelvic floor relaxation, Valsalva voiding, Crede voiding (manual bladder compression), double voiding; tx UTI before initiating further Rx (recurrent UTI warrants active tx)
- **Medications:** Indications for tx include adverse impact on pt QoL, recurrent UTI, renal insufficiency, hydronephrosis, urinary retention (may require surgical eval)
  **a-blockers: 1st-line tx** of BPH; provide immediate benefit (in contrast to 5α-reductase inhibitors); *most require dose titration*; ↓ smooth muscle contraction at bladder neck/prostate; reassess efficacy using IPSS 2–4 wks after initiating tx; Meta-analysis of alfuzosin, doxazosin, tamsulosin, terazosin show equal efficacy (*Eur Urol* 1999;36:1); Prazosin not commonly used due to short half-life & CV s/e
    **Side effects:** Dizziness, asthenia, orthostasis, rhinorrhea, HoTN, ↓ ejaculate volume/retrograde ejaculation; avoid in pts w/ prior cataract surgery given risk of intraoperative floppy iris syndrome; use caution with combination of terazosin/doxazosin and sildenafil/vardenafil due to HoTN
  **5α-reductase inhibitors:** Block conversion of testosterone → dihydrotestosterone, ↓ prostate volume; Dutasteride & finasteride equally effective in ↓ prostate volume & improving LUTS (EPICS, *BJU Int* 2011;108:388); benefit greater in men w/ prostate >30 g; PSA may be a surrogate for prostate size, & some recommend prescribing if PSA ≥ 1.5 (*NEJM* 2012;367:248); shared decision-making recommended; reassess efficacy using IPSS 3 mos after initiating tx; *may take up to 1 y to show efficacy*
    **Side effects:** Gynecomastia, ED, ↓ libido; possible assoc w/ high-grade prostate cancer (*NEJM* 2011;365:97); ↓ PSA by 2–2.5-fold so caution must be used in interpreting PSA values in men on tx ( *J Urol* 2005;174:877)
  **Anticholinergics:** Treat LUTS due to OAB; useful in BPH w/ irritative LUTS (urgency, ↑ voiding) w/ nl PVR ( *J Urol*

2011;185:1793); include tolterodine, oxybutynin, fesoterodine, darifenacin, solifenacin, fesoterodine, & trospium; monitor for urinary retention & ✔ PVR prior to initiation; *may take 12 wks to work*

**Side effects:** Dry mouth, blurry vision, ↑ HR, drowsiness, constipation; contraindicated in gastroparesis, glaucoma; darifenacin, solifenacin more selective w/ ↓ s/e; trospium has ↓ ability to cross blood–brain barrier & has ↓ CNS effects (*Urol Clin North Am* 2006;33:465); ER versions better tolerated

**Combination therapy:** Combinations more effective than monotherapy in the long-term; include doxazosin + finasteride (MTOPS, *NEJM* 2003;349:2387) & tamsulosin + dutasteride ( *J Urol* 2008;179:616); tolterodine + tamsulosin effective in BPH + OAB sx (freq, urgency, incontinence) ( *JAMA* 2006;296:2319)

**Phosphodiesterase inhibitors:** Tadalafil FDA-approved for tx of BPH; use caution in pts w/ CrCl < 30 mL/min, or who are on αB; may take up to 4 wks to work; contraindicated in pts on nitrates

**Saw palmetto:** Approved in Germany & France for tx of BPH, despite placebo-controlled RCT showing no benefit (*NEJM* 2006;354:557)

**Desmopressin:** May be used for refractory nocturnal polyuria

- **Surgical treatment:** Transurethral resection, botulinum toxin injection, microwave tx, laser ablation, prostatectomy, transurethral radiofrequency needle ablation

**Commonly Used a-adrenergic Receptor Antagonists**

| Name | Selectivity | Titration | Starting Dose | Max Dose/d |
|---|---|---|---|---|
| Terazosin | Nonselective | Yes | 1 mg PO qHS | 10 mg |
| Doxazosin IR | Nonselective | Yes | 1 mg PO daily | 8 mg |
| Doxazosin ER | Nonselective | Maybe | 4 mg PO daily[1] | 8 mg |
| Alfuzosin | Nonselective | No | 10 mg PO daily[2] | 10 mg |
| Tamsulosin | α-1A selective | Maybe | 0.4 mg PO daily[2] | 0.8 mg |
| Silodosin | α-1A selective | No | 8 mg PO daily[3] | 8 mg |
| **Commonly Used 5α-reductase Inhibitors** | | | | |
| Finasteride | Type 2 | No | 5 mg PO daily | 5 mg |
| Dutasteride | Type 1 & 2 | No | 0.5 mg PO daily | 0.5 mg |

[1]Before breakfast [2]After meal [3]With meal

- **Management of acute urinary retention:** Urgent catheter placement; if unable in primary care setting → ED/same-day urology clinic for cath; may attempt trial without catheter after 2–3 d of α-blockade (*BJU Int* 2011;109:88)
- **When to Refer:**
  **Complicated LUTS:** Abnl DRE/PSA, hematuria, pain, infection (assess/tx prior to referral), palpable bladder, neuro disease, acute/chronic urinary retention
  **Failure of conservative/medical mgmt**
  **Pt desires surgical intervention, <45 y, or incontinent**
  **Hx of prostate/bladder cancer or elevated PSA**

# MALE SEXUAL DYSFUNCTION

## Background (*Eur Urol* 2010;57:804; *NEJM* 2007;357:2472)

- **Erectile dysfunction:** Inability to achieve/maintain erection sufficient for sexual activity
  **Erectile function:** Complex interplay between cardiovascular, metabolic/hormonal, psychological, & nervous systems, primarily mediated by NO signaling
  **Epidemiology:** ↑ w/ age (5% total ED in pts 40–49 y, 15% in pts 70–79 y)
  **Risk factors:** ↑ age, smoking, DM, CVD (HTN, PAD), neuro disease, endocrinopathy (metabolic syndrome, hypogonadism, hyperprolactinemia), obesity, pelvic, perineal, penile trauma/surgery, pelvic XRT, Peyronie disease (scar tissue → painful, abnl curvature of penis when erect), Rx/recreational drug use, EtOH
  **Meds:** Antihypertensives, sympatholytics, anticholinergics, antidepressants, anxiolytics, antipsychotics, antiepileptics, antiandrogens, ketoconazole, niacin, cimetidine, opiates
  **Common comorbidities:** CVD, DM, depression, & EtOH abuse; mgmt of these conditions/risk factors may prevent/treat ED
  **Psychogenic ED:** Suggested by acute onset, preserved ability to obtain spontaneous erections (nocturnal/morning) & erections w/ masturbation

- **Ølibido:** EtOH, depression, fatigue, stress, illicits, meds, relationship issues, ↓ T
- **Premature ejaculation:** (1) Short ejaculatory latency, (2) Lack of control of ejaculation, (3) Distress due to premature ejaculation; prevalence of 20–30%; Multinational studies show average ejaculatory latency 5–6 min ( *J Sex Med* 2010;7:2947); may be comorbid w/ ED
- **Priapism:** Painful erection lasting >4 h; requires immediate tx (→ ED)
- **Dyspareunia:** Pain w/ intercourse for >3 mos; may be related to chronic pelvic pain syndrome, Peyronie disease, phimosis (inability to retract foreskin over glans), UTI/cystitis, psychological (hx abuse)
- **Hematospermia:** Blood in ejaculate; usually benign; ✔ U/A, UCx, gonorrhea/chlamydia based on clinical suspicion; consider PSA, referral to Urology for reassurance

## Evaluation ( *J Urol* 2005;174:230)

- **History:** D in desire, ejaculation, orgasm, penile curvature, genital pain; nocturnal/AM erections, ability to achieve erection/ejaculation from masturbation; distinguish complaints about ejaculation or orgasm from ED; ED severity (e.g., International Index of Erectile Function [IIEF-5]), chronology of sx; LUTS; Ψ hx, sexual orientation, relationship problems, partner's sexual function; may be helpful to interview partner when feasible; screen for CV disease; EtOH/illicit use
- **Exam:** *Gen:* 2° sexual characteristics; *Neuro:* Visual fields (pituitary tumor), genital/perianal sensation, rectal tone; *Chest:* Gynecomastia, *CV:* Femoral/LE pulses; *Derm:* Facial/body hair; *GU:* Penis (phimosis, plaques); testicles (size, firmness), DRE (rectal tone, prostate)
  **Cremaster reflex:** Contraction of ipsilateral scrotum upon stroking inner thigh → assesses genitofemoral nerve
- **Workup:** Comorbid conditions (e.g., HbA1c, serum lipids), AM testosterone, ± PRL (if ↓ libido, e/o hypogonadism, see *"Male Hypogonadism"*; if prostate pathology suspected (e.g., abnl DRE, LUTS) or plan for testosterone replacement, ✔ PSA in addition to above; need to discuss risks/benefits of diagnosis and treatment (see *"Prostate Cancer"*)

## Treatment (*AFP* 2010;81:305; *Ann Intern Med* 2009;151:639; *Eur Urol* 2010;57:804; *NEJM* 2007;357:2472)

- **General approach:** Identify, treat, & optimize organic comorbidities & psychosexual dysfunction; **avoid ED tx when sexual activity not recommended** (i.e., in certain CAD pts, see *"CAD"*); involve partner when appropriate; counsel all pts re: ↑ risk of priapism w/ tx; inform pt priapism requires immediate medical attention
  **Stepwise progression of tx for ED:** Oral type 5 phosphodiesterase inhibitors (PDE5i) → intraurethral alprostadil → intracavernous vasoactive drug injection → vacuum erection device (VED) → surgery (penile prosthesis)
- **Lifestyle modification:** Smoking cessation, diet, wt loss, ↑ exercise, ↓ EtOH, medication modification, psychotherapy
- **SSRI-related ED:** ↓ dose, substitute another SSRI or non-SSRI (mirtazapine, bupropion), drug holidays, Rx PDE5i (below)
- **PDE5i: 1st-line Rx;** use does not result in *spontaneous* erection; requires sexual arousal, intact neural pathways/vasculature; **no effect on libido**; similar s/e & discontinuation among PDE inhibitors; insufficient evidence to recommend specific PDE5i (*Ann Intern Med* 2009;151:650); sildenafil & vardenafil should be taken on an empty stomach & not taken more than 1×/24 h; tadalafil may be taken w/ food
  **Mechanism:** ↑ NO → cavernosal smooth muscle relaxation → ↑ blood flow/erection in response to sexual stimuli; onset ~60 mins, but as early as 20 mins; may need to ↓ dose if liver disease, meds (esp CYP-450 3A4), age > 65 y, CKD
  **Side effects:** Flushing, nasal congestion, HA, dyspepsia, hearing disturbances, back pain/myalgias (tadalafil, avanafil), ↑ QT (vardenafil), priapism, vision loss (nonarteritic anterior ischemic neuropathy) & visual disturbance (sildenafil, vardenafil)
  **Cautions/Contraindications:** Caution in pts on α-blockers (e.g., tamsulosin) or antihypertensives, or EtOH use as may worsen HoTN; concomitant use w/ organic nitrates is contraindicated (→ profound HoTN); wait 24 h (sildenafil) or 48 h (tadalafil) before administering nitrates in an emergency situation; contraindicated in pts w/ recent CV events & clinically hypotensive pts
  **PDE5i failure:** Determine if PDE inhibition was adequate; may try a

different dose or inhibitor; discuss risks/benefits of other therapies

**PDE5 Inhibitors**

| Name | Starting Dose | | Dose Range | | Duration | Notes |
|---|---|---|---|---|---|---|
| | PRN | Daily | PRN | Daily | | |
| Sildenafil | 50 mg | N/A | 25–100 mg | N/A | 6–8 h | 1, 2 |
| Vardenafil | 10 mg | N/A | 5–20 mg | N/A | 6–8 h | 1, 2, 3 |
| Tadalafil | 10 mg | 2.5 mg | 5–20 mg | 2.5–5 mg | 24–36 h | 4 |
| Avanafil | 100 mg | N/A | 50–200 mg | N/A | >6 h | 1 |

**Notes:** (1) Absorption ↓ by fatty food; (2) May have visual s/e; (3) Avoid if hx/risk of ↑ QT; (4) May cause back pain & myalgia due to PDE11 inhibition

- **Alprostadil:** Prostaglandin that relaxes smooth muscle → vasodilatation & erection; available as an intraurethral pellet (insert 5–10 min before sex, lasts 1 h), & penile injection (more effective than pellet, inject 10–20 min before sex, lasts ~1 h or more); s/e include priapism, penile pain
- **Yohimbine:** ? placebo effect; not recommended by AUA due to concerns about effectiveness & safety (dizziness, HA, nausea, flushing, tachycardia, HTN)
- **Vacuum erection device:** ↓ pressure →↑ penile blood flow (maintained by elastic band)
- **Penile prosthesis:** Include semirigid, inflatable
- **Testosterone replacement therapy:** See *"Male Hypogonadism"*; contraindicated in hx prostate/breast cancer; may be indicated in suspected hypogonadism, failure of PDE5i Rx; may be beneficial when combined w/ PDE5i; not indicated for tx of ED in setting of nl serum testosterone
- **Premature ejaculation:** Pause & squeeze technique, stop–start technique, masturbation prior to sex, desensitizing agents/topical anesthetics (lidocaine–prilocaine condoms), SSRIs (sertraline 25–50 mg PO QD, paroxetine 5–20 mg PO QD; may also be taken as needed 3–4 h prior to intercourse), clomipramine (2nd line), consideration of PDE5i; consideration of psychotherapy/sex therapy if psychogenic component suspected
- **Indications for referral:** Priapism (ED referral), failure of PDE5i, hx pelvic/perineal trauma, significant penile deformity
- **Information for patients:** AFP 2010;81:313; Ann Intern Med

2009;151:1-44

# PROSTATE CANCER

## Background (*NEJM* 2011;365:2013)

- **Clinical heterogeneity:** Highly variable natural hx from indolent disease that will never cause a clinical problem to aggressive, metastatic disease that leads to death
- **Epidemiology:** ~240,000 men diagnosed annually in US, w/ ~30,000 deaths/y (*CA Cancer J Clin* 2013;63:11); in the PSA screening era, men in the United States have a 1 in 6 lifetime risk of developing prostate CA, & a ~3% chance of dying of prostate CA; 30% of men older than 50 y & 70–90% of men ages 80–90 y have prostate cancer at autopsy (*CA Cancer J Clin* 1997;47:273)
- **Risk factors:** ↑ age, African ancestry (early onset/more aggressive disease), obesity **Possible RF:** ↑ fat, ↓ vegetable diet, vit E & zinc supplementation (*JNCI* 2003;95:1004)
  **Family hx:** 1° or 2° relative w/ prostate CA ↑ risk by ~2-fold (*Int J Cancer* 2003;107:797) BRCA1/2 carrier (↑ 1.8-fold, 4.7-fold), Lynch syndrome ( *JNCI* 1999;91:1310; 2002;94:1358)
- **Prevention:** Soy-rich diet (overall risk = 0.7) (*Int J Cancer* 2005;117:667)
  **5a-reductase inhibitors:** Not approved for prevention; trials of finasteride & dutasteride show a ↓ in overall incidence of prostate CA but a slight ↑ in high-grade prostate CA; no detectable effect on overall or prostate cancer-specific survival (*NEJM* 2011;365:97)
  **Vit:** Vit C & selenium do not ↓ the risk of prostate CA (SELECT, *JAMA* 2009;301:39; 52)
- **PSA:** Neutral serine protease that liquefies semen & is secreted by prostate & salivary epithelial cells; half-life ~2 d; best measured *prior to* DRE, which can ↑ PSA (& ∴ anxiety) slightly but w/o clinically significant effect (*Arch Intern Med* 1995;155:389); ↑ prostate size → ↑ PSA ∴ as men age, PSA ↑ w/ prostate size; ULN is controversial; in healthy ♂ > 50 y, prostate CA found on bx in 67% w/ PSA > 10 ng/mL and in 22% w/ PSA btw 2.6-9.9 ng/mL (*JAMA* 1997;277:1452; *NEJM* 1991;324:1156)

**ØPSA found w/:** 5α-reductase inhibitors (↓ PSA by ~50%, unrelated to CA risk, which Δ threshold for concern in pts undergoing PSA screening) ( *J Urol* 2005;174:877), ↑ BMI

≠ **PSA found w/:** BPH, prostatitis, perineal trauma, ejaculation, prostate cancer, urinary retention, instrumentation (i.e., foley catheter), bicycle riding

- **Presentation:** Most cases of prostate cancer detected by abnl PSA or DRE

## Screening (*NEJM* 2011;365:2013)

- **Highly controversial and evolving field:** Annual PSA screening + DRE did not result in mortality benefit in 1 RCT, although >40% of pts in the control group underwent PSA screening during the study, which may have affected results (PLCO, *JNCI* 2012;104:125), while another RCT found PSA screening (on avg every 4 y) ↓ prostate cancer-related mortality w/o effect on overall mortality compared to no PSA screening (at 11 y f/u, needed to screen 1055 men to prevent 1 death due to prostate cancer, NNT 37) (ERSPC, *NEJM* 2012;366:981); two meta-analyses of 6 RCTs of PSA screening ± DRE, including the ERSPC & PLCO trials did *not* show a prostate cancer mortality benefit (*BMJ* 2010;341:c4543; *BJU Int* 2011;107:882)
- **Appropriate candidates for screening:** Pts should have routine access to medical care, demonstrate compliance, & be available for f/u of abnl results

**Benefits of Screening**

| |
|---|
| Early detection & ? cancer-specific survival benefit, esp in pts at ↑ risk of prostate CA |
| ⊖ Results may provide reassurance |
| **Risks of Screening** |
| Low but nonzero rates of impotence, incontinence, bowel problems, infection, pain, & mortality from bx & tx of tumors that would never have caused clinical problems |
| Cost & pt anxiety |
| **Shared Decision-making** (Adapted from *Ann Intern Med* 2013;158:761; *CA Cancer J Clin* 2010;60:70) |
| (1) Inform pt prostate CA can be a serious problem that screening may detect at earlier stage |
| (2) Invite pt to participate in deciding whether or not to be screened; point out that pt may change his mind & a decision is not urgent |
| (3) Inform pt of a possible small mortality benefit seen in some trials w/ screening; discuss that evidence is mixed w/ some experts in favor & some against; review major society guidelines |
| (4) Inform pt that many prostate cancers detected by screening would never have caused problems if left undetected, & that these pts would likely have died of other causes |
| (5) Even if the PSA & DRE are nl, a pt may still have prostate cancer; if the PSA or DRE are abnl a biopsy may be necessary, & even this may not conclusively r/o cancer; the PSA may be elevated for other reasons (BPH) |
| (6) Tx of prostate cancer, even if detected early, may entail surgery or radiation, which have significant s/e |

- **PSA interpretation:** Cut-off for ULN controversial, & a value of 4 ng/mL typically used (Se 21%, Sp 91%, PPV 30%) (*CA Cancer J Clin* 2010;60:70); NPV 85% if PSA $\leq$ 4 (*NEJM* 2004;350:2239); role of PSA velocity, density, fractionation in detection of prostate CA unclear (*Cancer* 2007;109:1689)
- **Digital rectal exam:** May detect tumors in the posterior/lateral zones, however 25–35% of tumors arise in other parts of the prostate; Cancer may manifest as an induration, nodule, or asymmetry; Se 59%, Sp 94%, PPV 28%, NPV 99% (*Fam Pract* 1999;16:621); unclear whether combination of PSA + DRE results in clinical benefit

**Prostate CA Screening Guidelines** *(*Adapted from *Ann Intern Med* 2013;158:761*; NEJM* 2011;365:2013*)*

| Recommendation | USPSTF* | AUA | ACP | ACS |
|---|---|---|---|---|
| Shared decision-making | Yes (on pt request) | Yes (*J Urol* 2013;190:419) | Yes | Yes |
| Age to discuss screening | Recommends against screening | 55–69 y; discuss w/ men <55 y if high risk† | 50–69 y unless high risk† | 50 y if avg-risk, 40–45 y if high risk† |
| Stop screening | N/A | 70 y or life expectancy <10–15 y | <50 y, >69 y, life expect <10–15 y | Life expectancy <10 y |
| Screening tests | N/A | PSA | PSA + DRE | PSA ± DRE |
| Freq of screening | N/A | q2y | PSA > 2.5 q1y | PSA > 2.5 q1y<br>PSA < 2.5 q2y |
| Criteria for bx referral | N/A | Consider age, FHx, race, DRE, PSA (total, free, velocity, density), prior bx, PMHx | | PSA ≥ 4, abnl DRE<br>PSA 2.5–4, individualized risk eval |

*USPSTF recommends against routine screening (Grade D) but encourages shared decision-making if pt requests screening (*Ann Intern Med* 2012;157:120)

†African-American pts & those w/ 1st-degree relatives w/ prostate cancer diagnosed before 65 y

- **Risk calculation:** deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp; prostatecancer-riskcalculator.com
- **Indications for biopsy:** Abnl DRE, regardless of PSA; if PSA ↑ (see table), consider repeat several wks later & refer for bx if benign causes of elevated PSA r/o
- **Documentation:** Discussion of risks/benefits of screening & shared decision-making important from a medical–legal & liability standpoint, esp if pt declines screening
- **Patient information:** cancer.org/prostatemd (American Cancer Society, links to video for pts on risks/benefits of screening); www.prosdex.com/index_content.htm; uspreventiveservicestaskforce.org/prostatecancerscreening/prostateca (USPSTF); http://www.mayoclinic.com/health/prostate-cancer/HQ01273 (Mayo Clinic)

# PROSTATITIS

## BACTERIAL PROSTATITIS (*AFP* 2010;82:397; *JAMA* 1999;282:236; *NEJM* 2006;355:1690)

- **Prostatitis:** Acute or chronic (>3 mos) prostate inflammation, most commonly caused by bacteria; *E. coli* most common followed by other GNRs (*Klebsiella, Proteus, Pseudomonas*) & *Enterococcus* (*Am J Med* 1999;106:327); gonorrhea & chlamydia can also infect the prostate
  **Complications:** Bacteremia, pelvic abscess, metastatic infection, epididymitis
  **Risk factors:** Prostate biopsy, immunocompromise, anatomic abnormalities, urinary catheters
  **Ddx:** UTI, cystitis, urethritis, BPH, chronic pelvic pain syndrome, epididymitis

| | | |
|---|---|---|
| **Symptoms** | Sudden onset fevers, chills, pelvic/perineal pain, dysuria, urgency, freq, hesitancy, weak stream, cloudy urine | May be subtle or asx: urgency, freq, hesitancy, weak stream, pain w/ ejaculation; consider in pts w/ recurrent UTIs |
| **Exam (DRE)** | Swollen, warm, tender prostate | Swollen, warm, tender prostate, or normal exam |
| **Workup** | U/A, UCx, urine gram stain; avoid prostatic massage (may lead to bacteremia); ✔ gonorrhea & chlamydia | Compare midstream U/A, UCx, gram stain before & after 1 min prostate massage; confirmed by bacteria only in postmassage UCx or bacterial counts 10 × ↑ after massage; ✔ gonorrhea & chlamydia |
| **Therapy** | **Similar for acute/chronic prostatitis; Gram ⊖ organisms:** Ciprofloxacin 500 mg PO BID, levofloxacin 500 mg PO QD, or TMP-SMX DS PO BID × 4–6 wks; **Gram ⊕:** Cephalexin 500 mg PO q6h; **Chlamydia:** Doxycycline or azithromycin; adjust abx based on culture; β-lactams & nitrofurantoin have poor prostate penetration; for recurrent infections, treat w/ longer course (3 mos) of different abx | |
| **Referral indications:** Urinary retention, severe sx, suspicion for prostatic abscess (e.g. fever for >36 h after abx tx initiated) | | |

- **Patient information:** JAMA 2012;307:527

## CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME

- **Chronic pelvic pain syndrome:** Chronic pelvic pain for ≥3 of 6 mos; may be inflammatory or noninflammatory w/o infection; unclear if related to bacterial or other cryptic infection
- **Ddx:** BPH, ureteral stricture, prostatic abscess, prostate cancer, urethritis, epididymitis, orchitis, cystitis, proctitis, IBS, lumbar

radiculopathy

- **History:** Pain in abdomen, rectum, prostate, perineum, penis, and/or testicles, dysuria, hesitancy, weak stream; similar presentation to chronic bacterial prostatitis, but negative UCx & no hx UTIs; screen for sexual dysfunction, depression
- **Exam:** Prostate may/may not be tender; ✔ for hernias, testicular masses, hemorrhoids
- **Workup:** U/A, UCx; imaging guided by sx (e.g., abdominal CT, scrotal u/s)

### Treatment (*AFP* 2010;82:397; *NEJM* 2006;355:1690)

- **Empiric treatment of bacterial prostatitis:** Controversial; RCT fail to show benefit, & no clear guidelines exist, however some advocate for empiric trial of abx
- **Symptomatic treatment:** NSAIDs or celecoxib useful if pain is primary symptom
- **a-blockers ± 5a-reductase inhibitors:** Controversial ( *JAMA* 2011;305:78); RCT of alfuzosin failed to show benefit (*NEJM* 2008;359:2663); however, αB ± 5α-reductase inhibitors commonly prescribed; some use trial of at least 3 mos; for s/e, titration, & administration; may be used with or w/o abx
- **Other:** Quercetin, pregabalin, gabapentin, nortriptyline
- **Urology referral:** Persistent/severe LUTS

## SCROTAL & TESTICULAR LESIONS

### Background

- Any skin lesion (dermatitis, neoplasm, benign growth) can occur on scrotum & cause sx
- **History:** Onset, duration, severity, location, referral of pain, prior tx, exacerbating/ameliorating factors (voiding, BMs), assoc sx (fevers, chills, night sweats, wt loss), sexual hx, Ψ hx, surgical hx, trauma, STI
- **Workup:** Color duplex U/S is imaging modality of choice when dx unclear
- **Indications for referral:** Surgical emergencies (→ ED immediately)

for painful/edematous scrotum in setting of trauma (torsion, rupture, hematocele), strangulated inguinal hernia:

**Fournier gangrene:** Necrotizing fasciitis of perineum; painful/swelling/induration of penis/scrotum/perineum, cellulitis/edema, ± crepitus, fever → ED referral

**Testicular torsion:** Testis twists around spermatic cord → occlusion of blood flow

**Suspected cancer:** Intratesticular masses are presumed cancer until proven o/w; refer suspected testicular tumors urgently to urologist

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## Acute Epididymitis

- **Background:** Most common cause of scrotal pain in all age groups; usually due to infection (spread from bladder, urethra, prostate) or ischemia; testicle & epididymis often involved → epididymo-orchitis; orchitis alone rare unless viral
- **Causes:** *Infectious:* Bacterial (<35 y: Gonorrhea/chlamydia; >35 yo: *E. coli*), viral (mumps, coxsackie), granulomatous (TB); *Noninfectious:* Behçet syndrome (oral/genital ulcers, uveitis), amiodarone (pain at head of epididymis), tumor, prolonged sitting, heavy lifting

### Features of Acute Epididymitis

| | Acute Epididymitis | Testicular Torsion |
|---|---|---|
| History | Acute or gradual onset, fever present | Sudden onset, fever absent, ± N/V |
| Exam | Testicle in nl position; pain in epididymis | Testicle may be "high riding" or horizontal; pain in testicle |
| Cremaster reflex | Present | Ipsilateral reflex may be absent |
| Scrotal U/S | ↑ blood flow | ↓ blood flow |

- **Risk factors:** Sexual activity, bladder outlet obstruction, urogenital malformation
- **Exam:** Swollen/tender spermatic cord ± testicle ± urethral discharge

  **Cremaster reflex:** Contraction of ipsilateral scrotum upon stroking inner thigh → assesses genitofemoral nerve; may be absent in torsion
- **Workup:** H&P, urethral swab/culture (GC/CT if d/c present), midstream U/A, Cx

**Scrotal U/S:** Usually not necessary (recommended for orchitis, r/o tumor/torsion)

- **Treatment:** Scrotal support, analgesics (NSAIDS, ± opiates), ice, empiric abx
  **Gonorrhea/chlamydia suspected:** Ceftriaxone + azithromycin/doxycycline
  **If STI unlikely:** Levofloxacin 500 mg PO QD × 10 d then tailor based on culture results
- **Follow-up:** Pain/fever usually resolve within 3 d; induration may last wks/mos; if no improvement: Re-evaluate, repeat Cx, scrotal U/S; if STI, sexual partners within previous 60 d should be treated; abstinence until tx complete; see *"STI"*

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## CHRONIC EPIDIDYMOORCHITIS/ORCHALGIA/EPIDIDYMALGIA (*Rev Urol* 2003;5:209)

- **Definition:** Scrotal pain > 3 mos; may be intermittent, bilateral, range from mild–severe
- **Risk factors:** May be assoc w/ hx or risk of STI; poorly understood
- **Exam:** Epididymal tenderness (up to 50% will have nl exam); check external genitals, prostate, inguinal/lower abdomen, back
- **Workup:** Midstream U/A, Cx, STI testing; urethral swab/culture/GS if pain or d/c
  **Scrotal ultrasound:** Esp if indurated epididymis, or difficult exam due to pain
- **Treatment:** Typically self-limited & will eventually resolve (may take mos/y); very difficult to treat; little evidence to support tx regimens
  **Conservative mgmt:** NSAIDs, opiates (± referral to pain specialist), scrotal support, avoid painful activities, warm compresses
  **Empiric abx:** 4–6 wks; evidence lacking for effectiveness/regimen
  **Referral:** For consideration of spermatic cord block (can repeat every couple of mos if effective); surgery (epididymectomy/orchiectomy) may not ↓ pain; last resort

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## SPERMATOCELE/EPIDIDYMAL CYST

- **Definition:** Retention cyst of epididymal head; contain spermatozoa found in 30% of ♂
- **Exam:** Distinct, nontender swelling behind/above testicle, compression → pain
- **Workup:** U/S if dx in question
- **Treatment:** Typically asx → reassurance; If sx → urology referral

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## HYDROCELE

- **Definition:** Peritoneal fluid collection within tunica vaginalis; often present at birth, most resolve by 1 y; can spontaneously occur/recur
- **Risk factors:** Scrotal trauma, scrotal infection, STI
- **Exam:** Painless swelling of 1/both testicles, transilluminates
- **Workup:** U/S if doesn't fully transilluminate or if it obscures of other scrotal contents
- **Treatment:** Generally ASx, no Tx required; refer to urologist if pain/size limits activity

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## VARICOCELE

- Dilation of the pampiniform plexus; 90% on L side due to compression of the L renal vein by the aorta/SMV → ↑ pressure in the left spermatic vein → venous congestion; very common (15% of ♂); unilateral R varicocele should prompt w/u for IVC/right renal vein thrombosis or malignant obstruction (e.g., renal cell carcinoma); possible assoc w/ ↓ fertility
- **Exam:** "Bag of worms" in scrotum, ↑ size w/ standing/valsalva; may c/o dull pain/heaviness in scrotum
- **Workup:** Consider abdominal CT to evaluate for mass if right-sided or sudden onset/worsening
- **Treatment:** Generally asx; refer to urologist if painful or assoc w/ infertility

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## TESTICULAR CANCER (*AFP* 2008;77:469)

- **Pathology:** Germ cell tumors include seminomas & nonseminomas

(comprise 95%) & sex cord stromal tumors (5%)

- **Epidemiology:** Most common tumor in ♂ 15–35 y; assume tumor until proven otherwise; ~8000 cases/y in US, ~400 deaths/y (*CA Cancer J Clin* 2013;63:11)
- **Risk factors:** Abdominal/inguinal cryptorchidism, testicular dysgenesis, FHx; surgery to correct cryptorchidism ↓ CA risk & facilitates monitoring; HIV (seminomas—tx the same as in noninfected pts) ( *JCO* 2003;21:1922)
- **Screening:** USPSTF recommends *against* screening asx pts (*Ann Intern Med* 2011;154:483); Due to high cure rate, unclear whether screening by testicular self-exam or PCP exam ↓ mortality; absence of RCT showing mortality benefit (*Cochrane Database Syst Rev* 2011:CD007853); consider screening in pts w/ risk factor after shared decision-making
- **Exam:** Intratesticular mass ± pain/swelling/hardness; does not transilluminate;
  usually unilateral, R > L; bilateral likely lymphoma; ✔ for gynecomastia
- **Workup:** Color duplex U/S, urology referral ✔ tumor markers (AFP, LDH, β -hCG)

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## Other Causes of Scrotal Pain/Masses

- **Strangulated inguinal hernia:** Surgical emergency → send to ED
- **Cutaneous scrotal abscess, infection of scrotal skin:** I&D; abx rarely needed
- **Pyocele:** Infected hydrocele, 2° to scrotal/abdominal infection
- **Torsion of testicular appendix:** Usually in prepubertal boys; sudden onset pain often localized to superior testicle, cremaster reflex intact, blue dot seen at superior aspect of testicle in 40%; must r/o testicular torsion; tx: Self-limited, none needed
- **Mumps orchitis:** Fever, HA, myalgia, parotid swelling

# NOTES

# DEMENTIA

## Background

- **Definition:** Chronic, acquired decline in memory **and** ≥1 other cognitive domain that affects functioning (language, agnosia [inability to recognize objects], apraxia [inability to perform motor tasks], executive function [abstract thinking/planning/complex behavior]); sx must not be caused by another disease (e.g., depression or systemic illness); must distinguish from "nl aging," which involves mild decline in memory (e.g., ↓ ability to multitask, ↓ speed of info recall) w/o functional impairment
  **Mild cognitive impairment:** Cognitive/memory problem worse than normal aging, but not meeting dementia definition & w/ minimal (if any) impaired function (*JAMA* 2007;297:2391; 2008;300:1566; NEJM 2011;364:2227); progression to dementia ~6–25%/y
- **Epidemiology:** ~5.4 million pts in US; dementia affects 2–3% of adults at age 65 y, prevalence doubles every 5 years, reaching ~50% of pts >85 y
- **Risk factors:**
  **Definite:** Age, FHx, AF, ApoE4 (late onset AD) (*NEJM* 1995;333:1242), Down syndrome
  **Possible:** Hx delirium, head trauma, stroke, CV factors (smoking, HTN, HLD, obesity, DM), fewer years of formal education
  **Protective:** No strong data on any intervention beyond lifestyle modification; unclear evidence on intellectual/social activity, antioxidants, statins, Ω-3 fatty acids, Mediterranean diet, Ginkgo biloba (*JAMA* 2008;300:2253)

**Dementia Syndromes**

| Type | Symptoms | Treatment |
|---|---|---|
| **Alzheimer (AD)** (50–80%) (*Lancet* 2011;377:1019) | Memory deficit prominent; language, visual–spatial disturbances, indifference, neuropsych sx; parkinsonian sx = late manifestation | *Mild-mod:* Donepezil, rivastigmine, galantamine<br>*Mod–sev:* Memantine ± donepezil |
| **Vascular (VD)** (10–20%) (*Lancet Neurol* 2003;2:89) | Abrupt onset, stepwise deterioration, fluctuating course, executive dysfunction may be prominent, hx stroke, focal neuro s/sx | Galantamine (*Lancet* 2002;359:1283); risk factor modification |
| **Mixed** (50% of AD) (*JAMA* 2004;292:2901) | Abnormalities characteristic of >1 dementia occur simultaneously (most commonly AD & VD together) | Galantamine, rivastigmine; risk factor modification |
| **Lewy body** (5–10%) **(LBD)** (*AFP* 2006;73:1223) | Dementia onset around the time of parkinsonian sx (in PD dementia onset >1 y after motor sx); Hallucinations, delusions, fluctuating cognition, sleep d/o, autonomic dysfunction (falls, orthostasis) | Rivastigmine (*Lancet* 2000;356:2031) or donepezil (*Ann Neurol* 2012;72:41)<br>**Avoid** neuroleptics (i.e., haloperidol) which may be fatal |
| **Frontotemporal (FTD)** (12–25%) (*AFP* 2010;82:1372) | Personality/social/language/behavior problems prominent early sx; memory less affected; onset late 50s–early 60s | Sx-based tx, SSRIs |
| **Parkinson (see "PD")** (*Lancet Neurol* 2012;11:697) | Cognitive decline >1–2 y after onset of motor sx; executive & visual–spatial sx are prominent early | Rivastigmine (*NEJM 2004;351:2509*); quetiapine for psychotic sx |
| **Other:** EtOH, Creutzfeldt–Jakob disease, cerebral amyloid angiopathy, HIV-associated | | |
| **Reversible Causes of Cognitive Impairment** | | |
| Chronic subdural hematoma, delirium, depression, normal pressure hydrocephalus (cognitive & gait problems, urinary incontinence), hypothyroidism, malignancy, medications, infections (neurosyphilis, encephalitis, meningitis, Lyme), hypoglycemia, electrolyte imbalances, Vit $B_{12}$ or thiamine deficiency, heavy metal poisoning | | |

## Evaluation and Prognosis (*AFP* 2005;71:1745; 2011;84:895; *JAMA* 2007;297:2391)

- **Screening:** Controversial (*JAMA* 2007;298:2409); USPSTF found insufficient evidence for/against routine screening (*Ann Intern Med* 2003;138:925)
- **History:** Important to talk to family members/caregivers about difficulties (managing finances, difficulty w/ learning/memory/language, driving); timeline/progression (to distinguish from delirium); medications; r/o depression; assess pt insight on deficits
- **Exam:** Neuro exam, including gait/balance, cogwheel rigidity, tremors
  *Cognitive screening:* Mini-mental exam (score <24 87% Se, 82% Sp)

(*JAMA* 1993;269:2386); ↓ Se for PD due to prominence of executive dysfunction; Mini-Cog (memorycare.org/The%20Mini-Cog.pdf, 76% Se, 89% Sp) (*J Am Geriatr Soc* 2003;51:1451)

- **Workup:** Dx mainly clinical; CBC, Chem-12, $B1_2$, TFTs, RPR (based on suspicion)

  **Brain imaging:** Controversial; American Academy of Neurology recommends noncontrast head CT or brain MRI in all pts w/ dementia (*Neurology* 2001;56:1143)

  **Neuropsychological testing:** Identifies & attempts to quantify domain & degree of impairment (*AFP* 2010;82:495); may guide safety eval
- **Prognosis:** Highly variable (mos to >20 y); etiology- and age-based, dependent on co-morbidities; pts w/ advanced dementia in nursing homes typically die of PNA, fevers, eating problems (*NEJM* 2009;361:1529); hospice/palliative care involvement helpful (*JAMA* 2007;298:2527)

## Treatment (*AFP* 2006;73:647; 2011;83:1403; *NEJM* 2010;362:2194)

- **Supportive care:** Exercise (*JAMA* 2003;290:2015; 2008;300:1027), occupational training, caregiver training & support, EtOH abstinence/moderation; minimize pain; treat depression, which may manifest as agitation; citalopram has shown efficacy in depression in dementia (*Br J Psychiatry* 1990;157:894); sleep hygiene; monitor for medical illness (i.e., UTI, PNA) & medication toxicity; identification of situations that trigger behavioral problems; aromatherapy, music therapy, massage, pet therapy
- **Cholinesterase inhibitors (CI):** Efficacy on cognitive performance for donepezil, galantamine, or rivastigmine similar in mild-mod AD (MMSE 10–26); galantamine & donepezil beneficial in severe AD (MMSE < 10); after 8–12 wks trial of tx, reassess clinical status & continue if improvement noted; restart if clinical deterioration after discontinuation; may help w/ neuropsych sx in AD (*JAMA* 2003;289:210)

**Pharmacotherapy of Dementia**

| Drug & Dose | Side-effects/Comments |
|---|---|
| **Donepezil**<br>5 mg PO QD × 4 wks<br>→ 10 mg QD | CI; benefit in severe AD alone (*Lancet* 2006;367:1057) & w/ memantine (*NEJM* 2012;366:893) & in LBD (*Ann Neurol* 2012;72:41); well tolerated due to ↓ peripheral anticholinergic activity; transient diarrhea, nausea; rare sx bradycardia |
| **Galantamine**<br>4 mg PO BID × 4 wks, up titrate 4 mg BID qmos to 12 mg BID; ED available | CI; benefit reported in severe AD (*Lancet Neurol* 2009;8:39) & VD (*Lancet* 2002;359:1283); cognitive benefits sustained for >3 y in AD (*Arch Neurol* 2004;61:252); ↑ nausea, anorexia, wt loss compared to donepezil; take w/ food |
| **Rivastigmine**<br>1.5 mg PO BID, uptitrate q2wks to 6 mg BID; Transdermal available | CI; efficacious in PD dementia (*NEJM* 2004;351:2509), LBD (Lancet 2000;356:2031); ↑ severe nausea, anorexia compared to donepezil; HA; take w/ food; may worsen tremor in PD; significantly less GI s/e w/ transdermal patch; patch may cause rash |
| **Memantine**<br>5 mg PO QD → 5 mg BID → 5/10 → 10 BID in qwk increments | Neuroprotective NMDA antagonist; beneficial alone & in combination w/ donepezil in mod–severe AD (*JAMA* 2004;291:317; *NEJM* 2003;348:1333); s/e include dizziness, hallucinations & confusion (rare) |
| **Vitamin E**<br>1000 IU PO BID | Controversial (*Cochrane Database Syst Rev* 2008:CD002854); may ↓ clinical progression (*NEJM* 1997;336:1216; *Neurology* 2001;56:1154) |

- **Antipsychotics:** Both typical & atypical antipsychotics ↑ risk of death (*NEJM* 2005;353:2335); s/e >> benefits for tx of psychosis, agitation, & aggression for atypical antipsychotics (i.e., olanzapine, quetiapine, risperidone) (*NEJM* 2006;355:1525); no benefit in improving neuropsychiatric sx for typical antipsychotics (i.e., haloperidol) (*JAMA* 2005;293:596); shared decision-making, frank discussion of risks/benefits w/ caregivers, continuous reassessment, & documentation necessary if behavioral sx cannot be managed by other means (*JAMA* 2005;294:1963)
- **Driving:** Clinical Dementia Rating (CDR) can be useful in assessing driving safety (*Neurology* 1993;43:2412); Pts w/ a CDR ≥2 are unsafe to drive; pts w/ a CDR of 0.5–1 should be evaluated for driving ability if the following risk factors present: (1) hx motor vehicle accidents or tickets; (2) MMSE ≤ 24; (3) Caregiver concerns; (4) Aggressive/impulsive behavior; (5) Driving <60 miles/wk; (6) Situational avoidance; (7) EtOH use, medications that affect the CNS, sleep d/o, hx falls, or hearing/visual/mobility impairment (*Neurology* 2010;74:1316); pts may be referred for on-road driving assessment (*AFP* 2006;73:1029; *JAMA* 2010;303:1632); documentation that recommendations conferred to family/pt/caregiver is essential; mandatory reporting of unsafe drivers varies by state
- **Wandering:** Safe Return (alz.org/Services/SafeReturn.asp) provides

bracelets/jewelry/wallet card identification for dementia pts at ↑ risk of becoming lost

- **Money:** Durable financial power of attorney, joint accounts, living trust (*JAMA* 2011;305:698)
- **Patient information:** alz.org; theaftd.org; FTD (AFP 2010;82:1378); LBD (AFP 2006;73:1223); AD (AFP 2011;83:1415); behavioral problems (AFP 2006;73:653); caregiver support (AFP 2000;62:2621); driving w/ dementia (AFP 2006;73:1035); MCI (JAMA 2009;302:452); dementia (AFP 2010;304:1972); finances (AFP 2011;305:1610)

# END-OF-LIFE & ADVANCE CARE PLANNING

## Background *(Ann Intern Med 2010;153:256; 2012;156:ITC2-1; NEJM 2004;350:7)*

- Different cultures handle end-of-life discussions in unique ways (*AFP* 2005;71:515); PCP participation in family meetings of hospitalized pts & at the end of life assoc w/ ↑ satisfaction
- **Advanced directive:** Pt, in consultation with family/PCP, plans future medical care should he/she become incapable of making decisions
- **Health care proxy:** Pt-assigned agent who knows pt's values & makes decisions on the pt's behalf; jurisdiction includes all medical decisions, not just those pertaining to life-sustaining tx; does NOT require involvement of a lawyer or judge; ask pt "If you were sick who would make decisions for you?" (*AFP* 2012;85:461); order of surrogate decision-makers is usually spouse, adult children, parents, siblings
- **Durable power of attorney:** Legally assigned agent who may make medical, financial, & other decisions on pt's behalf; must be assigned w/ assistance of a lawyer
- **Instructional directive:** Explicit instructions for the provision of future care; most commonly used are the Living Will & DNR/DNI/do not hospitalize orders
- **Living will:** Written statement expressing whether or not (& under what conditions) pt would accept life-sustaining tx; applicable only when pt unable to speak for him/herself & is terminally ill or

permanently unconscious; applicable to tx such as dialysis, tube feedings, or life support; many states use Five Wishes Forms: http://www.agingwithdignity.org/five-wishes.php

- **MOLST/POLST:** Medical (Provider) Orders for Life-sustaining Treatment; form outlines preferences for life-sustaining tx (specifics vary by state); after form is signed, medical orders become legally binding across the state
- **Hospice:** Comprehensive medical, spiritual, social, pain, & sx mgmt for pts w/ limited life expectancy, typically <6 mos; pts may receive substantial financial benefit through coverage of nursing, meds, hospital equipment (*AFP* 2008;77:807); may be provided at home or in skilled nursing facilities; also provides bereavement support for survivors for up to 1 y; open hospice/"bridge to hospice" allows pt to receive life-prolonging tx (i.e., chemotherapy) & some add'l hospice support services (*JCO* 2001;19:2057); covered by Medicare & most private insurance/Medicaid; specific criteria for eligibility exist for different diseases (*NEJM* 2004;357:321); guidelines for prognosis available at secure.ucop.edu/agrp/docs/la_hospice.pdf; recommendations for language during discussion of hospice also available (*Ann Intern Med* 2007;146:443)
- **Palliative care:** Focuses on symptom mgmt, quality of life, goals of care regardless of prognosis in pts w/ serious illness

## Communication (*AFP* 2005;72:1263; 2008;77:167; *NEJM* 2004;350:2582)

- **General principles:** Remain optimistic/hopeful & realistic/truthful; align provider values/wishes w/ pt & family; useful phrases: "We hope for the best, & want to be prepared for the worst" (*Ann Intern Med* 2003;138:439); "I wish (stage IV lung cancer) were curable, but I've never seen it happen"; "I'll always be honest w/ you (i.e., when giving bad news)"; sincere interest in pt & family builds rapport & trust, e.g., asking a spouse/partner "how did you meet?" & thanking veterans for their service
- **Communication of prognosis:** Ask pt if they have a sense of prognosis & "how much time you might have?" When discussing survival times, concede uncertainty & provide estimates such as "many years," "several years," "many months," "several months," "many weeks," &

"days to several weeks" (see "Breaking Bad News" in *"Pt Counseling"* chapter)

- **Holding a Discussion:**
  **Assess decision-making capacity:** Ability to communicate choice, understand/retain relevant info, appreciate situation & benefits/consequences of proposed & alt interventions, manipulate info rationally & reason (*NEJM* 1988;319:1635; 2007;357:1834); *Capacity* determinations may be made by *any* treating provider & do not require legal determinations; psychiatry input may be useful if a mood d/o affects pt decision-making; *Competence* is the legal right of a pt to make decisions & must be determined by a judge
  **Introduce topic:** "Have you thought about what care you would want if seriously ill?"
  **Assess pt understanding of condition:** "So that we are on the same page, what is your understanding of your medical condition?"
  **Discuss risks & benefits of tx options**
  **Complete living will/advanced directives & document:** Sample forms by state uslwr.com/formslist.shtm
  **Encourage pt to share decision w/ family members,** who may be called on to make medical decisions; this helps relieve family guilt, esp if they one day need to withdraw care
- **Patient information:** AFP 2004;70:725; 2008;77:817; 2012;85:467; JAMA 2012;308:200; caringinfo.org (state-specific health care proxy & living will forms)

# FALL PREVENTION

## Background (*Ann Intern Med* 2012;157:197; *JAMA* 2009;302:2214)

- **Epidemiology:** 30–40% of pts >65 y fall at least once/y), & 60% of pts w/ a previous fall will fall again (*J Gerontol* 1991;46:M164); 10–15% of falls → fracture or serious injury (*Lancet* 2005;366:1885)
- **Etiology:** 80% sensorineural (↓ visual, tactile, proprioception, motor responses, weakness), 10% syncope, 10% acute illness (PNA, stroke, anemia, dehydration)
- **Risk factors:** Age, h/o hx falls, pain, EtOH
- **Chronic disease:** Parkinson's, OA, dementia, ↓ vision, weakness,

orthostatic HoTN, urinary incontinence, ↓ proprioceptive & vestibular systems

- **Meds:** Antihypertensives, sleep aids, βB, hypoglycemic agents, SSRIs, MAOIs, antipsychotics, antiarrhythmics, BZDs, diuretics
- **Environmental hazards:** Stairs, curbs, poor lighting, cluttered floors, poor footwear

## Evaluation (*J Am Geriatric Soc* 2008;56:1575; *JAMA 2007*;297:77; 2010;303:258)

- **Screening:** Ask adults >65 y if they have fallen in the past y; if positive → multifactorial fall assessment below (*J Am Geriatric Soc* 2011;59:26)
- **History:** Circumstances of fall, injury, prodrome (palpitations, dizziness, confusion, CP); "Did you hit your head?"; screen for syncope "Do you remember falling?" Presence of risk factors (above); medication review, ask if any meds changed; EtOH use; joint pain/arthritis; "How long were you on the floor before you could get up?" fear of falling; visual changes/problems; describe footwear worn
- **Exam:** Orthostatic VS, visual acuity & visual fields, focused neuro exam (esp for deficits, reflexes, muscle strength), CV exam (esp for arrhythmias, valvular disease like AS; see *"Valvular Heart Disease"*); test for neuropathy; examine gait, balance, muscle strength, feet, & footwear
  - **Get up & go test:** Rise from chair, walk 10 ft, turn around, return to chair, & sit down; pt may use assistive device; pts of normal mobility can do in <15 seconds
  - **Sit to stand test:** Pt folds arm across chest, stands, & sits as quickly as possible 5×; normal <15 seconds; predicts frequent falls (Se 55%, Sp 65%)
- **Workup:** HCT, glucose, $B1_2$, Chem-7, TFTs, 25OH-Vit D, med levels
- **Head trauma while on anticoagulant therapy:** Due to ↑ risk of ICH or SAH, imaging recommended on all anticoagulated pts w/ even mild/minor head trauma (*Lancet* 2001;357:771); some advocate for 24 h observation followed by a 2nd CT scan to detect delayed bleeds (*Ann Emerg Med* 2012;59:451)

## Management (*AFP* 2011;84:1267; *JAMA* 2013;309:1406; *NEJM* 2003;348:42)

- **General principles:** Guided by cause, (see *"Syncope," "Anemia"*); often interdisciplinary, involves PT eval (for balance, strength, gait), home safety assessment, assistive devices (walker, cane); medication mgmt (incl discontinuation of high-risk medications if possible); eval & tx of osteoporosis; grab bars in bathroom; Ophtho referral; Podiatry referral
- **Prevention:** Balance and resistance training, exercise & strength training; early mobilization (*JAMA* 2012;308:2573); nonskid, well-fitted footwear; bedside commode or urinal
- **Medic alert bracelet:** Esp if pt does not have someone to check in on them
- **Vitamin D:** Prevents fractures (*NEJM* 2012;367:40); may prevent falls by ↓ muscle atrophy; goal 25OHVit D level >30; maintenance dose in Vit D replete pts is 800 U/d (*Ann Intern Med* 2012;157:197; *Cochrane Database Syst Rev* 2009;3:CD00340) (see *"Vitamin D. Deficiency"*)
- **Warfarin:** A h/o falls is not an absolute contraindication for warfarin; shared decision-making & risk evaluation advised (*Am Heart J* 2011;161:241; *Am J Med* 2012;125:773)
- **Patient information:** JAMA 2010;303:288

# URINARY INCONTINENCE

## Background (*JAMA* 2004;291:996; 2010;303:2172; *NEJM* 2010;363:1156)

- **Definitions:** *Hesitancy:* difficulty initiating urination; *Urgency:* sudden urge to urinate
  **Functional incontinence:** Physical or cognitive inability to toilet (or reach toilet)
  **Overactive bladder:** Sx of urgency, frequency, nocturia ± urge incontinence
  **Overflow incontinence:** Incomplete bladder emptying or overdistension → dribbling
  **Stress incontinence:** Incontinence due to ↑ abdominal pressure (i.e., cough, exertion) & sphincter/pelvic floor weakness
  **Urge incontinence:** Urgency + involuntary urination due to

bladder overactivity/irritation

**Mixed incontinence:** Urge incontinence + stress incontinence; common in women

- **Epidemiology:** 15–30% of pts >65 y
- **Risk factors:** Age, cognitive impairment, obesity, ↑ parity, prostate disease/surgery, ↓ mobility
- **Pathophysiology:** Not a normal part of aging; multifactorial in the elderly: ↓ bladder sensation/contractility, ↓ cognition, ↓ mobility/dexterity, detrusor overactivity, ↑ nocturia, comorbid disease (CHF, DM), medications, ↑ postvoid residual

  **Reversible causes: DIAPERS: D**elirium, **I**nfection, urethral/vaginal **A**trophy, **P**harmaceuticals, **E**tOH/**E**xcess glucose (DM), **R**estricted mobility, **S**tool impaction
- **Consequences:** Falls, UTI, candida infections, cellulitis, pressure ulcers, sleep deprivation, isolation, depression

## Evaluation (*AFP* 2013;87:543; *JAMA 2008;299:1446)*

- **History:** Pts >65 y should be questioned about voiding habits, since many will not volunteer h/o incontinence; triggers (i.e., cough, laugh, exercise); frequency, volume, urgency, dysuria, interference w/ daily activities/sleep; Bowel & sexual function, hematuria, meds, fluid & caffeine consumption, voiding diary, access to bathrooms
- **Exam:** Mobility; pelvic exam; consider DRE for masses/prostate size/fecal impaction; check for pressure ulcers, infection; volume status
- **Workup:** U/A, consider Chem-7; UCx, HbA1c, & $B1_2$ based on clinical suspicion; Bladder U/S for sudden onset urge incontinence & urinalysis to r/o bladder pathology (diverticulum, mass, etc.)

  **Cough stress test:** Pt w/ full bladder coughs & pad over perineum checked for urine

  **Postvoid residual:** Remaining urine in bladder measured by catheter or U/S after pt attempt to urinate; **PVR >200 mL** suggests obstruction or bladder weakness

  **Urodynamic tests:** Invasive—indicated if dx unclear, empiric tx failure, surgery planned; measures speed & volume of urine flow, bladder pressure & volume, bladder volume necessary to trigger

urgency, bladder contractions

## Treatment (*AFP* 2005;71:315; 2006;74:2061; 2013;87:634; *JAMA NEJM* 2004;350:786)

- **Behavior modification: 1st-line tx;** frequent voiding while awake (q2h), relaxation, & deep breathing w/ sense of urgency, Kegels; wt loss (*NEJM* 2009;360:481), ↓ caffeine/EtOH, ↓ fluid intake, esp at night, smoking cessation; pads & protective garments; prompted voiding in pts w/ dementia; treat constipation & coughing
- **Pharmacotherapy of urge and mixed incontinence and overactive bladder:** Avoid antimuscarinics (AM) in pts w/ dementia on cholinesterase inhibitors (CI) due to ↑ functional decline w/ combination Rx (*BMJ* 2012;344:e3063); use if behavioral tx fail or symptomatic/severe disease; CI s/e include dry mouth, constipation, urinary retention which ↓ pt use

### Medical Therapy for Incontinence

| Drug & Dose Titration | Notes |
|---|---|
| **Solifenacin** (Antimuscarinic, AM) 5 mg → 10 mg QD | More effective than tolterodine in urge incontinence (*Eur Urol* 2005;48:464) |
| **Oxybutynin** (AM)<br>IR: 2.5 mg BID–TID → 20 mg/d<br>ER: 5 mg QD → 30 mg QD<br>TD: 1 patch q3d, Gel: 1 mL QD | Less anticholinergic sx w/ ER & TD compared to IR; IR & ER are generic |
| **Tolterodine** (AM)<br>IR: 1–2 mg BID, ER: 2–4 mg QD | Better tolerated than oxybutynin & equally effective; may be combined w/ tamsulosin for urge incontinence in ♂ (*JAMA* 2006;296:2319); may cause dementia-like sx/hallucinations (*NEJM* 2003;349:2274) & ↑ INR in pts on warfarin |
| **Fesoterodine** (AM)<br>4 mg QD → 8 mg QD | Useful in overactive bladder (*Urology* 2010;75:62) & more effective than tolterodine; nonhepatically metabolized, s/e constipation |
| **Trospium** (AM)<br>IR: 20 mg BID, ER: 60 mg QD | Renally cleared; ∴ fewer medication interactions & avoid in CKD; take on empty stomach; does not enter CNS |
| **Darifenacin** (AM)<br>7.5 → 15 mg QD | Useful in overactive bladder (*Int J Clin Pract* 2006;60:119); provides more "warning time" for urination |
| **Mirabegron** (β3 agonist)<br>25 mg → 50 mg QD | ↓ Freq & incontinence in OAB/urge incontinence; s/e include HTN, UTI, constipation, abdominal pain (*Int Urogynecol J* 2012;23:1345); may interact w/ metoprolol |
| **Topical estrogen**<br>0.01% 2–4 g/d × 7 d, then ↓ to 1–2 g/d × 7 d, then 1 g 3×/wk | Improves sx of incontinence in [♀], available in vaginal crm, ring, or tablets (*Cochrane Database Syst Rev* 2009;CD001405); oral estrogen ↑ incontinence |

- **Overflow incontinence:** Depends on cause & may include tamsulosin, surgery to relieve obstruction, nerve stimulation, correction of prolapse, intermittent catheterization
- **Male urge incontinence:** α-blockers (tamsulosin, terazosin, doxazosin) may be preferable to antimuscarinics due to ↓ s/e; if α-blocker ineffective, may add tolterodine
- **Treatment of stress incontinence:** Behavioral tx as above (*NEJM* 2008;358:1029); electrical/magnetic stimulation, vaginal pessaries, periurethral bulking agent injection, & perineal/bladder/ureteral slings may be used if behavioral tx ineffective; surgery contraindicated in ♀ who wish to have future children
- **Referral:** Painful incontinence, fistulas, hematuria (w/o UTI), neuro conditions, persistence despite medication & conservative measures, h/o pelvic surgery/XRT, botulinum toxin to treat overactive bladder, pelvic organ prolapse
- **Patient information:** NAFC.org; simonfoundation.org; JAMA 2003;290:426; 2010;303:2208.

# ABBREVIATIONS

| | |
|---|---|
| **1°** | primary first degree |
| **2°** | secondary |
| **2/2** | secondary to |
| **3TC** | lamivudine |
| **3V** | 3 vessel |
| **5-ASA** | 5-aminosalicylic acid |
| **5′-NT** | 5′-nucleotidase |
| **5HT** | serotonin |
| **6-MP** | 6-mercaptopurine |
| **6-TG** | 6-thioguanine |
| **A1c** | hemoglobin A1c |
| **a1AT** | a-1 antitrypsin |
| **AA** | Alcoholics Anonymous |
| **a/w** | associated with |
| **AAA** | abdominal aortic aneurysm |
| **AAD** | antiarrhythmic drug |
| **AAFP** | American Academy of Family Physicians |
| **aB** | alpha-blocker |
| **Ab** | antibody |
| **ABE** | acute bacterial endocarditis |

**ABG** arterial blood gas

**ABI** ankle-brachial index

**abnl** abnormal

**ABPA** allergic bronchopulmonary aspergillosis

**ABRS** acute bacterial rhinosinusitis

**abx** antibiotics

**A/C** air conditioning

**AC** acromioclavicular

**ACC** adrenal cortical carcinoma

**ACD** allergic contact dermatitis

**ACE** angiotensin converting enzyme

**ACEI** ACE inhibitor

**ACI** anemia of chronic inflammation

**ACL** anticardiolipin antibody

**ACLE** acute cutaneous lupus erythematous

**ACLS** advanced cardiac life support

**ACOG** American College of Obstetrics and Gynecology

**ACP** American College of Physicians

**ACR** American College of Radiologists

American College of Rheumatologists

**ACS** acute coronary syndrome

American Cancer Society

**ACT** acceptance and commitment therapy

**ACTH** adrenocorticotrophic hormone

**ACV** acyclovir

**AD** atopic dermatitis

Alzehimer's disease

**ADA** adenosine deaminase American Diabetes Association

**adenoCA** adenocarcinoma

**ADH** antidiuretic hormone

**ADHD** attention deficit hyperactivity disorder

**ADL** activities of daily living

**AED** antiepileptic drug

**AF** atrial fibrillation

**AFB** acid-fast bacilli

**AFL** atrial flutter

**AFP** α-fetoprotein

**AFTP** ascites fluid total protein

**AG** anion gap

**Ag** antigen

**AGC** atypical glandular cells

**AGN** acute glomerulonephritis

**AHA** American Heart Association

**AHI** apnea-hypopnea index

**AI** aortic insufficiency

**AICD** automatic implantable cardioverter defibrillator

**AIDS** acquired immunodeficiency syndrome

**AIHA** autoimmune hemolytic anemia

**AIN** acute interstitial nephritis

**AIP** acute interstitial pneumonia

**AK** actinic keratosis

**alb** albumin

**AKI** acute kidney injury

**ALF** acute liver failure

**ALL** acute lymphoblastic leukemia

**ALS** amyotrophic lateral sclerosis

**alt** alternative

**ALT** alanine aminotransferase

**AM** anti-muscarinic

**AMA** anti-mitochondrial antibody

**AMH** asymptomatic microscopic hematuria

**AMI** anterior myocardial infarction

**AML** acute myelogenous leukemia

**AMS** altered mental status

**ANA** antinuclear antibody

**ANC** absolute neutrophil count

**ANCA** antineutrophilic cytoplasmic antibody

**angio** angiogram

**AoV** aortic valve

**AOE** average onset

**AOM** acute otitis media

**AP** anterior-posterior antipsychotic

**APAP** acetaminophen

**APC** activated protein C

**APL** acute promyeloctic leukemia

**APLA** antiphospholipid antibody

**APLS** antiphospholipid antibody syndrome

**AR** allergic rhinitis

**ARB** angiotensin receptor blocker

**ARDS** acute respiratory distress syndrome

**ARED** age-related eye disease

**ARS** acute retroviral syndrome (HIV)

**ARV** antiretroviral

**ARVC** arrhythmogenic right ventricular

**ARVD** arrhythmogenic RV dysplasia

**AS** aortic stenosis

**ASA** aspirin

**ASC** atypical squamous cells

**ASCCP** American Society for Colposcopy and Cervical Pathology

**ASC-US** atypical squamous cells of unknown significance

**ASD** atrial septal defect

**ASIS** anterior superior iliac spine

**ASO** anti-streptolysin O

**AST** aspartate aminotransferase average survival time

**ASTHM** American Society of Tropical Medicine and Hygeine

**asx** asymptomatic

**AT** atrial tachycardia

**ATII** angiotensin II

**ATIII** antithrombin III

**ATN** acute tubular necrosis

**ATRA** all-*trans*-retinoic acid

**ATZ** atazanavir

**AUA** American Urological Association

**AUB** abnormal uterine bleeding

**AV** atrioventricular

**AVA** aortic valve area

**AVB** atrioventricular block

**avg** average

**AVM** arteriovenous malformation

**AVNRT** AV nodal reentrant tachycardia

**AVR** aortic valve replacement

**AVRT** AV reciprocating tachycardia

**AZA** azathioprine

**AZT** zidovudine

**Aφ** alkaline phosphatase

**b/c** because

**b/l** bilateral

**BAL** bronchoalveolar lavage

**bB** beta-blocker

**BBB** bundle branch block

**BCC** basal cell carcinoma

**BCx** blood culture

**BD** bile duct

**BG** blood glucose

**bili** bilirubin

**BiPAP** bilevel positive airway pressure

**BiV** biventricular

**BM** bone marrow bowel movement

**BMD** bone mineral density

**BMI** body mass index

**BMP** basic metabolic panel (Chem-7)

**BMS** bare metal stent

**BNP** B-type natriuretic peptide

**BOOP** bronchiolitis obliterans with organizing pneumonia

**BP** blood pressure

**BPH** benign prostatic hypertrophy

**BPO** benign prostatic obstruction

**BPPV** benign paroxysmal positional vertigo

**BRBPR** bright red blood per rectum

**B-sx** B-symptoms

**BSA** body surface area

**BT** bleeding time

**BUN** blood urea nitrogen

**BV** bacterial vaginosis

**bx** biopsy

**BZD** benzodiazepines

**C/A/P** chest/abdomen/pelvis

**c/w** compared with consistent with

**c/o** complains of

**CA** cancer

**CAA** cerebral amyloid angiopathy

**CABG** coronary artery bypass grafting

**CAD** coronary artery disease

**CAH** congenital andrenal hyperplasia

**cal** calorie

**CALLA** common ALL antigen

**CAM** complimentary and alternative medicine

**CAP** community-acquired pneumonia

**CAPD** chronic ambulatory peritoneal dialysis

**CAS** carotid artery stenting

**CaSR** calcium-sensing receptor

**CAT** COPD assessment test

**CB** conjugated bilirubin

**CBC** complete blood count

**CBD** common bile duct

**CBE** clinical breast exam

**CBT** cognitive behavioral therapy

**CCB** calcium channel blocker

**CCP** cyclic citrullinated peptide

**CCS** Canadian Cardiovascular Society

**CCY** cholecystectomy

**CD** Crohn's disease

**CDC** Centers for Disease Control and Prevention

**CDE** certified diabetes educator

**CDR** clinical dementia rating

**CEA** carcinoembryonic antigen carotid endarterectomy

**ceph** cephalosporin(s)

**CF** cystic fibrosis

**Cftx** ceftriaxone

**CFTR** cystic fibrosis transmembrane conductance regulator

**CFU** colony forming units

**cGMP** cyclic guanosine monophosphate

**CHB** complete heart block

**CHD** congenital heart disease

**CHL** conductive hearing loss

**CHF** congestive heart failure

**CHO** carbohydrate

**CI** cardiac index cholinesterase inhibitor

**CIAKI** contrast-induced acute kidney injury

**CIDP** chronic inflammatory demyelinating polyneuropathy

**CIN** cervical intraepithelial neoplasia

**CK** creatine kinase

**CKD** chronic kidney disease

**CLL** chronic lymphocytic leukemia

**CMC** carpalmetacarpal (joint)

**CML** chronic myelogenous leukemia

**CMML** chronic myelomonocytic leukemia

**CMP** cardiomyopathy

**CMV** cytomegalovirus

**CN** cranial nerve

**CNB** core needle biopsy

**CNS** central nervous system

**CO** carbon monoxide cardiac output

**COP** cryptogenic organizing pneumonia

**COPD** chronic obstructive pulmonary disease

**COX** cyclooxygenase

**CP** chest pain chronic pancreatitis

**CPA** cerebellopontine angle

**CPAP** continuous positive airway pressure

**CPD** calcium pyrophosphate deposition disease

**CPK** creatine phosphokinase

**CPPD** calcium pyrophosphate dihydrate

**Cr** creatinine

**CRC** colorectal cancer

**CrCl** creatinine clearance

**CREST** calcinosis, Raynaud's phenomenom, esophageal dysmotility, sclerodactyly, telangiectasias

**CRH** cortisol-releasing hormone

**crm** cream

**CRP** C-reactive protein

**CRS** chronic rhinosinusitis

**CRT** cardiac resynchronization therapy

**CsA** cyclosporine A

**CSF** cerebrospinal fluid

**CSM** carotid sinus massage

**CT** chlamydia trachomatis computed tomography

**CTA** CT angiogram

**CTD** connective tissue disease

**CTS** carpal tunnel syndrome

**CV** cardiovascular

**CVA** costoverterbral angle

**CVAT** costoverterbral angle tenderness

**CVD** cardiovascular disease collagen vascular disease

**CVID** common variable immunodeficiency

**CVP** central venous pressure

**CVVH** continuous veno-venous hemofiltration

**CW** chest wall

**cx** culture

**CXR** chest radiograph

**CyA** cyclosporine

**d** day

**d/c** discharge discontinue

**D&C** dilatation and curettage

**ΔMS** change in mental status

**DA** dopamine

**DAD** diffuse alveolar damage

**DAH** diffuse alveolar hemorrhage

**DAT** direct antiglobulin test

**DB** direct bilirubin

**DBP** diastolic blood pressure

**DBS** deep brain stimulation

**DCCV** direct current cardioversion

**DCIS** ductal carcinoma *in situ*

**DCMP** dilated cardiomyopathy

**dDAVP** desmopressin

**Ddx** differential diagnosis

**DES** drug-eluting stent diethylstilbestrol

**derm** dermatologic

**DFA** direct fluorescent antigen detection

**DFI** diabetic foot infection

**DGI** disseminated gonoccal infection

**DGP** deamidategliandinpeptide

**DHEA** dehydroepiandrosterone

**DHT** dihydrotestosterone

**DI** diabetes insipidus

**DIC** disseminated intravascular coagulation

**diff.** differential

**DIP** desquamative interstitial pneumonitis distal interphalangeal (joint)

**DJD** degenerative joint disease

**DKA** diabetic ketoacidosis

**$DL_{CO}$** diffusion capacity of the lung

**DLE** discoid lupus erythematosus drug-induced lupus

**DM** dermatomyositis diabetes mellitus

**DM1** Type 1 diabetes mellitus

**DM2** type 2 diabetes mellitus

**DMARD** disease-modifying anti-rheumatic drug

**DMPA** depot medroxyprogesterone acetate

**DMV** department of motor vehicles

**DNR/DNI** do not resuscitate, do not intubate

**d/o** disorder

**DOE** dyspnea on exertion

**DOT** directly-observed therapy

**DPI** dry powder inhaler

**DPP** dipeptidyl peptidase

**DRE** digital rectal exam

**DRESS** drug reaction with eosinophilia and systemic symptoms

**DRSP** drug-resistant *S. Pneumoniae*

**DRV** darunavir

**DS** double strength

**DSE** dobutamine stress echo

**DST** dexamethasone suppression test

**DTR** deep tendon reflex

**DU** duodenal ulcer

**DUB** dysfunctional uterine bleeding

**DVT** deep vein thrombosis

**dx** diagnosis

**DXA** dual-energy X-ray absorptiometry (DEXA)

**EAD** extreme axis deviation

**EAV** effective arterial volume

**EBL** endoscopic band ligation

**EBV** Epstein-Barr virus

**EC** emergency contraception

**ECG** electrocardiogram

**echo** echocardiogram

**e.g.** *exempli gratia*, for example

**ECMO** extracorporeal membrane oxygenation

**ECT** electroconvulsive therapy

**ED** emergency department erectile dysfunction

**ED&C** electrodessication and curettage

**EDP** end-diastolic pressure

**EDV** end-diastolic volume

**EE** ethinyl estradiol

**EEG** electroencephalogram

**EF** ejection fraction

**EFV** efavirenz

**EGD** esophagogastroduodenoscopy

**EGFR** epidermal growth factor receptor

**EHEC** enterohemorrhagic E coli

**EI** entry inhibitor

**EIA** enzyme-linked immunoassay

**EIB** exercise-induced bronchospasm

**EIC** epidermal inclusion cyst

**ELISA** enzyme-linked immunosorbent assay

**EM** erythema migrans

**EMA** endomysial antibody

**EMB** ethambutol

**EMG** electromyelography

**ENA** extractable nuclear antigen

**ENF** enfuvirtide

**ENT** ears, nose, & throat

**e/o** evidence of

**EOM** extraocular movement

**EP** electrophysiology

**Epo** erythropoietin

**EPS** electrophysiology study

**ER** extended release

**ERCP** endoscopic retrograde cholangiopancreatography

**ERV** expiratory reserve volume

**ESA** erythropoiesis stimulating agent

**ESL** English as a second language

**ESLD** end-stage liver disease

**ESR** erythrocyte sedimentation rate

**ESRD** end-stage renal disease

**est** estimated

**ESV** end-systolic volume

**ET** essential thrombocythemia

**ETEC** enterotoxigenic e.coli

**EtOH** alcohol

**ETR** etravirine

**ETT** exercise tolerance test

**EUS** endoscopic ultrasound

**eval** evaluation

**FB** foreign body

**FBG** fasting blood glucose

**f/c** fevers/chills

**FDA** Food and Drug Administration

**FDP** fibrin degradation product

**Fe** iron

**FEV1** forced expiratory volume in 1 second

**FFP** fresh frozen plasma

**FHH** familial hypocalciuric hypercalcemia

**FHx** family history

**FI** fusion inhibitor

**FMD** fibromuscular dysplasia

**FMF** familial Mediterranean fever

**FMP** final menstrual period

**FNA** fine needle aspiration

**FOB** fecal occult blood

**FOBT** fecal occult blood testing

**FPG** fasting plasma glucose

**FPV** fosamprenavir

**FQ** fluoroquinolone

**FRC** functional residual capacity

**freq** frequency

**FSGS** focal segmental glomerulosclerosis

**FSH** follicle stimulating hormone

**fT4** free T4

**FTA-ABS** fluorescent treponemal Ab absorption

**FTC** emtricitabine

**FTD** Frontotemporal dementia

**FTI** free thyroxine index

**FTT** failure to thrive

**f/u** follow-up

**FUO** fever of unknown origin

**FVC** forced vital capacity

**G6PD** glucose-6-phosphate dehydrogenase

**GAD** glutamic acid decarboxylase

**GAS** group A strep

**GAVE** gastric antral vascular ectasia

**GB** gallbladder

**GBM** glomerular basement membrane

**GBS** Guillain-Barré syndrome group B strep

**GC** gonococcus (*N. gonorrhoeae*)

**GCA** giant cell arteritis

**GC/CT** gonorrhea/chlamydia

**G-CSF** granulocyte colony stimulating factor

**GCS** Glasgow coma scale

**GDM** gestational diabetes mellitus

**GE** gastroesophageal

**gen** generation

**GERD** gastroesophageal reflux disease

**GFD** gluten-free diet

**GFR** glomerular filtration rate

**GGT** γ-glutamyl transpeptidase

**GH** growth hormone

**GI** gastrointestinal

**GIB** gastrointestinal bleed

**GIST** gastrointestinal stromal tumor

**GLP-1** glucagon-like peptide-1

**glu** glucose

**GN** glomerulonephritis

**GNR** gram negative rods

**GnRH** gonadotropin releasing hormone

**GpA** granulomatous with polyangiitis (formerly Wegener's)

**GPC** gram positive cocci

**GPI** glycoprotein IIb/IIIa inhibitor

**GRA** glucocorticoid-remediable aldosteronism

**GTC** generalized tonic-clonic (seizure)

**GTT** glucose tolerance test

**GU** genitourinary gastric ulcer

**GVHD** graft-versus-host disease

**h** hour(s)

**H2RA** $H_2$-receptor antagonist

**h/o** history of

**HA** headache

**HAART** highly active antiretroviral therapy

**HAV** hepatitis A virus

**Hb** hemoglobin

**HBIG** hepatitis B immune globulin

**HBV** hepatitis B virus

**HCAP** healthcare-associated pneumonia

**HCC** hepatocellular carcinoma

**HCMP** hypertrophic cardiomyopathy

**Hct** hematocrit

**HCTZ** hydrochlorothiazide

**HCV** hepatitis C virus

**HD** hemodialysis

**HDL** high-density lipoprotein

**HDV** hepatitis D virus

**HEENT** Head, ear, eyes, nose, throat

**HELLP** hemolysis, abnormal LFTs, low platelets

**HEV** hepatitis E virus

**HF** heart failure

**HFpEF** heart failure with preserved ejection fraction

**HGPRT** hypoxanthine-guanine phosphoribosyl transferase

**HHS** hyperosmolar hyperglycemic state

**HHT** hereditary hemorrhagic telangiectasia

**HHV8** human herpes virus 8

**HINTS** head impulse nystagmus test of skew

**HIT** heparin-induced thrombocytopenia

**HIVAN** HIV-associated nephropathy

**HL** Hodgkin lymphoma

**HLD** hyperlipidemia

**HM** hand motion

**HOCM** hypertrophic obstructive cardiomyopathy

**HoTN** hypotension

**hpf** high power field

**HPG** hypothalamic-pituitary-gonadal axis

**HPI** history of the present illness

**HPT** hyperparathyroidism

**HPV** human papilloma virus

**HR** heart rate

**HRIg** human rabies Ig

**HRS** hepatorenal syndrome

**HRT** hormone replacement therapy

**HS** hereditary spherocytosis

**HSCT** hematopoietic stem cell transplantation

**HSIL** high-grade squamous intraepithelial lesion

**HSM** hepatosplenomegaly

**HSP** Henoch-Schönlein purpura

**HST** home-based sleep study

**HSV** herpes simplex virus

**ht** height

**HTLV** human T-lymphotropic virus

**HTN** hypertension

**HUS** hemolytic uremic syndrome

**HVSG** hepatic vein slope gradient

**hx** history

**I&D** incision & drainage

**IBD** inflammatory bowel disease

**IC** inspiratory capacity

**iCa** ionized calcium

**ICA** internal carotid artery islet cell antibody

**ICD** implantable cardiac defibrillator irritant contact dermatitis

**ICH** intracranial hemorrhage

**ICP** intracranial pressure

**ICS** inhaled corticosteroid

**ICU** intensive care unit

**IDDM** insulin-dependent diabetes mellitus

**IDSA** Infectious Diseases Society of America

**IDV** indinavir

**IE** infective endocarditis

**IF** intrinsic factor

**Ig, IG** immunoglobulin

**IGF** insulin-like growth factor

**IGRA** interferon-γ release assay

**IFN** interferon

**II** integrase inhibitor

**IIP** idiopathic interstitial pneumonia

**ILD** interstitial lung disease

**ILI** influenza-like illness

**IM** intramuscular

**IMI** inferior myocardial infarction

**incl** including

**infxn** infection

**inh** inhaled

**INH** isoniazid

**INR** international normalized ratio

**IOM** Institute of Medicine (US)

**IOP** intraocular pressure

**IPF** idiopathic pulmonary fibrosis

**IPMN** intraductal papillary mucinous neoplasm

**IPSS** international prostate symptom score

**IPV** intimate partner violence

**IR** immediate release

**IS** in situ

**ITP** idiopathic thrombocytopenic purpura

**IUD** intrauterine device

**IVB** intravenous bolus

**IVC** inferior vena cava

**IVDU** intravenous drug use(r)

**IVF** intravenous fluids

**IVIg** intravenous immunoglobulin

**JVD** jugular venous distention

**JVP** jugular venous pulse

**KOH** potassium hydroxide

**KS** Kaposi's sarcoma

**KUB** kidneys ureters & bladder (radiograph)

**LA** left atrium long-acting lupus anticoagulant

**LAA** left atrial appendage

**LABA** long-acting $\beta_2$-agonist

**LAD** left anterior descending coronary artery left axis deviation lymphadenopathy

**LAE** left atrial enlargement

**LAN** lymphadenopathy

**LAP** leukocyte alkaline phosphatase

**LAP** left atrial pressure

**LBBB** left bundle branch block

**LBD** Lewy body dementia

**LBP** low back pain

**LBW** low body weight

**LCA** left coronary artery

**LCIS** lobular carcinoma *in situ*

**LCL** lateral collateral ligament

**LCx** left circumflex coronary artery

**LDH** lactate dehydrogenase

**LDL** low-density lipoprotein

**LE** lower extremity

**LES** lower esophageal sphincter

**LFTs** liver function tests

**LGIB** lower gastrointestinal bleed

**LH** luteinizing hormone

**LL** lower lobe

**LLQ** left lower quadrant

**LM** left main coronary artery

**LMN** lower motor neuron

**LMP** last menstrual period

**LMWH** low-molecular-weight heparin

**LN** lymph node

**LOC** loss of consciousness

**LOS** length of stay

**LP** lumbar puncture light perception

**LpA** lipoprotein A

**lpf** low power field

**LR** lactated Ringer's likelihood ratio

**LQTS** long QT syndrome

**LSIL** low-grade squamous intraepithelial lesion

**LTBI** latent tuberculosis infection

**LTRA** leukotriene receptor antagonist

**LUSB** left upper sternal border

**LV** left ventricle

**LVAD** LV assist device

**LVEDP** LV end-diastolic pressure

**LVEDV** LV end-diastolic volume

**LVEF** left ventricular ejection fraction

**LVH** left ventricular hypertrophy

**LVOT** left ventricular outflow tract

**LVP** large volume paracentesis

**LVSD** LV systolic dimension

**MAC** mitral annular calcification *Mycobacterium avium* complex

**MAHA** microangiopathic hemolytic anemia

**MALT** mucosa-associated lymphoid tissue

**MAO(I)** monoamine oxidase inhibitor

**MAP** mean arterial pressure

**MAT** multifocal atrial tachycardia

**MBL** monoclonal B-cell lymphocytosis

**MBS** modified barium swallow

**MCC** Merkel cell carcinoma

**MCD** minimal change disease

**MCI** mild cognitive impairment

**MCL** medial collateral ligament

**MCP** metacarpal phalangeal (joint)

**MCTD** mixed connective tissue disease

**MCV** mean corpuscular volume

**MDD** major depressive disorder

**MDI** metered dose inhaler

**MDMA** 3,4-methylenedioxymeth-amphet-amine (Ecstasy)

**MDR** multidrug resistant

**MDS** myelodysplastic syndrome

**MELD** model for end-stage liver disease

**MEN** multiple endocrine neoplasia

**MET** metabolic equivalent

**MG** myasthenia gravis

**mgmt** management

**MGUS** monoclonal gammopathy of uncertain significance

**MI** myocardial infarction

**MIBI** sestamibi

**MIC** minimum inhibitory concentration

**min** minute

**min.** minimal

**MLF** medial longitudinal fasciculus

**MM** multiple myeloma

**MMA** methylmalonic acid

**MMEFR** maximal mid-expiratory flow rate

**MMF** mycophenolate mofetil

**MMR** measles mumps rubella

**MMSE** mini-mental status exam

**MN** membranous nephropathy

**MNZ** metronidazole

**mod** moderate

**MODS** multiple organ dysfunction syndrome

**MODY** mature onset diabetes mellitus of the young

**MOLST** medical orders for life-sustaining treatment

**mos** months

**MPA** medroxyprogesterone acetate

**MPN** myeloproliferative neoplasm

**MPGN** membranoproliferative glomerulonephritis

**MPTP** methylphenyl tetrahydropyridine

**MR** magnetic resonance mitral regurgitation

**MRA** magnetic resonance angiography

**MRCP** magnetic resonance cholangiopancreatography

**MRI** magnetic resonance imaging

**MRSA** methicillin-resistant *S. aureus*

**MRV** magnetic resonance venography

**MS** mental status mitral stenosis multiple sclerosis

**MSK** musculoskeletal

**MSM** men who have sex with men

**MSSA** methicillin-sensitive *S. Aureus*

**MSU** monosodium urate

**MTb** *Mycobacterium tuberculosis*

**MTP** metatarsal phalangeal (joint)

**MTX** methotrexate

**MV** mitral valve

**MVA** mitral valve area

**MVC** motor vehicle crash maraviroc

**MVP** mitral valve prolapse

**MVR** mitral valve replacement

**Mf** macrophage

**Na** sodium

**NAAT** nucleic acid amplification testing

**NLP** no light perception

**N/V** nausea and/or vomiting

**N/V/D** nausea/vomiting/diarrhea

**NAC** N-acetylcysteine

**NADPH** nicotinamide adenine dinucleotide phosphate

**NAFLD** non-alcoholic fatty liver disease

**NAMCS** National Ambulatory Medical Care Survey

**NASH** non-alcoholic steatohepatitis

**NBTE** nonbacterial thrombotic endocarditis

**NCHS** National Center for Health Statistics

**NCI** National Cancer Institute

**NCS** nerve conduction studies

**NE** norepinephrine

**NFV** nelfinavir

**NG** nasogastric

**NGT** nasogastric tube

| | |
|---|---|
| **NH3** | ammonia |
| **NHL** | Non-Hodgkin's lymphoma |
| **NIDDM** | non-insulin dependent diabetes mellitus |
| **NIF** | negative inspiratory force |
| **NIHL** | noise-induced hearing loss |
| **NIPPV** | noninvasive positive pressure ventilation |
| **NJ** | nasojejunal |
| **nl** | normal |
| **NM** | neuromuscular |
| **NMDA** | N-methyl D-aspartate |
| **NMJ** | neuromuscular junction |
| **NNH** | number needed to harm |
| **NNRTI** | non-nucleoside reverse transcriptase inhibitor |
| **NNS** | number needed to screen |
| **NNT** | number needed to treat |
| **NSTI** | necrotizing soft tissue infections |
| **NTC** | normal transit constipation |
| **NO** | nitric oxide |
| **NOS** | not otherwise specified |
| **NPJT** | non-paroxysmal junctional tachycardia |
| **NPO** | nothing by mouth |
| **NPV** | negative predictive value |

**NRT** nicotine replacement therapy

**NRTI** nucleoside reverse transcriptase inhibitor

**NS** normal saline

**NSAID** nonsteroidal anti-inflammatory drug

**NSCLC** non-small cell lung cancer

**NSF** nephrogenic systemic fibrosis

**NSIP** non-specific interstitial pneumonia

**NSTEMI** non-ST elevation myocardial infarction

**NSTI** necrotizing soft tissue infection

**NTC** normal transit constipation

**NTD** neural tube defect

**NTG** nitroglycerin

**NUD** non-ulcer dyspepsia

**NVE** native valve endocarditis

**NVP** nevirapine

**NYHA** New York Heart Association

**O/D** overdose

**o/w** otherwise

**O + P** ova and parasites

**OA** osteoarthritis

**OAB** overactive bladder

**OCD** obsessive compulsive disorder

**OCP** oral contraceptive pill

**OD** overdose

**OG** osmolal gap

**OGT** orogastric tube

**OGTT** oral glucose tolerance test

**OHS** obesity hypoventilation syndrome

**OI** opportunistic infection

**OM** obtuse marginal coronary artery

**OME** otitis media with effusion

**OMFS** oral and maxillofacial surgery

**ONJ** osteonecrosis of the jaw

**OP** oropharynx

**OR** odds ratio operating room

**OSA** obstructive sleep apnea

**OTC** over-the-counter

**p/w** present(s) with

**para** paracentesis

**PA** pulmonary artery

**PAC** premature atrial contraction pulmonary artery catheter

**PAD** peripheral arterial disease

**PAN** polyarteritis nodosa

**PAPA** pyogenic arthritis, pyoderma gangrenosum, acne syndrome

**PASP** pulmonary artery systolic pressure

**PAV** percutaneous aortic valvuloplasty

**pb** problem

**PBC** primary biliary cirrhosis

**PCI** percutaneous coronary intervention

**PCKD** polycystic kidney disease

**PCL** posterior cruciate ligament

**PCN** penicillin

**PCOS** polycystic ovary syndrome

**PCP** primary care provider *Pneumocystis* pneumonia

**PCR** polymerase chain reaction

**PCT** porphyria cutanea tarda proximal convoluted tubule

**PCV** polycythemia vera

**PCWP** pulmonary capillary wedge pressure

**PD** Parkinson's disease peritoneal dialysis

**PDA** patent ductus arteriosus posterior descending coronary artery

**PDGF (R)** platelet-derived growth factor (receptor)

**PE** pulmonary embolism physical exam

**PEA** pulseless electrical activity

**PEEP** positive end-expiratory pressure

**PEF** peak expiratory flow

**PEG** polyethylene glycol

**PEP** post-exposure ppx

**PET** positron emission tomography

**PFO** patent foramen ovale

**PFT** pulmonary function test

**PGA** polyglandular autoimmune syndrome

**pheo** pheochromocytoma

**pHTN** pulmonary hypertension

**PI** protease inhibitor

**PID** pelvic inflammatory disease

**PIF** prolactin inhibitory factor

**PIP** peak inspiratory pressure proximal interphalangeal (joint)

**PKD** polycystic kidney disease

**PLT** platelets

**PM** polymyositis

**PMF** primary myelofibrosis

**PMHx** past medical history

**PMI** point of maximal impulse

**PML** progressive multifocal leukoencephalopathy

**PMN** polymorphonuclear leukocyte

**PMR** polymyalgia rheumatica

**PMS** premenstrual syndrome

**PMV** percutaneous mitral valvuloplasty

**PMVT** polymorphic ventricular tachycardia

**PNA** pneumonia

**PND** paroxysmal nocturnal dyspnea

**PNH** paroxysmal nocturnal hemoglobinuria

**PNS** peripheral nervous system

**PO** oral intake

**POBA** plain old balloon angioplasty

**POF** premature ovarian failure

**POI** primary ovarian insufficiency (aka premature ovarian failure)

**POLST** provider order for life-sustaining treatment

**pop** population

**POTS** postural orthostatic tachycardia syndrome

**PPD** purified protein derivative

**PPH** primary pulmonary hypertension

**PPI** proton pump inhibitors

**PPM** permanent pacemaker

**PPV** positive predictive value

**Ppx** prophylaxis

**PR** PR segment on ECG pulmonary regurgitation

**PRBCs** packed red blood cells

**PrEP** pre-exposure prophylaxis

**PRL** prolactin

**PRPP** phosphoribosyl-1- pyrophosphate

**PRWP** poor R wave progression

**PS** pulmonic stenosis

**PsA** psoriatic arthritis

**PSA** prostate specific antigen

**PSC** primary sclerosing cholangitis

**PSG** polysomnography

**PSGN** post streptococcal glomerulonephritis

**PSHx** past surgical history

**PsA** psoriatic arthritis

**PSV** pressure support ventilation

**psych** psychiatric

**Pt** patient

**pts** patients points

**PT** prothrombin time physical therapy

**PTA** percutaneous transluminal angioplasty

**PTH** parathyroid hormone

**PTH-rP** parathyroid hormone-related peptide

**PTSD** post-traumatic stress disorder

**PTT** partial thromboplastin time

**PTU** propylthiouracil

**PTX** pneumothorax

**PUD** peptic ulcer disease

**pulm** pulmonary

**PUVA** psoralen + ultraviolet A

**PV** portal vein polycythemia vera

**PVC** premature ventricular contraction

**PVD** peripheral vascular disease posterior vitrous detachment

**PVE** prosthetic valve endocarditis

**PVR** post-void residual pulmonary vascular resistance

**PZA** pyrazinamide

Ψ psychiatric

**qac** before every meal

**qhs** every bedtime

**QoL** quality of life

**Qw** Q wave

**r/i** rule in

**r/o** rule out

**RA** refractory anemia rheumatoid arthritis right atrium

**RAA** right atrial abnormality

**RAD** right axis deviation

**RAE** right atrial enlargement

**RAI** radioactive iodine

**RAIU** radioactive iodine uptake

**RAL** raltegravir

**RAPD** rapid afferent pupillary defect

**RARS** refractory anemia with ringed sideroblasts

**RAS** renal artery stenosis

**RAST** radioallergosorbent test

**RBBB** right bundle branch block

**RBC** red blood cell

**RBF** renal blood flow

**RC** rotator cuff

**RCA** right coronary artery

**RCC** renal cell carcinoma

**RCMP** restrictive cardiomyopathy

**RCRI** revised cardiac risk index

**RCT** randomized controlled trial

**RD** retinal detachment

**RDW** red cell distribution width

**RHF** right heart failure

**RE** reticuloendothelial

**REM** rapid eye movement

**RES** reticuloendothelial system

**RF** rheumatoid factor risk factor

**RFA** radiofrequency ablation

**RFB** rifabutin

**RHC** right heart catheterization

**RHD** rheumatic heart disease

**RI** reticulocyte index

**RIBA** recombinant immunoblot assay

**RIF** rifampin

**rMPI** radionucleoside myocardial perfusion imaging

**RMSF** Rocky Mountain spotted fever

**ROM** range of motion

**ROMI** rule out myocardial infarction

**ROS** review of systems

**RP** retroperitoneal

**RPGN** rapidly progressive glomerulonephritis

**RPV** rilpivirine

**RR** relative risk respiratory rate

**RRT** renal replacement therapy

**RTA** renal tubular acidosis

**RTV** ritonavir

**RUQ** right upper quadrant

**RUSB** right upper sternal border

**RV** residual volume right ventricle

**RVAD** RV assist device

**RVH** right ventricular hypertrophy

**RVOT** RV outflow tract

**RVSP** RV systolic pressure

**Rx** therapy, prescription

**Rxn** reaction

**s/e** side effect

**s/p** status post

**s/sx** signs and symptoms

**SA** sinoatrial short-acting

**SABA** short-acting $\beta_2$-agonist

**SAAG** serum-ascites albumin gradient

**SAH** subarachnoid hemorrhage

**SAPHO** synovitis, acne, pustulosis, hyperostosis, osteitis syndrome

**SARS** severe acute respiratory syndrome

**SBE** subacute bacterial endocarditis self breast exam

**SBP** spontaneous bacterial peritonitis systolic blood pressure

**SBT** spontaneous breathing trial

**SBO** small bowel obstruction

**SC** subcutaneous

**SCD** sudden cardiac death

**SCID** severe combined immunodeficiency

**SCLC** small cell lung cancer

**SCLE** subacute cutaneous lupus erythematosus

**SD** starting dose

**Se** sensitivity

**sec** second

**SERM** selective estrogen receptor modulator

**sev** severe

**SES** socioeconomic status

**SHBG** sex hormone binding globulin

**SI** sacroiliac suicidal ideation

**SIADH** syndrome of inappropriate antidiuretic hormone

**SIEP** serum immunoelectrophoresis

**SIMV** synchronized intermittent mandatory ventilation

**SIRS** systemic inflammatory response syndrome

**SJS** Stevens Johnson syndrome

| | |
|---|---|
| **SL** | sublingual |
| **SLA** | soluble liver antigen |
| **SLE** | systemic lupus erythematosus |
| **SLP** | speech language pathology therapist |
| **SMA** | smooth muscle antibody |
| **SMV** | superior mesenteric vein |
| **SNF** | skilled nursing facility |
| **SNHL** | sensorineural hearing loss |
| **SNRI** | serotonin-norepinephrine reuptake inhibitor |
| **soln** | solution |
| **SOB** | shortness of breath |
| **Sp** | specificity |
| **SPEP** | serum protein electrophoresis |
| **SPN** | solitary pulmonary nodule4 |
| **SQV** | saquinavir |
| **SR** | sinus rhythm |
| **ss** | single strength |
| **SSc** | systemic sclerosis |
| **SSRI** | selective serotonin reuptake inhibitor |
| **SSTI** | skin + soft tissue infection |
| **SSS** | sick sinus syndrome |
| **ST** | sinus tachycardia |

**STARI** Southern tick-associated rash illness

**STC** slow transit constipation

**STD** sexually transmitted disease

**STI** sexually transmitted infection

**STE** ST segment elevation

**SUD** substance use disorder

**SV** stroke volume

**SVC** superior vena cava

**SVR** systemic vascular resistance

**SVT** supraventricular tachycardia

**sx** symptom(s)

**sz** seizure

**T** testosterone

**$T_3$RU** $T_3$ resin uptake

**TAA** thoracic aortic aneurysm

**TAC** trigeminal autonomic cephalgia

**TB** tuberculosis total bilirubin

**TBG** thyroid binding globulin

**TBI** toe brachial index

**TBW** total body weight

**TCA** tricyclic antidepressant

| | |
|---|---|
| **TCD** | transcranial doppler |
| **TD** | transdermal |
| **TDF** | tenofovir |
| **TdP** | torsades de pointes |
| **TdT** | terminal deoxynucleotidyl transferase |
| **TEE** | transesophageal echo |
| **TEN** | toxic epidermal necrolysis |
| **TENS** | transcutaneous electrical nerve stimulation |
| **TFTs** | thyroid function tests |
| **TG** | triglycerides |
| **TIA** | transient ischemic attack |
| **TIBC** | total iron binding capacity |
| **TINU** | tubulointerstitial nephritis and uveitis |
| **TIPS** | transjugular intrahepatic portosystemic shunt |
| **TIW** | three times a week |
| **TLC** | total lung capacity |
| **TM** | tympanic membrane |
| **TMA** | thrombotic microangiopathy |
| **TMJ** | temperomandibular joint |
| **TMNG** | toxic multinodular goiter |
| **TMP-SMX** | Trimethoprim-sulfamethoxazole |

**TMPT** thiopurine methyl transferase

**Tn** troponin

**TOA** tubo-ovarian abscess

**TP** total protein

**tPA** tissue plasminogen activator

**TP-EIA** *T. pallidum* enzyme immunoassay

**TPMT** thiopurine methyl transferase

**TPN** total parenteral nutrition

**Tpo** thrombopoietin

**TPO** thyroid peroxidase

**TPPA** treponema pallidum particle assay

**TPV** tipranavir

**TR** tricuspid regurgitation

**TRALI** transfusion-related acute lung injury

**TRH** thyrotropin releasing hormone

**TRS** TIMI risk score

**TRUS** transrectal ultrasound

**TS** tricuspid stenosis

**TSH** thyroid stimulating hormone

**TSI** thyroid-stimulating immunoglobulin

**TSS** toxic shock syndrome transsphenoidal surgery

**TST** tuberculin skin test

**TTE** transthoracic echo

**TTG** tissue transglutaminase

**TTKG** transtubular potassium gradient

**TTP** tender to palpation

**TV** tricuspid valve

**TVUS** transvaginal ultrasound

**Tw** T wave

**TWF** T wave flattening

**TWI** T wave inversion

**tx** treat, treatment

**TZD** thiazolidinediones

**U** units

**U/A** urinalysis

**U/S** ultrasound

**UA** unstable angina uric acid

**UACR** urine albumin:creatinine ratio

**UACS** upper airway cough syndrome

**UAG** urine anion gap

**UC** ulcerative colitis

**UCB** unconjuganted (indirect) bilirubin

**UCx** urine culture

**UDT** urine drug testing

**UE** upper extremity

**UES** upper esophageal sphincter

**UFC** urine free cortisol

**UFH** unfractionated heparin

**UGIB** upper gastrointestinal bleed

**UIP** usual interstitial pneumonitis

**UMN** upper motor neuron

**UL** upper lobe

**ULN** upper limit of normal

**UOP** urine output

**UPCR** urine protein:creatinine ratio

**UPEP** urine protein electrophoresis

**UPF** ultraviolet protective factor

**UR** urgent revascularization

**URI** upper respiratory tract infection

**USPSTF** United States Preventive Services Task Force

**UTI** urinary tract infection

**UV** ultraviolet

**V/Q** ventilation-perfusion

**VA** visual acuity

**VAD** ventricular assist device

**VATS** video-assisted thoracoscopic surgery

**VBI** vertebrobasilar insufficiency

**VC** vaginal candidiasis vital capacity

**VD** vascular dementia

**VDRL** venereal disease research laboratory (syphilis test)

**VEGF** vascular endothelial growth factor

**VF** ventricular fibrillation vocal fold

**VFR** visiting friends and relatives

**VHC** valved holding chamber

**VLDL** very-low-density lipoproteins

**VOD** veno-occlusive disease

**VPA** valproic acid

**VRS** viral rhinosinusitis

**VSD** ventricular septal defect

**VST** venous sinus thrombosis

**$V_T$** tidal volume

**VT** ventricular tachycardia

**VTE** venous thromboembolus

**VU** vesicoureteral reflux

| | |
|---|---|
| **vWD** | von Willebrand's disease |
| **vWF** | von Willebrand's factor |
| **VZV** | varicella zoster virus |
| | |
| **w/** | with |
| **w/d** | withdraw, withdrawal |
| **w/o** | without |
| **w/u** | workup |
| **WB** | weight bearing |
| **WBC** | white blood cell (count) |
| **WCT** | wide-complex tachycardia |
| **WHO** | World Health Organization |
| **wk** | week |
| **WM** | Waldenström's macroglobulinemia |
| **WMA** | wall motion abnormality |
| **WPW** | Wolff-Parkinson-White syndrome |
| | |
| **XRT** | radiation therapy |
| | |
| **yo** | year old |
| | |
| □ | male |

| | |
|---|---|
| ♀ | female |
| ✓ | check |
| ☤ | psychiatric |

# NOTES

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